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Abstracts
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*Primary and Hospital Care*


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Do early handoffs in internal medicine wards affect the quality and cost of care?
Christophe Fehlmann1, Martine Louis Simonet1, Christophe Gaudet-Blavignac1, Jérôme Stirnemann1, Katherine Blondet1,2,3
1Service de Médecine Interne Générale, DMIRG, HUG; 2Service des Sciences de l’Information Médicale, DISIM, HUG; 3Direction Médicale, HUG, Genève, Switzerland

Introduction: Continuity of care is a key feature for high quality of care. To maintain the continuity of care of patients in the hospital, physicians conducting handoffs to transfer patient information and accountability from one provider or team to another. Prior studies show that handoffs are associated with an increased risk of complications and an increased length of stay. We were interested in studying the association between early handoffs (handoffs occurring between residents within the first 72 hours of a patient’s admission) and length of stay (LOS), use of resources (number of blood tests and procedures) and incidence of serious adverse events (transfers to ICU, intermediate care or death).

Methods: This is a retrospective cohort study of adult patients admitted to the General Internal Medicine Ward of Geneva University Hospital between 2012 and 2014, with a LOS >72 hours. We compared patients admitted by physicians other than the usual day team with patients who were admitted by the primary day team in univariate and multivariate linear and logistic regression models. Our outcomes were LOS, use of resources and incidence of serious adverse events. We adjusted the models for potential confounders.

Results: We included 11948 patients, 38% of whom were in the early handoff group. Our preliminary analyses show that an early handoff, in particular with a change of attending, is independently associated with an increase of LOS (+6.4%, 3.5–9.5, p <0.01 and +17.9, 14.6–21.2, p <0.01 respectively). Although early handoffs are not significantly associated with a higher use of resources, it was associated with more serious adverse events (OR = 1.3, 1.1–1.7, p <0.05) in the early handoffs group. Our subgroup analyses show that the association between early handoff and LOS loses significance when the patients are admitted on a public holiday.

Conclusion: Early handoffs affected the quality of care, especially the length of stay for patients admitted during weekdays. This emphasizes the importance of identifying and handing off pertinent and essential key information to enable care continuity when the medical team in charge of the patient changes. As restricting the number of handoffs is unrealistic, we should aim to improve the handoff training for both residents and supervisors, by standardizing the process content, to maintain the continuity, safety and effectiveness of care for hospitalized patients.

Should we stop to care about the transition because it’s not cost-effective?
Antoine Gambier1, Carole Nachar2, Pierre Voirol3
1Internal Medicine Department, University Hospital of Lausanne; 2Pharmacy Department; 3Medical Directorate, University Hospital of Lausanne (CHUV), Lausanne, Switzerland

Background: Patients hospitalized with heart failure (HF) present the highest rate of readmission within 30 days, above 20%. Reduction of early readmission is a major concern as quality and cost control indicator. Parts of these are potentially avoidable (PARE) and algorithms can estimate an adjusted expected range based on
Prescription of homeopathy in outpatient care: what physicians believe and what they intend

Stefan Markun, Thomas Rosemann, Marc Maeder, Sima Djialali

Background: Homeopathy is a highly controversial topic. Postulated mechanisms explaining homeopathy’s mode of action remain unconvincing for natural scientist and non-surprisingly, the aggregated evidence from rigorous randomized controlled trials suggests that homeopathy is no more effective than placebo. However, homeopathy continues to be prescribed also by physicians educated in academic medicine. Whether prescribing physicians believe in specific effects despite their education in natural sciences or whether they knowingly prescribe homeopathy to exploit non-specific/placebo effects and what might cause such homeopathy prescriptions is largely unknown. These issues, however, have important educational and ethical implications.

Methods: In 2015, we performed a cross-sectional survey among all physicians working in outpatient care in the Swiss Canton of Zurich. We assessed their prescription behaviour; believes in mode of action and accordable intentions behind the prescriptions. Furthermore, associations with prescribing homeopathy were investigated.

Results: From 4072 approached physicians in outpatient care 1531 responded (response rate 38%). Homeopathy was prescribed by 345 (23%) of the physicians. Prescribers’ believed modes of action were “the law of similars” (42%), placebo effect- and other interpersonal effects (up to 35%), “Water memory” (19%) and “quantum physics” (19%). Unambiguously accordable intentions behind prescriptions were achievement of specific effects in 50% and non-specific/placebo effects in 21%. Among all physicians (prescribers and non-prescribers included) only 55% thought that the available evidence rather disprove efficacy of homeopathy. Perception of patient requests for homeopathy and certain medical specializations were among factors strongly associated with prescribing homeopathy.

Conclusion: One in five physicians in outpatient care prescribed homeopathic remedies. Half of the homeopathy prescribers physicians intended specific effects, questioning the sustainability of their education in natural sciences. One in five prescribing physicians made use of homeopathy as a non-specific/placebo treatment and are therefore transgressing ethical directives. To explain why physicians prescribe homeopathy we need to better understand social and educational factors as well as homeopathy’s attractiveness in different medical specializations.

Informed decision making in colorectal cancer screening: influence of decision Aids and primary care physician on participants’ intention to screen and preference for colonoscopy or faecal immunochemical tests (FIT)

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Introduction: Colorectal cancer (CRC) screening reduces CRC mortality and incidence. Faecal immunochemical tests (FIT) and colonoscopy are both recommended but vary greatly in their attributes. Primary care physicians (PCP) were shown to favour colonoscopy as a screening test for their patients in a recent study conducted in the French-speaking region of Switzerland. In the perspective of a CRC screening programme in the canton of Geneva (Switzerland) that would offer both tests through informed decision via the PCP, we aimed to investigate the a priori influence of written and visual decision aids and PCP counselling in the choices of individuals regarding CRC screening.

Method: We conducted a population-based survey using a self-reported questionnaire sent in 2016 to 4500 randomly selected Geneva residents aged between 50 and 69. Participants were provided with written and visual decision aid tools used in the ongoing CRC screening programme of the adjacent canton (Vaud) illustrating the potential benefit of CRC screening and the pros and cons of FIT and colonoscopy. Intention to screen and choice of screening test after the consideration of the aids was assessed. Influence of the PCP on the decision of the participant was also evaluated.

Results: Overall, 1517 participants were included in the analyses. A majority of participants (73%) considered that the decision aids clearly illustrated the benefit of CRC screening, and 53% were incited by the latter to undertake CRC screening. Based on the decision aids provided, 41% of the participants chose FIT as the preferred screening test, 46% favoured colonoscopy and 13% were undecided. A large proportion of participants (84%) stated that their decision to undertake CRC screening would be influenced by their PCP, and 85% reported that their choice of the test would be influenced by what their PCP would recommend.

Conclusion: Written and visual aid tools provide useful information for CRC screening decision-making. The participants were quite balanced in their preference concerning FIT and colonoscopy after considering the decision aids. This should be considered by PCPs when counselling patients about CRC screening, given their significant influence on screening decisions, in order to avoid a shift towards colonoscopy.
Use of corticosteroids for subacute cough in primary care

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Introduction: Subacute cough (lasting 3–8 weeks) as a symptom of upper respiratory tract infections is very common in primary care consultations. Many colleagues reported that they often prescribe corticosteroids for subacute cough. However, the basis for an evidence-based decision for or against corticosteroids is weak. We aimed to determine the proportion of general practitioners (GPs) using corticosteroids for subacute cough.

Methods: All GPs registered with the Institutes of Primary Care Basel or Lucerne could participate in an online survey. They received an invite by e-mail containing the case vignette of a 32-year-old, healthy non-smoker without asthma, who has had dry cough for 4 weeks. They were then asked if they would prescribe steroids, followed up by six (if yes) or two (if no) questions.

Results: 183 of 472 (39%) GPs replied. 141 of 183 (77%) prescribed steroids for subacute cough. 99% of those GPs replying to the follow-up questions used inhaled steroids, 18% used oral steroids. Symptom 200/80 twice per day for 2 weeks was the most common inhaled steroid. Prednisone 20 mg per day for 5 days was the most common oral steroid. 42% and 21% also prescribed codeine and dextromethorphan, respectively. These proportions were similar among those GPs who did not prescribe steroids (43% and 16%). Overall, 94 GPs would like to participate in an intervention study on the efficacy of corticosteroids on subacute cough.

Conclusion: Despite weak evidence corticosteroids are frequently used for subacute cough in the course of upper respiratory tract infections in primary care. An intervention study on the efficacy of corticosteroids for subacute cough should be planned.

Association between alcohol and caffeine consumption and nocturnal leg cramps in patients over 60 years old: a case-control study

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Introduction: Nocturnal leg cramps are a specific kind of cramps affecting almost half of patients over 60 years old. They reduce patients’ quality of sleep and have a negative impact on their quality of life. The aim of this study was to evaluate the association between nocturnal leg cramps and the consumption of alcoholic beverages and caffeine in patients over 60 years old attending general practices.

Methods: Case-control study with a Bayesian approach for sensitivity analysis. Participants were voluntary ambulatory patients over 60 years old consulting their family doctor. Cases, i.e. patients suffering from cramps, were matched with controls (free from cramps) for age, sex, medical history and medications known to trigger cramps. Alcohol and caffeine consumption were assessed through the E3N Food frequency questionnaire.

Results: We found an association between the global consumption of alcoholic beverages and nocturnal leg cramps (OR 6.5 95% credibility interval [1.68; 38.05], posterior probability 99.82%). Caffeine consumption was not significantly associated with nocturnal leg cramps.

Conclusion: We identified an association between alcohol consumption and nocturnal leg cramps among patients over 60 years old attending general practices. These findings have implication for the prevention of cramps. They also open new avenues for the further exploration of the as yet uncertain pathophysiology of cramps, considering effects of ageing and alcohol on muscular fibres.
Performance of the quick SOFA score in the emergency department
Selin Tugul1, Pierre-Nicolas Carron2, Bertrand Yersin2, Thierry Calandré2, Fabrice Dami2
1Service of Internal Medicine, Department of Medicine, 2Emergency Department; 3Infectious Diseases Service, Department of Medicine, CHUV, University Hospital and University of Lausanne, Lausanne, Switzerland

Introduction: Sepsis, according to the new definition, is a life-threatening organ dysfunction with high mortality. In order to promptly identify septic patients with the worst prognosis outside the intensive care unit (ICU), a new bedside score was proposed: the quick SOFA score (qSOFA). It remains relatively untested in emergency settings. We measured the performance of the qSOFA and 2 other clinical scores at the emergency department's triage to identify the most severely infected patients among a population of patients transported by emergency medical services (EMS) to our emergency department (ED).

Methods: We performed a retrospective study of all patients transported to the Lausanne University Hospital, from January 1st to December 31st 2012. All patients with a suspected or proven infection through the ED stay were included. qSOFA, SIRS and Sepsis scores were retrospectively calculated upon arrival to the ED. End points were: ICU admission, ICU stay >3 days and mortality at 48 hours.

Definitions: qSOFA score: ≥ two of the following criteria: systolic blood pressure (SBP) ≤100 mm Hg, respiratory rate (RR) ≥22/min, and altered mental status (Glasgow Coma Scale (GCS) <15). SIRS score: ≥ two of the following criteria: heart rate >90/min, RR >20/min, temperature <36 °C or ≥38.3 °C. Sepsis score: SIRS score plus one sign of organ dysfunction or hypoperfusion (GCS <15, oxygen saturation <90% or SBP <90 mm Hg).

Results: Among the 11'411 patients transported to the University hospital, 890 patients fulfilled the criteria of a final diagnosis of infection; four had missing data and were excluded. 886 (7.8%) patients without organ dysfunction after the ED stay, and 442 had a sepsis with organ failure. Sensitivity of the qSOFA and sepsis scores for mortality at 48h reached 60%, 42.4% for the sepsis score, and 58.8% for the SIRS score. The sensitivities were practically identical for the stay in ICU ≥ two of the following criteria: systolic blood pressure (SBP) ≤100 mm Hg, respiratory rate (RR) ≥22/min, and altered mental status (Glasgow Coma Scale (GCS) <15). SIRS score: ≥ two of the following criteria: heart rate >90/min, RR >20/min, temperature <36 °C or ≥38.3 °C. Sepsis score: SIRS score plus one sign of organ dysfunction or hypoperfusion (GCS <15, oxygen saturation <90% or SBP <90 mm Hg).

Conclusion: The qSOFA score, as well as existing clinical scores, perform poorly to early identify upon arrival to the ED, the most seriously infected patients.

"Smarter Medicine" implementation: a single centre retrospective analysis
Lionel Chok, Johann Debrunner, Sandra Jaeggl, Carmen Kusic, Esther Bächli
Department of Internal Medicine, Medical Clinic, Uster Hospital, Uster, Switzerland

Introduction: Inspired by the US Choosing Wisely® campaign, the Swiss Society of General Internal Medicine (SSGM) released in May 2016 a list of 5 treatments or diagnostic tests frequently used in the Hospital and considered as unnecessary, since not improving patient care and increasing health care costs. The Swiss initiative was called “smarter medicine.” "Smarter medicine" recommendations were implemented on our Department on August 9th. “Smarter medicine” recommendations were changed physician behaviour by reducing the count of blood orders. The simple and low-cost interventions used to implement the “smarter medicine” seem to have changed physician behaviour by reducing the count of blood orders. These results are promising and we need a wide implementation of the “smarter medicine” recommendation to reduce resource wasting. Whether the “smarter medicine” will impact patient and clinical outcome remains however unknown and further studies are needed to clarify this issue.

Results: Volume of blood drawn was also significant lower in the three months after (median blood volume drawn per patient 56 mL, IQR 27–99) than before recommendation (median 65 mL, IQR 68–108, P = 0.01) (fig. 2).

Conclusions: Inappropriate blood draws may lead to anemia, patient discomfort and false positive results. The simple and low-cost interventions used to implement the “smarter medicine” seem to have changed physician behaviour by reducing the count of blood orders. These results are promising and we need a wide implementation of the “smarter medicine” recommendation to reduce resource wasting. Whether the “smarter medicine” will impact patient and clinical outcome remains however unknown and further studies are needed to clarify this issue.
elderly patients with acute PE who are particularly vulnerable to adverse outcomes.

**Methods:** We aimed to evaluate the prognostic performance of the computed tomography obstruction index (CTOI) and right ventricular dysfunction (right ventricular [RV] to left ventricular [LV] diameter ratio >0.9) in elderly patients with PE. We studied 291 patients aged ≥65 years with acute symptomatic PE in a prospective multicenter Swiss cohort study. CTPA was performed at each participating study center and then anonymously sent to Lausanne University Hospital, where the images were independently evaluated by two board-certified radiologists. Outcomes were 90-day overall and PE-related mortality, and recurrent venous thromboembolism (VTE) during the whole follow-up period. We examined associations of the CTOI and the RV/LV diameter ratio with mortality and VTE recurrence using survival analysis, adjusting for provoked VTE, the Pulmonary Embolism Severity Index, and anticoagulation as a time-varying covariate.

**Results:** Overall, 15 patients died within 90 days (6 from definite or possible PE). While the CTOI was not associated with 90-day overall mortality (adjusted hazard ratio [HR] per 10% CTOI increase 0.92; 95% confidence interval [CI] 0.70–1.21; P = 0.54), it was significantly associated with PE-related 90-day mortality (adjusted sub-hazard ratio [SHR] per 10% CTOI increase 1.36; 95% CI 1.03–1.81; P = 0.03). The RV/LV diameter ratio was neither associated with overall nor PE-related 90-day mortality. The CTOI (adjusted SHR per 10% CTOI increase 1.27; 95% CI 1.12–1.45; P <0.001) and the RV/LV diameter ratio (adjusted SHR per unit increase 2.74; 95% CI 1.26–5.95; P = 0.01) were both significantly associated with VTE recurrence.

**Conclusion:** In elderly patients with acute PE, the CTOI was associated with PE-related 90-day mortality but not with overall mortality. The RV/LV diameter ratio did not predict mortality. Both measures predicted VTE recurrence.

### Association of predictors with 90-day mortality

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<td>0.51</td>
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</tbody>
</table>

*Adjustment was done for provoked VTE, the Pulmonary Embolism Severity Index, and anticoagulation as a time-varying covariate.

### Association of predictors with VTE recurrence

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Crude SHR (95% CI)</th>
<th>P value</th>
<th>Adjusted SHR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTOI (per 10%)</td>
<td>1.21 (1.07; 1.38)</td>
<td>0.003</td>
<td>1.27 (1.12; 1.45)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV/LV diameter ratio (per unit)</td>
<td>1.56 (0.67; 3.67)</td>
<td>0.31</td>
<td>2.74 (1.26; 5.95)*</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Adjustment was done for provoked VTE, the Pulmonary Embolism Severity Index, and anticoagulation as a time-varying covariate.

### Figure 1: Kaplan-Meyer survival curves.

Patients in Q5 also had a longer LOS: median and (interquartile range): 15 (7–26) vs. 9 (2–18) days, respectively, p <0.001; this difference persisted after multivariate adjustment (p <0.001 on log-transformed data).

**Conclusion:** Patients with high NT-pro-BNP levels are at higher risk of in-hospital mortality and longer LOS. NT-pro-BNP levels can be a helpful tool for predicting in-hospital patient outcome.
Trends in the main classes of drugs prescribed at discharge from a university general internal medicine unit

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Background: The characteristics of patients admitted to internal medicine change with time. Patients are increasingly older and present with more comorbidities, which impacts prescription patterns. We aimed to measure the trends in the pattern of medications prescribed at discharged from a department of Internal Medicine of a university hospital.

Methods: Retrospective study including 18 075 adult patients discharged between 2009 and 2015. Drugs prescribed at discharge were coded according to the anatomical therapeutic chemical (ATC) nomenclature of the World Health Organization.

Results: The three most commonly classes of drugs prescribed were “alimentary tract and metabolism (including insulins)”; “nervous system”; and “blood and blood forming organs” (table). The five most prescribed drugs were analgesics (8.4% of all drugs prescribed); antithrombotic agents (ATC code B01, 8.0%); psycholeptics (including hypnotics and sedatives, 7.2%); drugs for constipation (7.0%) and drugs for acid related disorders (6.0%). Most prescribed groups increased during the study period, excepting ATC group B “blood and blood forming organs”; “cardiovascular system”; and “dermatologicals”. In 2015, over eight out of ten patients discharged received at least one drug from “alimentary tract and metabolism” or “nervous system” (figure; all trends are significant at p < 0.001).

Conclusion: The pattern of drug prescription has changed, with an increase in drugs for alimentary tract and metabolism and nervous system. The reasons for and the consequences of the very high prevalence of drugs for the nervous system should be further investigated.

Keywords: Prescribed drugs; Hospital; discharge

**Figure 1: Trends for the major groups of drugs.**

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**EPIEDEMOLOGIE**

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Is the risk of fracture increased among participants with thyroid function within the reference range?


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**Introduction:** Hyperthyroidism is associated with an increased risk of osteoporosis and fractures. However, it is not clear whether high thyroid-stimulation hormone (TSH) within its reference range and low free thyroxine (FT4) levels lead to increased fracture risk. Furthermore, the target TSH to reach with levothyroxine treatment of hypothyroidism remains controversial. We aimed to evaluate the association between TSH within the reference range, FT4, and incident fractures.

**Methods:** We performed an individual participant data analysis of thirteen prospective cohort studies across three continents with a median follow-up of 12.1 years (interquartile range 8.5–12.9). We included adults with baseline serum TSH within the reference range (0.45–4.49 mIU/L). The primary outcome was incident hip fracture. Secondary outcomes were incident clinical vertebral, non-vertebral, and any fractures. For clinical relevance, we categorized participants’ TSH as: 0.45–0.99 mIU/L; 1.00–1.49 mIU/L; 1.50–2.49 mIU/L; 2.50–3.49 mIU/L; and, 3.50–4.49 mIU/L (reference group). FT4 was assessed as one standard deviation increase within each study, because FT4 assay methodology differed between cohorts. Analyses were stratified by sex and age.

**Keywords:** Hyperthyroidism; Osteoporosis; Fractures; Thyroid-stimulation hormone (TSH); Free thyroxine (FT4); Hypothyroidism; Levothyroxine; Clinical vertebral; Non-vertebral; Any fractures.
Changes in antidiabetic drug treatment in a Swiss population-based sample. The CoLaus study

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Background and aims: Treatment of type 2 diabetes mellitus (T2DM) evolves with time, but little information is available regarding its determinants in the general population. We aimed to assess changes and determinants associated to antidiabetic treatment in a Swiss population-based sample.

Methods: Two hundred and ten participants with T2DM from the CoLaus study. Antidiabetic drug treatment was assessed at baseline (2003–2006) and follow-up (2009–2012), and categorized into maintainers, changers and reducers/quitters.

Results: At baseline, 146 (69.5%) of the 210 participants received antidiabetic treatment. Of the 146 participants treated, 124 (84.9%) received oral antidiabetics alone, 8 (5.5%) insulin alone and 14 (9.6%) insulin and oral antidiabetics. During the 5.5 year follow-up, 108 (74.0%) patients remained, 27 (18.5%) changed and 11 (7.5%) reduced or stopped treatment. Patients who changed therapy had higher baseline fasting plasma glucose (FPG) levels than the others (10.3 ± 3.7 vs. 7.8 ± 2.0 and 7.6 ± 2.0 mmol/L for maintainers and reducers/quitters, respectively, p = 0.001) and also lower levels of FPG <7.0 mmol/L (74.0%, vs. 39.8% and 45.5% for maintainers and reducers/quitters, respectively, p = 0.002). At follow-up, patients who changed therapy had the highest prevalence of FPG decrease relative to baseline (55.6%, vs. 46.3% and 9.1% for maintainers and reducers/quitters, respectively, p = 0.002). During a 5.5 year follow-up, less than one fifth of patients with T2DM had his/her drug treatment changed. Changes in T2DM treatment lead to an improvement of the unfavourable FPG status. The reasons and impact of quitting or reducing treatment should be further explored.

Keywords: Type 2 diabetes; antidiabetic drugs; treatment; epidemiology; trends

Dietary behaviors influence inflammatory markers: results from the CoLaus study

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Introduction: Our aim is to assess the impact of dietary intake (single foods, macro and micronutrients, dietary patterns and scores) on inflammatory markers (CRP, IL-6, TNF-α and leucocyte count).

Methods: Data from 3774 participants of the population-based CoLaus study. Dietary intake was assessed using a semi-quantitative food frequency questionnaire. Single foods, nutrients, three naive (using principal components analysis) and four oriented (Mediterranean, Alternative Healthy Eating Index) dietary scores were computed from the food frequency questionnaire. Single foods, nutrients, three naive (using principal components analysis) and four oriented (Mediterranean, Alternative Healthy Eating Index) dietary scores were assessed with a food frequency questionnaire. Single foods, nutrients, three naive (using principal components analysis) and four oriented (Mediterranean, Alternative Healthy Eating Index) dietary scores were assessed with a food frequency questionnaire.

Results: CRP was positively associated (p <0.01, table 1) with the “meat and chips” pattern, and negatively associated with the “fruits and vegetables” pattern, the Mediterranean and the Alternative Healthy Eating Index (AHEI) scores, fruits, carrots, potatoes and chips. After adjusting for age, body mass index (BMI), gender, smoking habits, education, sedentarity, total calorie intake and diabetes, the negative association with the “fruits and vegetables” pattern, the Mediterranean and the Alternative Healthy Eating Index scores, and fruits remained significant (p <0.01, table 2). Leucocyte count was positively associated (p <0.01, table 1) with the “meat and chips” pattern and negatively associated with the “fruits and vegetables” pattern, the AHEI scores, a high intake of fiber, vitamin A, vitamin C, and vitamin D. After adjusting for age, gender, smoking habits, education, sedentarity, total calorie intake and diabetes, the negative associations with the “meat and chips” and the “fruits and vegetables” patterns remained significant (p <0.01, table 2). Conversely, no significant associations were found between all dietary markers and TNF-α and IL-6 after multivariate adjustment.
Conclusions: (un)healthy dietary behaviors have a small but significant impact on inflammatory markers in the general population. The effect of individual nutrients or foods appears to be of less clinical importance.

Legislative changes and 22-year trends in individual alcohol consumption in a Swiss adult population
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Introduction: Alcohol misuse is an important determinant of health and a major contributor to the burden of disease worldwide. With regard to alcohol use regulations, Switzerland has a long history of efforts to regulate alcohol production, sale and use, at the cantonal and federal levels. Evidence on the impact of legislative changes on individual alcohol consumption is limited. Using an observational study design, we assessed trends in individual alcohol consumption of a Swiss adult population following the public policy changes that took place between 1993 and 2014, while considering individual characteristics and secular trends.

Method: We used data from the “Bus Santé” study, an annual health survey conducted in random samples of the adult population in the State of Geneva, Switzerland. Individual alcohol intake was assessed using a validated food frequency questionnaire. Individual characteristics including education were self-reported. Seven policy changes (six about alcohol and one about tobacco) that occurred between 1993 and 2014 defined 6 different periods. We predicted alcohol intake using quantile regression with multivariate analysis for each period adjusting for participant characteristics and tested significance periods. Sensitivity analysis was performed including drinkers only, the 10th percentile of highest drinkers and smoker’s status.

Results: The study included data from 18,963 participants (aged 18–75 years). Between 1992 and 2014, participants’ individual alcohol intake decreased from 7.3 to 5.4 g/day (26% reduction, p <0.001). Men decreased their alcohol intake by 35% compared to 31% for women (p <0.001). The decrease in alcohol intake remained significant when considering drinkers only (30% decrease, p <0.001) and the 10th percentile highest drinkers (24% decrease, p <0.001). Consumption of all alcoholic beverages decreased between 1993 and 2014 except for the moderate consumption of beer, which increased. After adjustment for participants’ characteristics and secular trends, no independent association between alcohol legislative changes and individual alcohol intake was found.

Conclusion: Between 1993 and 2014, alcohol consumption decreased in the Swiss adult population independently of policy changes.
Sleep disorders are associated with trabecular bone score and osteoporotic fracture, not with bone mineral density

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Context: Sleep disorders and osteoporosis increase with age and are associated with mortality and economic burden. The prevalence of sleep-disordered breathing in Swiss women is 23% above 40 years and the remaining lifetime risk of osteoporotic (OP) fracture at 50 years is >50%. Poor sleep quality is associated with increased risk of fall and inconsistently with low bone mineral density (BMD), but the effect sizes were small and the mechanisms are unknown. Our study aimed to assess if sleep characteristics are associated with markers of bone health; BMD, microarchitecture assessed indirectly by trabecular bone score (TBS), and OP and non OP fractures.

Methods: OsteoLaus is a population-based cohort of 1500 randomly selected Caucasian women (50 to 80 y old) living in Lausanne, Switzerland. All women had lumbar spine BMD and TBS, hip BMD, vertebral fracture assessment, and questionnaire about OP and non OP fractures. A random selection of 660 women was included in the HypnoLaus Sleep cohort study and had a polysomnography. Total sleep time (TST), sleep onset latency (SOL), slow-wave sleep (SWS) and rapid eye movement sleep (REM) quantity, apnoea-hypopnoea index (AHI), oxygen desaturation index (ODI) and sleep efficiency were evaluated.

Results: After adjustment, sleep parameters were not associated with BMD, AHI and ODI were inversely associated with TBS. All the results for fractures were adjusted for age, BMI and psychoactive drugs. Sleep onset latency was associated with OP fractures (p <0.001), REM was associated with OP and non OP fractures (p <0.05). We created a score of “sleep quality” including 6 parameters: total sleep time, sleep onset latency, slow-wave sleep, REM sleep, AHI, and sleep efficiency. This score was significantly lower only for women with prevalent OP fracture: women with OP fracture vs women without fracture (~0.25 ± 0.09 vs. 0.05 ± 0.04, P <0.03).

Conclusion: Our study demonstrates for the first time that TBS is altered in women with high AHI or high ODI. We found however no relevant association between BMD and sleep characteristics. The sleep quality score was lower for women with OP fracture. Further studies are needed to: 1) explain how some sleep characteristics affect TBS; and 2) validate the score of “sleep quality” in other studies.

Use of polypill components in a Swiss population-based study

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Background: Cardiovascular diseases (CVD) are the first cause of mortality and morbidity worldwide. Insufficient adherence to cardiovascular therapy could explain in part this finding despite tremendous progress in CVD treatment. Lack of adherence could be prevented by a fixed combined dose of efficient medications for CVD prevention, the so-called polypill. We aimed to assess the prevalence of participants in a large population-based study in Lausanne already taking simultaneously individual components of polypills approved either worldwide or in Switzerland.

Methods: Cross-sectional study conducted between 2009 and 2012 in a sample of 3648 participants aged ≥65 years. Medications taken and associated medical conditions were assessed by questionnaire and confirmed by interview. Two major types of polypill equivalents were defined based on commercially available polypills. Polypill equivalent A contains aspirin, a statin and any antihypertensive drug and equivalent B a statin and any antihypertensive drug. In addition we further assessed two combinations that correspond to Swissmedic’s equivalent A contains aspirin, a statin and any antihypertensive drug. In addition we further assessed two combinations that correspond to Swissmedic’s equivalent B a statin and any antihypertensive drug. In addition we further assessed two combinations that correspond to Swissmedic’s equivalent B a statin and any antihypertensive drug. In addition we further assessed two combinations that correspond to Swissmedic’s equivalent B a statin and any antihypertensive drug. In addition we further assessed two combinations that correspond to Swissmedic’s equivalent B a statin and any antihypertensive drug. In addition we further assessed two combinations that correspond to Swissmedic’s equivalent B a statin and any antihypertensive drug. In addition we further assessed two combinations that correspond to Swissmedic’s equivalent B a statin and any antihypertensive drug. In addition we further assessed two combinations that correspond to Swissmedic’s equivalent B a statin and any antihypertensive drug.
Effect of vitamin D3 on self-perceived fatigue: a double-blind randomized placebo-controlled trial

Albina Nowak1, Lukas Boesch1, Erik Andres1, Edouard Battegay1, Thorsten Homemann2, Christoph Schmidt3, Heike Bischoff-Ferrari4, Paolo Suter5, Pierre-Alexandre Kravenbuehl5
1Innere Medizin, 2Institut für Klinische Chemie, 3Klinik für Endokrinologie, 4Klinik für Geriatrie, Universitätsspital Zürich, Zürich, 5Innere Medizin, Spital Linth, Uznach, Switzerland

Introduction: Vitamin D deficiency is frequent and has been associated with fatigue in uncontrolled trials.

Methods: This is the first double-blind placebo-controlled clinical trial to investigate the efficacy of per os vitamin D3 (cholecalciferol) in treating fatigue among otherwise healthy persons with low serum 25-hydroxyvitamin D (25(OH)D) levels. We enrolled 120 individuals (mean age 29 ± 6 years, 53% female) presenting with fatigue and vitamin D deficiency (serum 25(OH)D <20 µg/l). Participants were randomized to a single oral dose of 100,000 units of vitamin D or placebo. The primary endpoint was intra-individual change in the Fatigue Assessment Scale (FAS) at 4 weeks after treatment.

Results: The mean age of the participants was 29 ± 6 years, 53% were female. Mean FAS decreased significantly more in the vitamin D group (–3.3 ± 5.3; 95% confidence interval for change –14.1 to 4.1) compared with placebo (–0.8 ± 5.3; 95% confidence interval for change –9.0 to 8.7); (p-value = 0.01; FAS improved significantly only in the vitamin D (p-value <0.001) but not in the placebo (p-value = 0.24) Group.

Conclusion: Vitamin D treatment significantly improved fatigue in otherwise healthy persons with vitamin D deficiency. This study was registered at the www.ClinicalTrials.gov Protocol ID NCT02022475.

Lung cancer: sex difference in the lifetime risk and 10-year risk between 1995 and 2013 in a Swiss population

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Introduction: In Switzerland, lung cancer is a leading cause of cancer death. Because smoking is the major cause of lung cancer, trends in lung cancer incidence are following trends in smoking habits in the population, with a latency time of about 30 years. In Switzerland, there was a peak in men’s lung cancer incidence in the 1980s, followed by a decrease until now. Among women, the incidence has increased since the 1970s and, apparently, has not yet reached a peak. Because cancers are feared diseases, an adequate communication about the individual risk of developing cancer is important. Mortality and incidence are traditionally used to assess cancer burden. However, these metrics are difficult to interpret at the individual level. Providing the lifetime and 10-year risk of cancer could improve risk communication for patients and health professionals. Our aim was to estimate trends in the lifetime and 10-year risk of lung cancer, in men and women, between 1995 and 2013.

Methods: We used data from all lung cancer cases recorded between 1995 and 2013 and the Registre Valaisan des tumeurs (RVST) and the Registre Vaudois des Tumeurs (RVT). These two population-based registries collect data on all new cancer cases of women and men living in Valais and Vaud. Data on mortality were provided by the Federal Statistical Office. We estimated sex-specific lifetime risk and 10-year risk of lung cancer using the current probability method, which estimates cumulative risk of any condition accounting for competing risk and death.

Results: Between 1995 and 2013, 10453 cases of lung cancer were recorded. The lifetime risk of developing lung cancer decreased in men from 8.1% in 1995–1998 to 6.8% in 2009–2013 (fig. 1). During this same period, it increased in women from 2.8% to 4.1% (fig. 1). In both sexes, the 10-year risk of lung cancer increased with age until the age of 70 and decreased thereafter. Between 1995 and 2013, the 10-year risk of lung cancer decreased in men at all ages, excepted in men over 80 years of age in whom the risk increased. Among women, the 10-year risk increased in women above 50 years of age.

Conclusion: Lifetime and 10-year risk of cancer can improve cancer risk communication. Between 1995 and 2013, the lifetime risk of lung cancer decreased in men and increased among women.

Figure 1: Fatigue before and after vitamin D treatment.
FUTURE RESEARCH IN EPIDEMIOLOGY

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Stats in and risk of Alzheimer’s disease: evidence from Mendelian randomization

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Background: Observational studies suggest that statin use is inversely associated with the risk of Alzheimer’s disease (AD). Thus, it is important to investigate whether any statin impact on risk of AD represents an on-target effect (i.e., due to a specific inhibition of the 3-hydro-3-méthylglutaryl coenzyme A reductase (HMGCR)). Since known genetic variants recapitulate the effect of statins (inhibition of HMGCR), we used single-nucleotide polymorphisms (SNPs) in/near HMGCR gene to estimate the association between statin use and risk of AD.

Methods: Using the properties of genetic variants (presence from conception and inalterable nature), we applied a “Mendelian randomization” (MR) approach to estimate the causal effect of HMGCR inhibition on risk of AD, a form of drug target exploratory analysis. We used 3 independent (I2 < 0.25) SNPs in/near HMGCR (rs16872526, rs12916, rs5744707) and retrieved their association estimates with LDL-cholesterol, as reported in up to 183,465 individuals in the Global Lipids Genetic Consortium. We retrieved the same SNPs and their association estimates with AD from a large AD GWAS (including 17,008 cases and 24,004 controls). We then estimated a causal effect and a corresponding standard error (SE) for each SNP derived by the Wald and delta methods, respectively. Individual causal effect estimates were pooled using random-effects meta-analysis. Since APOE gene, which encodes ApoE (ApoE: found in chylomicrons and some lipoproteins), influence the odds of AD, we complemented the analysis by testing whether an ApoE-associated variant (rs7412) was related to risk of AD as a positive control. Analysis for APOE rs7412 was performed as described above.

Results: In Mendelian randomization analysis based on 17,008 AD cases and 37,154 controls, statin use (instrumented using HMGCR-related variants) was not associated with risk of AD (OR for AD: 1.00; 95% CI, 0.66–1.52). Using APOE rs7412 as a positive control, and scaling the results to the same difference in LDL-C, the odds of AD was strongly reduced (OR for AD: 0.49; 95% CI, 0.42–0.56).

Conclusions: This study shows that pharmacological inhibition of HMGCR (i.e., the on-target effect of statins) is unlikely to reduce the risk of AD. These findings provide evidence to make inferences about the clinical effect of statins and to help orientate research on any relationship between statin use and risk of AD.

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Anti-apolipoprotein A-1 IgG as predictors of coronary heart disease and all-cause mortality in the general population: results from the CoLaus study

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1CHUV, University Hospital and University of Lausanne, Lausanne; 2Hôpitaux Universitaires de Genève, Genève; 3Institut Universitaire de Médecine Sociale et Préventive, Lausanne, Switzerland

Background: Autoantibodies against apolipoprotein A-1 (anti-apoA-1 IgG) are emerging as an independent biomarker for cardiovascular disease in selected settings, but their associations with incident coronary heart disease and mortality in the general population is unknown. We aimed to determine whether anti-apoA-1 IgG: a) predict incident CHD and all-cause mortality in the general population, and b) are associated with single-nucleotide polymorphisms (SNPs) in a genome-wide association study (GWAS) of coronary heart disease and mortality.

Methods: Clinical, biological and genetic data were obtained from the population-based, prospective CoLaus study, including 5220 participants (mean age 52.6 years, 47.3% men) followed over a median duration of 5.6 years. The primary study outcome was adjudicated incident CHD, defined as adjudicated incident myocardial infarction, angina, percutaneous coronary revascularization or bypass grafting. Results: In subjects positive vs. negative for anti-apoA-1 IgG, total CHD rate was 3.9% vs. 2.8% (p = 0.077), while nonfatal CHD rate was 3.6% vs. 2.3% (p = 0.018). Multivariate-adjusted Hazard ratios (aHR) and (95% confidence intervals) were 1.58 (0.96; 2.60), and 1.53 (1.03; 2.26), for total and nonfatal CHD, respectively. The association was modified by a significant interaction between anti-apoA-1 IgG and a functional SNP in the CD14 receptor gene (rs9770199) explaining 0.67% of risk of CHD in non-TT rs2569190 carriers (aHRs = 1.73 (1.10; 2.73)), whereas being associated with the lowest risk in TT homozygotes (p-for-interaction = 0.015). After multivariate adjustment, anti-apoA-1 IgG positivity independently predicted all-cause mortality (aHR = 1.54, (1.12–1.13), P = 0.01), with each standard deviation of logarithmically transformed anti-apoA-1 IgG being associated with a 15% increase in mortality risk. Our GWAS yielded 9 SNPs belonging to the Fc receptor like-3 (FCRL3) gene that were significantly associated with anti-apoA-1 IgG levels, with the lead SNP (rs6427397, P = 1.54×10−8) explaining 0.67% of anti-apoA-1 IgG level variation.

Conclusion: Anti-apoA-1 IgG independently predict nonfatal incident CHD in the general population, the strength of this association being dependent on a functional polymorphism of the CD14 receptor gene. Our findings further indicate that preclinical autoimmunity to anti-apoA-1 IgG is linked to FCRL3, a susceptibility gene for autoimmune diseases, and may as well represent a novel mortality risk factor in the community.

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Cannabis use and risk of schizophrenia: a Mendelian randomization study

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Background: Cannabis use is observationally associated with an increased risk of schizophrenia, however whether the relationship is causal is not known. Observational studies cannot clarify causality and a randomized trial would be unethical.

Methods: We took 10 independent genetic variants previously identified to associate with cannabis use in 32,330 individuals to determine the nature of the association between cannabis use and risk of schizophrenia. Genetic variants were employed as instruments to recapitulate a randomized controlled trial involving two groups (cannabis users vs nonusers) to estimate the causal effect of cannabis use on risk of schizophrenia or related disorders. We compared with a meta-analysis of observational studies reporting ever use of cannabis and risk of schizophrenia, however whether the relationship is causal is not known. Observational studies cannot clarify causality and a randomized trial would be unethical.

Findings: Based on the genetic approach, use of cannabis was associated with increased risk of schizophrenia (OR of schizophrenia for users vs. non-users of cannabis: 1.37; 95% CI, 1.09 to 1.76; P-value = 0.007). The corresponding estimate from observational analysis was 1.43 (95% CI, 1.19 to 1.67; P-value for heterogeneity = 0.76). The genetic instrument did not show evidence of pleiotropy nor when accounting for tobacco exposure (OR of schizophrenia for users vs. non-users of cannabis, adjusted for ever vs. never smoker: 1.41; 95% CI, 1.09 to 1.83). Furthermore, the causal estimate remained robust to sensitivity analyses.

Interpretation: These findings add to the substantial evidence base that showed that association between use of cannabis and risk of schizophrenia is likely to be causal. Such robust evidence may inform public health message about the risks of cannabis use, especially regarding its potential mental health consequences.
Smartphone-app compared to standard blood pressure measurement – trial design and pilot data of the iPARR trial

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Introduction: Smartphones and smartwatches allow to measure and track vital signs traditionally assessed with dedicated equipment. As these devices and health-related apps become increasingly used by the general population, it is essential to assess the accuracy of new measuring methods. A recently developed algorithm calculates systolic blood pressure (SBP) from the pulse wave recorded with a smartphone camera. This app is the only smartphone based tool worldwide that works without calibration measurement or additional peripheral devices to estimate SBP, but works with a large database of pulse wave curves with varying data for gender, size, weight, age, tobacco use and systolic blood pressure. The iPARR trial compared the accuracy of this method with a traditional professional blood pressure monitor.

Methods: In this prospective, blind, single-center trial, 1000 adult subjects were recruited. Seven sequential blood pressure measurements were performed after five minutes of rest in a quiet room in a sitting position. The series started with a standard device (Omron HBP-1300 professional blood pressure monitor, appropriate cuff size) alternating with the tested smartphone app (Preventicus®, iPhone 4s). The photoplethysmographic signal was recorded by placing the finger on the smartphone camera for 3 minutes. Based on the pulse wave morphology and five additional parameters (age, size, weight, sex, tobacco use) the pulse wave files were analysed by Preventicus® without knowledge of the oscillometric values. Data is merged with external data ending February 2017 and will be present for the SGAIM meeting.

Results: (Pilot data) In a retrospective analysis pilot data of 500 patients showed a correlation of r = 0.81 and mean error of <10 mm Hg between the SBP measured with a standard device and a smartphone. A first pilot validation cohort of 85 subjects confirms the smartphone. A first pilot validation cohort of 85 subjects confirms the

Conclusion: Pilot data of an ongoing prospective blinded validation trial (PARR) shows that SBP estimation with smartphone app is a promising innovative tool that will be tested and developed further to be implemented in a smartwatch or suitable wristband. A validation cohort following ESH criteria will follow.

The iPARR trial data will be available for the SGAIM Meeting 2017.

Education and coronary artery disease

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Introduction: Higher educational attainment is observationally associated with a lower risk of coronary artery disease, however it is not known whether this association is causal. We used Mendelian randomization, a method where genetic data are used to provide causal estimates to make inferences about the role of an exposure on the risk of a disease outcome.

Methods: We used 162 genetic variants previously associated with education to assess whether a genetic predisposition towards higher education is associated with risk of coronary artery disease in public datasets with 589,377 participants of predominantly Caucasian origin and living in developed countries. The primary outcome was combined fatal and nonfatal coronary artery disease. Genetically-derived estimates were compared with updated observational estimates of the association between education and coronary artery disease from several large observational studies. Sensitivity analyses included checking for potential pleiotropic effects of the genetic variants (i.e., when genetic variants associate directly with coronary artery disease via pathways that bypass education) and testing whether genetic liabilities for coronary artery disease is associated with educational outcomes.

Results: A one standard deviation increase in the genetic predisposition towards higher education (i.e. 3.6 years of additional schooling) lowered the risk of coronary artery disease by a third (odds ratio [OR] = 0.67, 95% confidence interval [CI], 0.59 to 0.77), consistent with observational estimates. Equivalent increases in education were also causally associated with reductions in smoking, BMI and improvements in blood lipid profiles. Genetic variants did not present pleiotropic effects based on various sensitivity approaches (Egger and weighted median Mendelian randomization analyses). The reverse investigation, of whether genetic liabilities for risk of CAD are included checking for potential pleiotropic effects of the genetic variants (i.e., when genetic variants associate directly with coronary artery disease via pathways that bypass education) and testing whether genetic liabilities for coronary artery disease is associated with educational outcomes.

Conclusions: Higher educational attainment is causally associated with a reduced risk of coronary artery disease. This may be partly explained by changes to smoking, BMI and blood lipids. These findings offer support for policy interventions that increase education in order to improve population health.
What are the challenges for the management of residents in difficulty in a Swiss primary care division?

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Introduction: The prevalence of residents in difficulty is 7–15% and is a major concern in medical education. Remediation plans have shown a good efficacy, but residents in difficulty are often detected too late in their academic cursos. Difficulties concern mainly cognitive and clinical reasoning (85%), professionalism (51%), communication (49%) and collaborative problems (20%) and may occur simultaneously.

Nowadays most training hospitals in Switzerland do not have specific processes to identify and manage residents in difficulty. The aim of the study was to explore the challenges perceived by physicians at different hierarchical levels (residents (R), senior residents (SR), attendings (A), program chief (PC)) regarding the process of identifying, diagnosing and supporting residents in difficulty in a structured and programmatic way.

Methods: We conducted an exploratory qualitative study. Participants were invited from the Primary Care Division of the Geneva University Hospitals. Between December 2015 and July 2016, we conducted three focus groups (with SR, A, R) and one interview with the division’s PC. Focus groups and the interview were transcribed, coded, and analyzed qualitatively using a content thematic approach and Fishbein’s conceptual Framework.

Results: We identified similar and divergent factors regarding the implementation of such a programmatic approach among physicians of different hierarchical levels. Major findings show: – Supervisors (SR, A, PC) usually identified correctly residents in difficulty but they did not set up systematic remediation strategies. – Supervisors (SR, A) felt concerned about residents in difficulty and the possible adverse effect on patient care, but were afraid to harm their career by writing up poor institutional assessment. – Residents feared that sharing their own difficulties with their supervisors would impact negatively on their career. – Environmental constraints (lack of money, lack of time and resources…) were reported by the four levels.

Conclusion: We identified a lack of a programmatic approach for the management of residents in difficulty. Thus, this process depends on residents’ attitudes regarding their own performance, the type of difficulties identified, and both on hierarchical involvement and institutional support. Similar and divergent factors regarding the implementation of such a programmatic approach are present at the different hierarchical levels and need to be addressed specifically.

Does patients’ satisfaction change under team care in a chronic care management program instead of usual care by the family physician alone?

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Introduction: Interprofessional chronic care management (CCM) programs in teams of doctors and coaches (medical practice coordinators, specially trained medical assistants) look promising to identify, diagnosing and supporting residents in difficulty in a structured and programmatic way.

Methods: We evaluated 11 Swiss primary care health care group practices offering interprofessional team care (TCM) to patients with pulmonary disease and combinations of these conditions. Between May 2013 and December 2015, 564 consecutive patients entered the programs. 559 (99%) of them completed a patient’s satisfaction questionnaire about their family physician with 9 items derived from the medical practice satisfaction assessment (EPA). Items had to be rated on a 5-point Likert scale between 1 (bad) and 5 (excellent). After a one-year program cycle, patients were asked to answer the same questionnaire regarding their team (coach and doctor). We collected all of these evaluations data at 4 different times (1st, 2nd, 3rd, and 4th). A “before-and-after” ratings were compared using paired sample t tests, applying Bonferroni correction for single item testing.

Results: Of the 559 patients (71%) answered the second questionnaire. There was a statistically significant difference in overall rating of family physicians alone (M = 4.63; SD = 0.42) and teams of doctors and coaches (M = 4.72; SD = 0.41); t(395) = 4.38, p <0.001. Results of single item testing are displayed in table 1.

Conclusion: In our setting, CCM programs run by teams of doctors and coaches further improved an already high satisfaction of patients with chronic conditions. Patients seem particularly better informed about symptoms and disease and feel better supported in dealing with emotional problems by this team approach.

The Swiss Resident Watch (SWATCH) study: the gold standard for working hours determination: a comparison between self-declaration and time clock

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Background: Since the submission of Swiss residents in hospitals to the federal labour law, the worktime limit of 50 hours/week applies, but several cases became public in which the declaration of extra hours was unprecise. In 2015, the first Swiss resident time-motion study performed at the CHUV discovered that as many as 75% of extra hours were not reported with a self-declaration system. Therefore, we wanted to assess whether a time clock system prevents residents from not reporting extra hours.

Method: We compared working hours from residents working at the Cantonal Hospital Baden (KSB) and the Lausanne University Hospital (CHUV). To assess actual working time, data was extracted from the Medical Day study at each center in which trained observers followed residents during normal day shifts. To ensure comparability the same protocol, tablet software and instruction of observers was used. Actual worktime was defined as duration from entering to leaving the office. At KSB, residents registered their working hours at dedicated spots with individual badges. At CHUV, working hours were self-reported with monthly cards. Extra hours were defined as more than 660 min per day at KSB and 600 min at CHUV (including 80 respectively 30 minutes lunchbreak). Statistical testing was performed with two-sided, unpaired t-test.

Results: Demographic baseline characteristics are shown in table 1.

Table 1: Demographic baseline characteristics of residents.

<table>
<thead>
<tr>
<th>Item</th>
<th>KSB mean</th>
<th>SD</th>
<th>CHUV mean</th>
<th>SD</th>
<th>d</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.6</td>
<td>3.19</td>
<td>28.8</td>
<td>1.7</td>
<td>1.34</td>
<td>0.15</td>
</tr>
<tr>
<td>Months postgraduate</td>
<td>20.9</td>
<td>17.7</td>
<td>31.2</td>
<td>11.9</td>
<td>10.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Months experience in internal medicine</td>
<td>16.1</td>
<td>11.3</td>
<td>270</td>
<td>10.4</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Swiss diploma</td>
<td>66.7%</td>
<td>60.7%</td>
<td>63%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>57%</td>
<td></td>
<td>63%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td>standard deviation</td>
<td></td>
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</tr>
</tbody>
</table>
Effects of two job-sharing physicians versus a full time attending physician on quality of care and coworkers' satisfaction in a Swiss hospital

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Introduction: An increasing number of physicians choose to work part-time and consider job-sharing as an alternative to the traditional hospital practice model. Whether two part-time, job-sharing physicians provide the same output as a single working full-time has seldom been assessed. We therefore aimed to compare the effects of two job-sharing physicians versus a full time physician on quality of inpatients care and coworkers' satisfaction.

Methods: Intervention study conducted between 2014 and 2016 in an internal medicine ward of a Swiss teaching hospital. Patients (n = 549) were evaluated regarding quality of care; coworkers (30 house staff and 12 residents) were queried regarding satisfaction at work. A 6-month job-sharing period (1.6.2015–30.11.2015) with two attending physicians (Monday-Wednesday and Wednesday-Friday) was compared to a 6-month period (1.12.2014–31.5.2015) with one attending physician working full-time. Patients' outcomes were: 1) the number of biological or X-ray exams prescribed; 2) the time to send out the discharge letter, and 3) length of stay (LOS). Coworkers' outcome was self-rated satisfaction at work, assessed using validated questionnaires (COPSOQ and SAPHORA).

Results: Among the 549 patients, average LOS was shorter during the job-sharing period but a similar trend was also found for the entire hospital. Biological prescriptions were lower during the job-sharing period, X-ray prescriptions did not differ but the time needed to send out the discharge letter increased.

Conclusion: 1) Using time clocks to report working hour is more precise than self-reporting. 2) Self declaration is associated with underreporting. 3) Our study may have implications for working hour reporting policies in hospitals. 4) The cold numbers must be balanced with "overall considerations" of research and education "invested" in trainees by mentors and institutions.
Methods: Among 652 young (<40 years old) patients with SCD Registry of Northeast Italy, 125 (19%) were due to coronary atherosclerosis. 33 coronary artery specimens taken at autopsy were included in this study: (a) 6 “control” non-atherosclerotic coronary arteries from young patients died of cardiovascular-unrelated causes; (b) 18 atherosclerotic coronary arteries from young SCD victims (7 fibroatheromatous and 11 "non-atheromatous atherosclerosis" lesions); (c) 9 atherosclerotic coronary arteries from old cardiovascular patients. The expression of α-smooth muscle actin (α-SMA), smooth muscle myosin heavy chains (SMMHCs), heavy-calciподоб (h-CaD) and S100A4 were detected by means of immunohistochemistry and quantified morphometrically.

Results: The expression of α-SMA, SMMHCs and h-CaD was higher in the intima of non-atherosclerotic arteries from young patients and in atherosclerotic plaques from young SCD victims compared to atherosclerotic plaques from old patients. The expression of S100A4 was significantly lower in the intima of non-atherosclerotic arteries from young patients compared to atherosclerotic plaques from young SCD victims and old patients. Unlike old patients, the coronary media underlying atherosclerotic plaques from young SCD victims exhibited a strong positivity for α-SMA, SMMHCs and h-CaD.

Conclusions: Low-dose CT in young SCD victims exhibit a contractile phenotype characterized by increased expression of α-SMA, SMMHCs and h-CaD. In the setting of chronic stenosis, intima and media SMC contractility might contribute to coronary spasm and myocardial ischemia, precipitating SCD.

Low-dose CT for the diagnosis of pneumonia in elderly patients

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Background: Pneumonia ranks high among causes of morbimortality in the elderly. Its diagnosis is challenging because of the poor sensitivity and specificity of signs and symptoms and pitfalls in interpretation of chest x-rays (CXR). A recent study showed the value of CT in the diagnosis of pneumonia in the emergency room. Our objective was to assess whether low-dose CT modified the management of pneumonia in elderly patients and enabled discontinuation of empirical antimicrobial therapy.

Material and methods: Monocentric prospective interventional study conducted from April 2015 to April 2016. Inclusion criteria: patients more than 65 years old, hospitalized in internal medicine for a clinical diagnosis of pneumonia and who were prescribed antibiotic therapy. Patients treated for pneumonia during the last 6 months, having already undergone a CT or having received antimicrobial therapy for more than 48 hours were excluded. All patients had CXR and native low-dose CT within 72h after the hospitalization. The probability of pneumonia was assessed by the clinician on a 5 levels Likert scale before and after CT. The main outcome was the number of diagnoses that were changed after CT (upgraded or downgraded diagnosis).

Results: Among 898 screened patients, 203 were included: 98 women (48.3%), median age 84 years (65-103); 154 (75.9%) had community acquired pneumonia, 72 (35.5%) had been hospitalized during the previous 6 months. The median CURB-65 score was 2. There was an infrate on the CXR according to the clinician with a certain/high probability in 85 patients (41.9%). The 30-days mortality was 5.4%. Among 200 patients with available data, the probability of pneumonia before and after the CT is depicted in the table. The probability of the diagnosis was altered after CT in 134 (67%) patients: 67 were downgraded and 67 upgraded. Antibiotics were discontinued in 18 patients (9%) after CT.

Conclusions: To our knowledge, this is the first study assessing the use of thoracic CT in a geriatric population hospitalized for pneumonia. CT altered the diagnosis of pneumonia in 26% of patients and led to discontinuation of antimicrobial therapy in 9%. These results should be confirmed in a randomized clinical trial comparing usual management versus systematic CT.

Urinary incontinence in systemic sclerosis: results from an international multicenter study

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Introduction: Systemic sclerosis (SSc) can involve the urinary tract. However, the prevalence, disease specific risk factors for urinary incontinence (UI) are unknown. Our goal was to assess the prevalence of UI, explore the association with the main clinical and serological subsets and evaluate the impact of UI on quality of life in SSc.

Methods: 334 consecutive patients with SSc were included in five European tertiary centers. UI and quality of life were assessed through self-administered questionnaires. Logistic regressions models were performed to test the association between clinical forms, serologic status and UI. Multivariable logistic regressions were performed to adjust for confounders (age, sex, disability, diabetes, body mass index, caffeine consumption, dyspnea and pulmonary hypertension) and test further independent predefined SSc risk factors for UI.

Results: The prevalence of UI was 63% (95% CI: 60–68%). Limited cutaneous SSc (lcSSc) and anti-centromere antibodies (ACA) were both significantly associated with UI (adjusted OR 2.0; 95% CI: 1.1–3.7). Patients positive for ACA or suffering from lcSSc had frequent and heavy urinary leaks compared to other SSc patients. In a multivariable model, ACA (OR 2.8; 95% CI: 1.4–5.6), lcSSc (OR 2.2; 95% CI: 1.1–4.4), female sex (OR 11.3; 95% CI: 3.6–35.1), worsening of dyspnea (OR 6.8; 95% CI: 1.6–49.3), lower HAQ-DI (OR 3.3; 95% CI: 2.2–16–6.6), skin-finger thickening (OR 2.0; 95% CI: 1.1–3.8), and active finger ulceration (OR 3.9; 95% CI: 1.0–12.9) were independently associated with UI. Patients suffering from UI had decreased quality of life. Failure to include the calculated number of subject and the use of a self-administered questionnaire rather than an objective measure to assess UI are the main limitations of this study.

Conclusions: Self-reported UI is frequent in SSc and disproportionally affects lcSSc and patients positive for ACA. SSc patients with UI have low quality of life.

Diagnostic accuracy of undernutrition in hospital discharge data: improvements needed

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Background and aims: Prevalence of undernutrition among hospitalized patients is high, ranging between 20 to 60%. Undernutrition is associated with increased morbidity and mortality, longer hospital stay, decreased quality of life, and increasing health care costs. Hospital administrative databases are widely used for disease monitoring and health policies planning. Hence, adequate reporting of undernourished patients is necessary and its diagnostic accuracy should be high. To our knowledge, the diagnostic accuracy of undernutrition reporting in administrative data is poorly known. We aimed to examine the diagnostic accuracy of undernutrition reporting in a Swiss university hospital.
Methods: Retrospective cross-sectional study using administrative data for years 2013-14 from the Internal Medicine unit of the Lausanne university hospital (n = 2509). Two reference diagnoses were defined: 1) ‘confirmed’ undernutrition by a nutrition risk screening-2002 (NRS-2002) score ≥3 plus a body mass index (BMI) <18.5 kg/m², and 2) ‘probable’ undernutrition by a NRS-2002 ≥3 plus any prescription of nutritional management/support plus a BMI ≥18.5 and <20 kg/m² if age <70 years (<22 kg/m² if age≥70 years). Missing BMI values were imputed.

Results: Of the 2509 eligible patients, 262 (10.4%) were classified as ‘confirmed’ and 631 (25.2%) as ‘probable’ undernutrition. Sensitivity, specificity, negative and positive predictive values (and corresponding 95% confidence intervals) for undernutrition reporting using ‘confirmed’ undernutrition were 43.0 (37.0–49.3); 87.2 (85.8–88.6); 92.9 (91.7–94.0) and 28.2 (23.8–32.8), respectively. The corresponding values using both ‘confirmed’ and ‘probable’ undernutrition were 30.0 (27.2–32.9); 93.4 (92.0–94.6); 86.7 (84.7–88.7) and 75.1 (70.6–79.3), respectively. Similar findings were obtained after stratifying for gender or for age group, or restricting the analysis to patients with non-missing BMI data.

Conclusion: Undernutrition reporting in hospital discharge data has good specificity but its sensitivity and positive predictive values are low.

MÉDECINE SPÉCIALISÉE II / FACHMEDIZIN II

FM265
Evaluating thyroid disorders: should we measure both TSH and fT4 at the same time?
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Introduction: Because symptoms of thyroid dysfunction are not specific, laboratory confirmation by measuring thyroid-stimulating hormone (TSH) and free thyroxine (fT4) is essential. As small changes in TSH result in large changes in TSH, TSH alone is a sensitive marker of an abnormal TSH) may prevent unnecessary fT4 measurement in patients with thyroid dysfunction. Therefore, most guidelines for thyroid function testing recommend measuring both TSH and fT4 at the same time. Although some guidelines state that TSH alone may be sufficient to diagnose thyroid dysfunction, and some others recommend measuring the thyroid-stimulating hormone (TSH) and free thyroxine (fT4) within a few days, the recommendation varies, even among experts and national thyroid guidelines.

Conclusions: A two-step approach (T4 assessment only in the case of an abnormal TSH) may prevent unnecessary T4 measurement in up to 93% individuals. Simultaneous measurement of thyroid function with TSH and fT4 does not appear to be medically justified.

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Neutrophil extracellular traps in community-acquired pneumonia: effects of adjunct glucocorticoid treatment and association with adverse outcome
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Background: It has recently been discovered that Neutrophil Extracellular Traps (NETs) are formed as an antimicrobial mechanism upon activation of neutrophil granulocytes, leading to an effective entrapment and killing of a wide variety of bacteria and other microbes. Neutrophil activation plays a major role in the pathophysiological cascades of community-acquired pneumonia (CAP) which is the leading cause of infectious death worldwide. However, to date there are no clinical data on NETs in pneumonia.

Methods: This is a secondary analysis of a randomised, placebo-controlled, double-blind, multicenter trial. Patients aged >18 years with CAP were enrolled from seven tertiary care hospitals in Switzerland within 24 h of presentation. Patients were randomised (1:1 ratio) to receive either 50 mg of prednisone or placebo daily for 7 days. The primary endpoint was time-to-clinical stability (TTCS); secondary endpoints were length of stay, mortality, duration of antibiotic treatment, CAP complications. NETs were assessed by measurement of cell-free nucleosomes in serum and plasma by sandwich ELISA. Multivariate regression models adjusted for severity (pneumonia severity index, age, gender, metabolic factors, cardiovascular diseases and other comorbidities) were performed in order to analyze associations with TTCS, length of hospital-stay, mortality, duration of antibiotic treatment and CAP complications.

Results: A total of 310 randomised patients were included in the analysis. Overall, levels of NETs were significantly increased at time of emergency admission and declined over 7 days (2.67 vs. 1.81 abundance units (AU), p = 0.01). Baseline levels of NETs were associated with disease severity as well as reduced hazards of clinical stability [HR 0.97 (95% CI 0.94, 0.99), p = 0.041] and consecutive hospital discharge [HR of 0.90 (95% CI 0.82, 0.99), p = 0.012]. NETs were associated with a 3.81-fold odds ratio of 30-day mortality [95% CI 1.39, 10.4], p = 0.009] and prolonged duration of intravenous antibiotic treatment by 0.5 days (95% CI 0.1, 0.94, p = 0.015). NETs were significantly increased after 5 days in the prednisone group (1.19 vs. 0.79 AU, p <0.0005).

Conclusion: NETs are considerably increased in community-acquired pneumonia and represent a novel biomarker for outcome prediction, i.e. for staging of disease severity and identification of patients at risk. Effects of prednisone may partly be explained by modulation of NET formation.
Is subclinical thyroid dysfunction associated with dementia? Findings from a prospective cohort

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Introduction: Thyroid-stimulating hormone (TSH) measurement is recommended in etiologic dementia work-up. However, data on the association between subclinical thyroid dysfunction (SCDT) and dementia are limited, because well-performed prospective cohorts with long follow-up are lacking. We prospectively assessed the association of SCDT with incident dementia and decline in Modified Mini-Mental state (3MS) in a large cohort of older adults.

Methods: We studied participants from the Health, Aging, Body and Composition Study, with thyroid function measurement but no TSH management. We identified SCDT defined by TSH >10 mIU/L. We assessed incident dementia by the diagnosis of probable or possible AD or VaD based on the DSM-IV criteria. The association between SCDT and dementia was assessed with Cox models adjusted for age, sex, education, marital status, and Cornish factor scores. We also assessed whether the association was modified by BMI, physical activity, or sleep duration.

Results: Among 4071 participants with a median follow-up of 10.6 years, we identified 166 cases of incident dementia. The risk of dementia was similar across TSH tertiles (HR: 1.00, 95% CI: 0.72–1.38 for TSH 10.1–20, HR: 0.85, 95% CI: 0.60–1.22 for TSH >20). The association between SCDT and dementia was not modified by BMI, physical activity, or sleep duration.

Conclusion: Subclinical thyroid dysfunction is not associated with dementia. Further studies are needed to explore the potential role of TSH in the prevention and treatment of dementia.
dermatitis was adjudicated based on: 1) race-stratified 3MS change ≥1.5SD; 2) dermatitis diagnosis on hospital records and 3MS ≤90; 3) dermatitis drug. Subclinical hyperthyroidism (SHyper, TSH <0.45 mIU/L, free thyroxine [FT4] normal) and subclinical hypothyroidism (SHypo, TSH ≥4.50–19.99 mIU/L, FT4 normal) were compared with euthyroidism (TSH 0.45–4.94mIU/L). Dementia risk was assessed by competing-risk Cox regression and 3MS change over time by mixed-effects models, adjusting for age, race, education and baseline 3MS in the main analysis, and further for cardiovascular risk factors.

Results: Among 2558 participants, mean age was 75.1 (SD 2.8); 52% were women, 85% were euthyroid, 3% had SHyper and 12% SHypo. Over 9 years, 22% participants developed dementia. Among men, incidence of dementia was 38% for SHyper, 22% for euthyroidism and 17% for SHypo. Among women, it was 20% for SHyper, 24% for euthyroidism and 21% for SHypo. Compared to euthyroids, risk of dementia was increased in men with SHyper (adjusted HR 2.02 [95%CI 1.03;3.96]), but not in women (adjusted HR 0.73 [95%CI 0.40;1.35], P = 0.02 for interaction by gender). On average, men with SHyper had larger (–4.59 [95%CI –7.96; –1.22]) decline in 3MS than euthyroid men, while it did not differ in women with SHyper or SHypo.

Conclusion: Among older adults, men with SHyper had increased risk of dementia and large decrease in cognition, whereas women with SHyper and SHypo participants did not check. TSH among patients with dementia seems appropriate. Clinical trials are needed to assess if treating SHyper in older men reduces incidence and progression of cognitive impairment.

Table 2: Predictive accuracy for risk category ≥6 points.

<table>
<thead>
<tr>
<th>PTS</th>
<th>Sensitivity % (95%-CI)</th>
<th>Specificity % (95%-CI)</th>
<th>PPV % (95%-CI)</th>
<th>NPV % (95%-CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>within 3 months</td>
<td>76.9 (68.1–83.8)</td>
<td>62.5 (55.0–69.5)</td>
<td>56.8 (48.7–64.6)</td>
<td>80.8 (73.2–86.6)</td>
</tr>
<tr>
<td>within 12 months</td>
<td>72.9 (65.0–79.5)</td>
<td>67.0 (59.4–74.9)</td>
<td>69.9 (62.0–76.7)</td>
<td>70.8 (62.4–77.9)</td>
</tr>
<tr>
<td>within 24 months</td>
<td>72.7 (65.3–79.0)</td>
<td>74.6 (66.1–81.8)</td>
<td>80.1 (72.9–85.8)</td>
<td>66.2 (57.7–73.7)</td>
</tr>
</tbody>
</table>

Table 2: Derivation and validation of a clinical prediction model for the post-thrombotic syndrome

| Marie Miean, Andreas Limacher, Adriano Alatri, Drahomir Ajušek, Lucia Mazzola | Lasuna University Hospital, Division of General Internal Medicine, Lausanne; CTU Bern, and Institute of Social and Preventive Medicine, University of Bern, Bern; Heart and Vessel Department, Division of Angiology, Lausanne; Department of General Internal Medicine, Inselspital, Bern, Switzerland |
| Introduction: Not all patients carry the same risk of developing a post-thrombotic syndrome (PTS) after a first lower limb deep vein thrombosis (DVT) event. We sought to derive a clinical prediction model for prognosis to estimate the risk of PTS development within 24 months of an index DVT. |
| Methods: We used data from 276 patients with a first acute symptomatic DVT included in a prospective cohort as our derivation sample. We derived our prediction rule using logistic regression with backward selection. The occurrence of an index DVT based on the Villalta scale as the outcome, and 12 candidate variables as predictors. We used bootstrapping methods for internal validation. |
| Results: Analyzed patients had a median age of 74 years, 46% were women, 32% had a concomitant PE, and 18% presented an isolated DVT. The final diagnosis was adjudicated by two independent cardiologists. |
| Objective: Four strategies for very early rule-out strategies for acute myocardial infarction using high-sensitivity cardiac troponin I |
| Jasper Boedinghaus, Thomas Nestelberger, Raphaël Twerenbold, Karin Wild, Patrick Badertscher, Janosch Cupa, Tobias Bürger, Patrick Mächler, Sydney Corbière, Karin Grimm, Maria Rubini Grméz, Christian Puelacher, Samyut Shrestha, Dayana Flores Widmer, Jakob Fuhrmann, Petra Hillinger, Zaid Saitbi, Ursina Honegger, Nicola Schaerli, Nikola Kozuharov, Katarina Rentsch, Oscar Miró, Beatriz López, Javier Martin-Sanchez, Esther Rodriguez Adarés, Beatriz Navarrete, Damian Kawecki, Eva Galovanová, Jiri Parenica, Jens Lohrmann, Wanda Kloos, Andreas Buser, Nicolas Geigy, Dagmar I. Keller, Stefan Osswald, Stefan Reichling, Stefano Bassetti, Christian Mueller, Internal Medicine Department, University Hospital Basel, University of Basel; Cardiovascular Research Institute Basel (CRIB), University Hospital Basel, University of Basel; Department of Cardiology, University Hospital Basel, University of Basel; Department of Cardiology, University Hospital Brno and Medical Faculty, Masaryk University, Brno, Czech Republic; Blood Transfusion Centre, Swiss Red Cross and Department of Hematology, University Hospital Basel, University of Basel; Emergency Department, Kantonsspital Liestal, Liestal; Emergency Department, University Hospital Zürich, Zürich, Switzerland |
| Objective: Four strategies for very early rule-out of acute myocardial infarction (AMI) using high-sensitivity cardiac troponin I (hs-cTnI) have been identified. It remains unclear which strategy is most attractive for clinical application. |
| Methods: We prospectively enrolled unselected patients presenting to the emergency department (ED) with symptoms suggestive of AMI. Patients with cardiac troponin I (hs-cTnI) have been identified. It remains unclear which strategy is most attractive for clinical application. |
| Results: | Hs-cTnI levels were measured at presentation and after 1h in a blinded fashion. We directly compared all four hs-cTnI-based rule-out strategies: limit of detection (LOD, hs-cTnI <2 ng/L), single cut-off (hs-cTnI <5 ng/L), 1h-algorithm (hs-cTnI <5 ng/L and 1h-change
COPD management guidelines assembling effective care elements to reduce the burden of COPD to patients and health systems. Because comprehensive care is complex shortcomings in health service delivery for COPD are common.

Objectives: To test whether a multifaceted intervention delivered to general practitioners (GPs) and their practice assistants increases adherence to recommended key elements and processes of COPD care.

Methods: Cluster-randomized pragmatic clinical trial, 1:1 randomization on the GP-level. The intervention was designed to improve knowledge but also and particularly governing professional behavior by implementation of a primary care "COPD care bundle", a tool to support evidence-based decision making and practice. Data was collected using questionnaires at GP and patient level at baseline and one year after the intervention. The primary outcome measure was the implementation of 15 individual processes of care. The primary outcome was the composite score of implemented processes measured at the patient level.

Results: Thirty-five GPs and 216 patients median age 69 years, 59% female, 69% GOLD stadium A or B were enrolled, 161 patients completed follow-up (dropout rate 25%). After one year the composite score of implemented care processes increased from 4.7 to 6.1 (+1.4) in the intervention group and decreased from 5.3 to 4.4 (–0.9) in the control group. Linear regression model adjusting for baseline characteristics revealed a between-group difference of +2.0 (95% CI +1.2 to +2.8) implemented processes in favor of the intervention group. The effect remained statistically significant in sensitivity analyses simulating missing data due to dropout. Detailed analyses showed that the intervention significantly increased adherence in 10 out of 15 processes of care (fig.).

Conclusion: A multifaceted intervention comprising GP education and a COPD care bundle resulted in increased implementation of recommended care processes.

Corticosteroids in patients hospitalised with community-acquired pneumonia: systematic review and individual patient data meta-analysis
Matthias Briel¹, Simone Spoorenberg², Claudine Blum¹,²,³,⁴, Benjamin Kasenda³, Wim Jan Bos², Mitjam Christ-Crain³, Willem Jan Bos², Mirjam Christ-Crain³

Introduction: The benefits and harms of adjunctive systemic corticosteroids for community-acquired pneumonia (CAP) are inconclusive. We aimed to evaluate the effects of adjunctive corticosteroids in adults hospitalised with CAP on patient-important outcomes using individual patients' data of randomised placebo-controlled trials and to explore subgroup differences.

Methods: We systematically searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and trial registers plus
Methods: We enrolled 165 of 173 acute hip fracture patients from the original trial who had baseline information on HRQL (mean age 84 years, 79% females, 77% community dwelling). We then tested the effects of a simple home exercise program and vitamin D supplementation on HRQL in the first 12 months after hip fracture in an ancillary study of the Zurich Hip Fracture Trial that tested the interventions in a 2×2 factorial trial design.

Introduction: Exercise and vitamin D supplementation are inexpensive and accessible means of aiding the recovery process after hip fracture. However, information on the benefit of these interventions on health-related quality of life (HRQL) after hip fracture is missing. We tested the effects of a simple home exercise program and vitamin D supplementation on HRQL in the first 12 months after hip fracture in an ancillary study of the Zurich Hip Fracture Trial that tested the interventions in a 2×2 factorial trial design.

Methods: We enrolled 165 of 173 acute hip fracture patients from the original trial who had baseline information on HRQL (mean age 84 years, 79% females, 77% community dwelling). We then tested the effects of the simple home exercise program (home exercise program + standard physiotherapy vs. standard physiotherapy alone) and vitamin D supplementation (800 vs. 2000 IU/day) on HRQL over time. HRQL was measured as EQ-5D index score, calculated from the EQ-5D-3L questionnaire at baseline, 6 months and 12 months. At baseline, participants were asked to estimate their pre-fracture HRQL. Effects by treatment were analyzed using multivariable repeated-measures analysis adjusted for age, gender, body mass index, comorbidities, mini-mental state examination (MMSE), living status, and baseline serum 25-hydroxyvitamin D concentration.

Results: The adjusted EQ-5D index score significantly worsened from 0.71 pre-fracture to 0.57 over time, but did not differ by treatment. However, while all other groups remained stable after the 6-month decline, the control group receiving only low-dose vitamin D (800 IU/day) and no home exercise program experienced a significant further decline in the EQ-5D index score between 6 and 12 months of follow-up (p = 0.028). Notably, independent of the interventions and other covariates, patients with a better baseline MMSE score and those living in the community prior to their fracture, had a significantly lower decline in HRQL after hip fracture.

Conclusion: Based on our trial hip fractures have a long-lasting negative effect on HRQL up to 12 month after hip fracture. A simple home exercise program and high-dose vitamin D may help prevent a further decline in HRQL after the first 6 months of the index fracture.

Funding: This project was supported by the Baugarten Centre Grant for the Centre on Aging and Mobility, and by the University Research Priority Program “Dynamics of Healthy Aging” University of Zurich.

Vitamin D status and body composition

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1Department of Geriatrics and Aging Research, University Hospital Zurich, City Hospital Waid, and University of Zurich, Zurich, Switzerland
2Centre on Aging and Mobility, University Hospital Zurich and City Hospital Waid; 3Centre on Aging and Mobility, University Hospital Zurich and City Hospital Waid; 4University of Zurich Geriatric Network, Zurich, Switzerland

Introduction: Vitamin D has been linked to muscle health and insulin sensitivity. However, there is limited data on whether 25-hydroxyvitamin D (25(OH)D) status is associated with body composition. We
investigated if and to what extent 25(OH)D status is associated with body composition (muscle and fat mass), as well as insulin resistance among relatively healthy community-dwelling seniors.

Methods: We enrolled 271 seniors age 60 years and older (mean age 70.4 years, 53% women, 31.4% vitamin D deficient (<20 ng/ml)) undergoing elective surgery for unilateral knee replacement due to severe knee osteoarthritis (Baseline Exam Zurich Knee OA Trial). Analyses compared baseline body composition (percentages of total lean mass (TLM%) and total fat mass (TFM%), appendicular lean mass index (ALMI), and fat mass index (FMI)) assessed by dual-energy X-ray absorptiometry and insulin resistance between quartiles of baseline serum 25(OH)D levels using multivariable linear regression models. Models were controlled for age, gender, smoking status and physical activity.

Results: While we did not find a difference on muscle mass, participants in the lowest 25(OH)D quartile (4.7–17.5 ng/ml) had a higher FMI than participants in the third (26.1–34.8 mg/ml; 9.3 vs. 8.4 kg/m²; P = 0.044) quartile. Moreover, participants of the second 25(OH)D quartile (17.6–26.0 ng/ml) had higher β-cell function (77.9% vs. 59.6%; P = 0.018) consistent with their lower insulin sensitivity (152.8% vs. 215.3%; P = 0.035) compared with participants of the highest 25(OH)D quartile. Insulin resistance was more prevalent among participants in the lowest 25(OH)D quartile compared with the highest quartile (23.8% vs. 6.3%; P = 0.006).

Conclusions: Our findings suggest an inverse association between serum 25(OH)D level and FMI. Consistently, prevalence of insulin resistance was higher among seniors with low serum 25(OH)D status. Thus, based on these cross-sectional analyses a replete vitamin D status may support preserving a healthy body composition and help prevent insulin resistance among seniors.

Bioimpedance-derived phase angle and mortality among older people

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Background: Phase angle measured by bioelectrical impedance analysis (BIA) may be a marker of health state.

Objective: This historical cohort study of prospectively collected BIA measurements aims to investigate the link between phase angle and mortality in older people and evaluate whether a phase angle cut-off can be defined.

Design: We included all adults aged 65 years and over who underwent a BIA measurement by the Nutriguard® device at the Geneva University Hospitals. We retrieved retrospectively the phase angle and co-morbidities at the last BIA measurement and the mortality until December 2012. We calculated phase angle standardized for sex, age, and body mass index, using reference values determined with the same brand of BIA device. Sex-specific and standardized phase angle were categorized into quartiles. The association of mortality with sex-specific or standardized phase angle was evaluated through univariate and multivariate Cox regression models, Kaplan-Meier curves, and ROC curves.

Results: We included 1307 (38% women) participants, among whom 828 (44% women) died. In a multivariate Cox regression model adjusted for co-morbidities and setting of measurement (ambulatory vs. hospitalized), the protective effect against mortality increased progressively as the standardized phase angle quartile increased (HR 0.71 (95% CI 0.58, 0.86), 0.53 (95% CI 0.42, 0.67), 0.32 (95% CI 0.23, 0.43)). The discriminative value of continuous standardized phase angle, assessed as the area under the ROC curve, was 0.72 (95% CI 0.70, 0.75). We could not define an acceptable phase angle cut-off for individual prediction of mortality (LK), based on sensitivity and specificity values.

Conclusions: This study shows the association of phase angle and mortality in older patients, independently of age, sex, comorbidities, BMI categories, and setting of measurement.

Pain sites and severity, a national survey of health-related quality of life in Swiss community-dwelling older adults with pain

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Background: Regarding the epidemiology of pain in older adults, data are lacking about the association between pain severity and its impact on health-related quality of life (HRQoL). The purpose of this study was to investigate pain prevalence and sites, its self-reported interferences with daily life activities, and the effect of pain severity on HRQoL in a Swiss community-dwelling population aged ≥65 years.

Methods: This cross-sectional national survey included a sample of individuals selected randomly from population records, stratified by age and gender. Respondents answered a face-to-face interview addressing pain location, intensity and interference with activities, and quality of life variables. Logistic regression models were applied for binary outcomes, linear regression for continuous outcomes, and Poisson regression for count outcome. For each analysis, Wald Chi-square and 95% confidence intervals were used.

Results: Among the 2905 individuals considered, 36.4% reported pain. The results indicate that pain increases with age; more precisely, this increase concerns pain intensity from age 85 onward. Pain severity was strongly associated with HRQoL and functional impact, i.e., all scales involving physical activities were affected in those individuals reporting severe pain; it was also associated with the individuals' perception of their overall HRQoL. Pain severity had a significant effect on this perception.

Conclusions: Our results point to the importance of devoting attention to pain intensity rather than to the number of pain sites. Because of the demographic transition the management of pain problems should emphasize early referral and timely treatment in order to prevent the burden of disease and functional loss associated to pain severity.

Cognitive function in DO-HEALTH

Patricia Choccano-Bedoya1,2, Simeon Schietzel1,2, Sacha Beck1,2, Reto W. Kessrig3, Bruno Vellas3, Andreas Egli1,2, Heike Annette Bischoff-Ferrari1,2,1Centre on Aging and Mobility, University Hospital Zurich and City Hospital Waad; 2Department of Geriatrics and Aging Research, University Hospital Zurich, City Hospital Waad, and University of Zurich; 3University of Zurich Geriatric Network, Zurich; 4Department of Geriatrics, University of Basel, Basel, Switzerland; 5Department of Geriatrics, University of Toulouse, Toulouse, France

Introduction: Impaired cognition and impaired physical function are at the root of disability at older age and often occur together. In this study, we assess cognitive function among 2157 seniors from 5 European countries enrolled in the large DO-HEALTH study using two different screening tools (Montreal Cognitive Assessment and Mini Mental Examination). In addition, we correlated cognitive function with performance in physical function tests.

Methods: DO-HEALTH is the largest ongoing European Longevity Trial testing the role of vitamin D and/or omega 3-fats and/or a simple home exercise program among 2157 community-dwelling seniors 70 years and older from 5 European countries. Participants were required to have a Mini-Mental State Examination (MMSE) score of at least 26 to be eligible for the study. At baseline, cognitive function was additionally assessed using the Montreal Cognitive Assessment scores (MoCA). Physical function tests were conducted at the baseline clinical visit and included the short physical performance battery (SPPB) that comprises balance, gait speed and the repeated-sit-to-stand test.

Results and conclusions: First findings on baseline data from all 2157 DO-HEALTH seniors will be presented at the meeting.
Functional measures and fall status in DO-HEALTH
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1Department of Geriatrics and Aging Research, University Hospital Zurich, City Hospital Waad, and University of Zurich; 2Centre on Aging and Mobility; 3University of Zurich Geriatric Network, Zurich; 4Department of Geriatrics, University of Basel, Basel; 5Department of Geriatrics, University of Geneva, Geneva, Switzerland

Introduction: By 2030, seniors age 70 years and older will double, as will the number of seniors with falls and resulting impairments in function and mobility. In this study, we will compare functional status among fallers and non-fallers among 2157 seniors from 5 European countries enrolled in the large DO-HEALTH study.

Methods: DO-HEALTH is the largest ongoing European Longevity Trial testing the role of vitamin D and/or omega 3-fats and/or a simple home exercise program among 2157 community-dwelling seniors 70 years and older from 5 European countries. At baseline, we asked participants about their fall status in the year prior to enrollment and had a target recruitment of 40% for participants with a prior fall. In this study we will present baseline functional measures of gait speed, chair-rise test, and grip strength by fall status.

Results and conclusions: First findings on baseline functional data from all 2157 DO-HEALTH seniors from 5 European countries (Switzerland, Germany, Austria, France and Portugal) by fall status will be presented at the SGAIM Spring Meeting in May 2017.

Physical Frailty in DO-HEALTH
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Introduction: Physical frailty is at the root of accelerated aging, and is an independent predictor of worse clinical outcomes among older adults in acute care. By 2030, the personal, societal, and health economic burden of frailty is expected to at least double, in parallel to the projected growth of the older segment of the population. In this study, we will assess the prevalence of frailty among 2157 seniors from 5 European countries enrolled in the large DO-HEALTH study using the Linda Fried Frailty Score.

Methods: DO-HEALTH is the largest ongoing European Longevity Trial testing the role of vitamin D and/or omega 3-fats and/or a simple home exercise program among 2157 community-dwelling seniors 70 years and older from 5 European countries. At baseline, we assessed the phenotypic model of physical frailty operationalized by five characteristic domains (fatigue, weight loss, slowness, low activity level and weakness).

Results and conclusions: First findings on baseline frailty data from all 2157 DO-HEALTH seniors from 5 European countries (Switzerland, Germany, Austria, France and Portugal) will be presented at the SGAIM Spring Meeting in May 2017.

Cellular immunotherapy with multiple infusions of ex vivo expanded haploidentical natural killer cells after autologous transplantation for patients with plasma cell myeloma
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Plasma cell myeloma (PCM) is currently treated with chemotherapy and autologous stem cell transplantation (ASCT) but relapse rates remain high. Adoptive transfer of mature haploidentical natural killer (NK) cells is a promising approach to provide PCM patients with highly immunocompetent effector cells against myeloma function early post transplantation. Here we report on the current clinical Phase I/II trial of multiple preemptive infusions of good manufacturing practice (GMP) expanded NK cells to PCM patients. Ten patients were recruited (median age: 59y). All patients received 4 cycles of VTD chemotherapy (reaching 4xCR, 5xGPR and 1xPR) before high dose melphalan and ASCT. NK cells from haploidentical family donors were purified from leukapheresis by T cell depletion and NK cell selection. Highly pure NK cells (mean: 4.8×10^8 cells) were obtained with a minimal T cell contamination corresponding to a 6.1 log T cell depletion. After expansion ex vivo for 19 days in GMP-medium containing autologous irradiated feeder cells, interleukin-2 and -15, NK cell numbers increased 54-fold (range: 38- to 76-fold). In three NK cell products T cell contents were 10x above limit of clinical trial and were successfully reduced by 2° T cell-depletion from 11 to 0.3×10^6 cells/kg body weight (BW). NK cells were cryopreserved in escalating doses (1.3×10^8, 1.3×10^9 and multiple doses of maximal 1.0×10^8 cells/kg BW). The PCM patients received 65–460×10^8 expanded NK cells (median: 3.8×10^8 cells/kg BW, range: 0.9–5.7×10^8 cells/kg BW) as 3–8 infusions (median, 6 DLIs). The NK-DLIs were administered between day 2 and 21 after ASCT and were well tolerated without any acute adverse
CDX2 promotes leukemogenesis by modulating leukemic cell – BM niche interactions
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Objectives: The caudal-type homeobox (CDX) gene family regulates embryonic hematopoiesis via downstream HOX genes and interactions with the WNT signaling pathway. CDX2 expression is not detected in healthy bone marrow (BM) cells but present in ~80% of human acute myeloid (AML) and lymphoid leukemia (ALL). Ectopic activation in murine BM cells induces myeloid leukemia. Here, we explore the functional role and molecular targets of CDX2 in human leukemia.

Methods: CDX2 expression was modulated via lentiviral and siRNA treatment in human BM CD34+ and human leukemic cell lines. CDX2 modified and control cells were subjected to growth, colony forming (CFU), cell cycle, flow cytometry, adhesion and RT-PCR assays and analyzed in vivo upon xenotransplantation in NOD/SCID/IL2Rγ−/− (NSG) mice for bone marrow (BM) homing and leukemogenesis. DKK-1 protein levels were measured in the supernatant via ELISA and the effect of DKK-1 supplementation on leukemic versus healthy hematopoietic cells explored in vitro and in vivo assays.

Results: CDX2 knockdown in AML cells strongly reduced clonogenicity while leaving proliferation, apoptosis and cell cycle unaltered. Importantly, CDX2 knockdown profoundly suppressed in vivo leukemogenic properties. Gene set enrichment analyses (GSEA) of microarray data collected on CDX2 overexpressing versus control leukemic cells revealed WNT signaling and cell adhesion genes as the pathways most prominently regulated by CDX2. Surprisingly, CDX2 overexpressing leukemic cells showed both induction of activated β-Catenin and of secreted DKK-1, a known WNT inhibitor. In functional assays, CDX2 was shown to positively regulate leukemic cell adhesion to stromal cells via DKK-1. Interestingly, DKK-1 showed opposite effects on healthy hematopoietic stem/progenitor cells, reducing their clonogenicity and stromal cell adhesion. These data suggest that leukemic cells might use DKK-1 secretion to confer them competitive advantage for BM niche occupation by (1) increasing their adhesion capacity to stromal cells and (2) dislocating healthy hematopoietic stem/progenitor cells from the niche. Consistently, in vivo DKK-1 pre-treatment promoted leukemic cell homing to the BM.

Conclusion: Our data suggest that DKK2 plays important roles in human AML cells during in vivo leukemogenesis by sustaining their endogenous canonical WNT activity and concomitantly inducing DKK-1 secretion to alter stromal cells and healthy hematopoiesis.

Development of a peptide macrocycle factor XII inhibitor for safe anticoagulation therapy
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Introduction: Factor XII (FXII) is a plasma serine protease that was identified as a coagulation factor. FXII has a highly conserved amino acid sequence across disparate species, suggesting that this molecule does have a physiologic function. Mechanistic research based on animal models indicates that FXII contributes to thrombotic disease by triggering excessive coagulation. Inhibiting FXII has shown to reduce thrombosis without increasing the bleeding risk, a major side effect of currently approved anticoagulants. Recently, several protein-based FXII inhibitors were developed, out of which at least one is in clinical trial, but no high affinity small molecule inhibitor has been reported.

Methods: Bicyclic peptide synthesis, protease inhibition assays for the following serine proteases: tPA, uPA, factor Xla, plasma kallikrein, thrombin, plasmin, trypsin, factor VIIa, factor Xa, trypsin and factor Xila, structural model and structure analysis, plasma stability assays, aPTT and PT coagulant activity measurements, pharmacokinetics in mouse and rabbit, FeCl3 injury thrombosis model in mesenteric arteries in mouse.

Results: We have generated a potent and highly selective FXII inhibitor based on a macrocyclic peptide format (MW <2000 kDa). Recently, we had improved the potency and stability of the inhibitor using various approaches based on unnatural amino acid incorporation. The final peptide shows high inhibitory affinity and selectivity with a high stability in plasma (K1,2; plasma >96 h). The inhibitor prolonged intrinsic coagulation in human, mouse and rabbit plasma (EC50 human = 1 μM). Pharmacokinetic studies in mouse and rabbit showed that the peptide was active in vivo and no signs of toxicity or abnormal bleeding were observed. We then recorded thrombus formation in mesenteric arteries by intravital microscopy in mouse, a thrombosis model sensitive to defects in the intrinsic pathway of coagulation. The peptide could substantially reduce thrombus formation (peptide: 3/9 (33%), control: 7/8 (87%), P <0.05), full occlusion (peptide: 0/9 (0%), control: 5/8 (63%), P <0.05), time to thrombus formation (peptide: 20 ± 3.6 min, control: 9.6 ± 5.7 min, P <0.05).

Conclusion: Our results suggest that FXII inhibition by a peptide macrocyclic can potentially offer a safe anticoagulation therapy.
Mice generated by in vitro fertilization show a reduced platelet count accompanied by a heightened response to thrombin

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Background: Children conceived by assisted reproductive technology (ART) show vascular dysfunction, increased arterial pressure and early atherosclerosis, conditions associated with a higher risk of cardiovascular morbidity. The effect of ART on the synthesis, maturation and function of platelets is unknown. Therefore, we investigated platelet production and reactivity in a murine model of in vitro fertilization (IVF).

Methods: IVF mice were generated by in vitro insemination of oocytes from FVB female mice, followed by transfer to pseudopregnant NRMI females 48 h later. IVF and control (naturally born, C) male mice (n = 12) were euthanized at the age of 12 weeks. Total blood cell count, mean platelet volume (MPV) and reticulated platelet analysis was performed on EDTA blood, while platelet receptor expression (GPVI and Gpib) and platelet activation were determined by flow cytometry on citrated platelets.

Results: IVF mice showed a significantly reduced platelet count compared to control mice (860.15 ± 172x10^3/μl IVF vs 1119.5 ± 243 x10^3/μl C, p = 0.013), accompanied by a slightly reduced (albeit not significantly) mean platelet volume (MPV: 5.07 ± 0.35 μm3 IVF vs 5.25 ± 0.6 μm3 C, p = 0.41). Total blood leukocytes and erythrocytes counts were not different between the two groups. Newly synthesized platelets (reticulated platelets) stained by thiazole orange (TO) were significantly reduced in IVF mice (% TO positive platelets: 8.47 ± 3 C vs 4.9 ± 0.9 IVF, p = 0.003), indicating reduced production. Collagen receptor GPVI expression was unchanged (mean fluorescence intensity MFI: 2575 ± 329 C vs 2554 ± 442 IVF), and also vWF receptor Gpib levels were similar between the two groups of mice.

Conclusion: ITP patients are at risk for TEE. Those patients who underwent splenectomy, had chronic disease, needed a higher number of treatments for ITP, and smoke were more likely to develop TEE.
Hematopoietic stem cell transplant-associated thrombotic microangiopathy and acute graft-versus-host disease

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Introduction: Steroid refractory acute graft-versus-host disease (GvHD) remains a major complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT). GvHD has been associated with transplant-associated thrombotic microangiopathy (TA-TAM). Complement is thought to be a major mediator of endothelial damage. We hypothesize that a TA-TMA, related to dysregulation of the alternative complement pathway correlates with organ damage.

Methods: A retrospective analysis of 660 consecutive patients with hematological malignancies receiving an allo-HSCT at the University Hospital Basel in the period from 2003 to 2013 was performed. Data on the occurrence, risk factors and outcome of patients with TA-TMA and the correlation with acute GvHD was collected. Available biopsies of organs suspected to be affected by TAM and/or GvHD will be performed. Routine bone marrow biopsies for histological, immunohistochemical signs of TA-TAM and complement activation will be analyzed. Serum samples will be used to characterize markers of complement activation using plasma levels of C5b-9 and C5b-9 deposition in tissues biopsies.

Results: 660 patients (AML n = 260; ALL n = 152; MDS/MPN n = 93; lymphoid neoplasm n = 85; plasma cell disorder n = 53; bone marrow failure n = 17) underwent myeloablative (n = 432) and non-myeloablative (n = 228) allo-HSCT at a median age of 47 years (range 19-71 years). Forty-eight (7.3%) patients matched the established diagnostic criteria for TAM (increased LDH, platelet count <50 G/L or <50% of normal baseline, schistocytes >2 per high power field, creatinine increase). The median time to onset of TAM was 36 days post-transplant (range 22 to 67 days). Subjects with TA-TAM had significantly higher 3-year non-relapse mortality compared to those without (47.8% vs 18.2%, P <0.001). Grades 2 to 4 aGvHD and cytomegalovirus viremia were independent risk factors for TA-TAM, and serum LDH level >500 U/L as well as arterial hypertension were early signs of TA-TMA occurrence. Patients with clinically relevant aGvHD (≥ grade 2) had more TA-TAM than patients without aGvHD (45% versus 24%; P <0.001). TAM correlated with aGvHD severity; the higher the aGvHD grade, the more the patients who suffered from TAM.

Conclusions: Allo-HSCT recipients with grades 2 to 4 aGvHD or cytomegalovirus viremia should be closely monitored for the presence of TA-TMA. At the meeting first results of histological, immunohistochemical and complement activation analyses will be presented.

A model of platelets in the aging organism reveals increased numbers and enhanced activatability, possibly mediating a larger stroke burden

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Background: Age is a key risk-factor for cardiovascular disease (CVD). Platelets play a major role in CVD. Yet, little is known about age-dependent changes in their function. Thus, we used a mouse model of aging, in absence of any confounding factors, to analyze platelets in aging and their putative role in ischemia/reperfusion (I/R) brain injury.

Methods: To discern specific aging effects from confounding factors, we used young (12 weeks, young cohort; yoC) and very old (≥20-months, old cohort; oldC) C57BL/6 wildtype mice. Blood cell count and MPV were measured in EDTA-anticoagulated blood. Reticulated platelets were determined by triazoles-orange staining. Platelet clearance was measured on CD41-stained hepatic and splenic cryosections. Plasma glycocalcin (GC) was assayed by ELISA. Platelets were activated with thrombin or collagen I and analyzed by flow-cytometry. I/R brain injury was induced by transient middle cerebral artery occlusion for 30 mins followed by 48 h of reperfusion. Stroke size was assessed by triphenyltetrazolium chloride (TTC) staining; neurological function by RotaRod and Beden test.

Results: Platelet mass (number and size) was increased in the oldC. Reticulated platelet counts were higher in the yoC, suggesting decreased clearance in the oldC. This was supported by hepatic and splenic cryosection histology: areas positively covered by staining for CD41 in the yoC were larger than those in the oldC. The GC index was similar in the yoC and oldC. GP Ib/Ilba and P-selectin were increased in the oldC after activation with thrombin.

Autophagy pathways active during APL therapy – identification of key autophagic networks

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Introduction: Autophagy is an intracellular degradation system that ensures a dynamic recycling of cytoplasmic contents. It is required for self-renewal and cell survival under stress. There is accumulating evidence for additional functions of autophagy during myeloid development and therapy responses in acute myeloid leukemia (AML). In this study we aimed to identifying the autophagy-related network involved in AML therapy responses.

Methods: In this study, we analyzed primary APL/AML samples and cell lines to characterize the autophagy mechanisms active during all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) therapy. Techniques used were qPCR, western blotting, FACS, immunofluorescence microscopy, autophagic flux analyses, immunoprecipitation, lentiviral knockdown and overexpression systems, ChIP as well as promoter reporter analyses.

Results: In general, expression of most autophagy-related (ATG) genes was attenuated in primary AML patient samples and reactivated upon neutrophil acute promyelocytic leukemia (APL) and CD34+ differentiation. Importantly, we identified several of these myeloid differentiation associated ATG genes as novel transcriptional targets of the hematopoietic transcription factor PU.1. Regarding the autophagic mechanisms, we found that ATRA-induced autophagy during APL differentiation is Beclin-1 independent. Moreover, knocking down ATG16L2 but not ATG16L1, both genes are involved in
autophagosome maturation, in APL cells significantly attenuated neutrophil differentiation clearly indicating that ATG16L2 but not L1 is needed for a successful ATRA response. Moreover, we identified a novel link from the neutrophil enhancer kinase DAPK2 to autophagy via its binding to the ATG gene ATG5 upon ATRA treatment. On the other hand, DAPK2 is dispensable for ATO-mediated induction of autophagy but not cell death. We further showed that DAPK2 stabilizes the transcription factor p73 and that DAPK2 expression is transcriptionally regulated by p73 thereby creating a positive feedback loop during ATO-induced cell death.

Conclusions: Our data provide strong evidence for a particular, non-canonical subtype of autophagyoperative during neutrophil differentiation of APL cells as opposed to canonical autophagy in ATO therapy. Deciphering the particular autophagy pathway active during APL differentiation and cell death responses is a prerequisite to develop novel therapies that are based on autophagy modulation for this disease.

Figure: Autophagy in APL Therapy.

**FM289**

**Effects of the sympathicomimetic agonist mirabegron on disease course, allele burden, marrow fibrosis, and nestin positive stem cell niche in patients with JAK2-mutated myeloproliferative neoplasms: a prospective multicenter phase II trial SAKK 33/14**

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Introduction: Nestin+ mesenchymal stem cells (MSCs) are reduced in bone marrow of JAK2-V617F positive myeloproliferative neoplasms (MPN) patients due to damage of the sympathetic nerve fibers triggered by cytokines from the mutant clone. In a mouse model of therapy with a beta-3 sympathicomimetic agonist corrected the damage inflicted by the MPN clones on their niches and ameliorated the MPN phenotype. To test the effect on disease-control in patients with MPN we performed a phase II trial with the beta-3 sympathicomimetic agonist mirabegron.

Methods: The trial consisted of mirabegron 25 mg daily during the first week, followed by 50 mg daily for at least 24 weeks. Patients with a cytogenetically confirmed diagnosis of MPN and a JAK2-V617F allele burden >20% in granulocytes at study entry were eligible, if not treated with JAK2 inhibitors or interferon. Reduction of the JAK2-V617F allele burden >25% in granulocytes at study endpoint, one patient achieved a 25% reduction in allele burden by 24 weeks. Adverse events were mostly grade I or II on the CTCAE scale.

3 patients had grade III events. The mean blood counts were similar between start and end of therapy. In 20 patients bone marrow biopsy was available, showing an increase in the nestin+ MSCs cells from a median of 1.09 (IQR 0.38–3.27)/μm³ to 3.95 (IQR 1.98–8.79)/μm³ (p <0.0001) and a slight decrease of myelofibrosis from a median grade of 1.00 (IQR 0.50–2.00) (p = 0.02) between start and end of therapy.

Conclusion: Therapy with mirabegron for 24 weeks failed to reach the primary endpoint of reducing the JAK2-V617F allele burden ≥50% in MPN patients. However, an increase in the nestin+ MSCs in bone marrow and a slight decrease of myelofibrosis were found, suggesting that mirabegron can reverse the damage inflicted by the JAK2-V617F positive MPN clone on the nestin + stem cell niche.

**FM290**

**Utility of thromboelastometry analysis in patients with mild bleeding disorders**

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Background: Viscoelastic methods are regarded as promising concept to overcome the limitations of conventional laboratory assays in patients with haemostatic disorders, particularly in the perioperative setting. Their performance regarding frequently occurring mild bleeding disorders (MBD) such as mild Willebrand disease, platelet function disorder, or mild haemophilia is however unknown.

Aim: We conducted a prospective cross-sectional study to investigate the value of thromboelastometry analysis for diagnosis and prognosis of MBD.

Methods: Thromboelastometry analysis (ROTEM®) was conducted in all consecutive patients referred between January 2011 and March 2013 with a suspected bleeding disorder. Diagnostic work-up was done according to current guidelines.

Results: MBD was diagnosed in 111 out of 217 patients (52.1%), median age was 40.1 years, IQR 28.9, 59.2; 67.6% were female. Possible or definite platelet function disorder was diagnosed in 50 patients (42.7%), von Willebrand disease (vWD) in 24 patients (11.1%), mild haemophilia in 4 patients (1.8%), mild factor XI deficiency in 2 patients (0.9%), low von Willebrand factor associated with blood group 0 in 13 patients (6.0%), anticoagulation treatment in 3 patients (1.4%), and a systemic disorder in 15 patients (6.9%). Presence of MBD was not associated with a significant difference in thromboelastometry parameters (CT EXTEM, MCF EXTEM, CT INTEM, MCF INTEM, MCF FIBTEM). In addition, no significant differences were observed with regard to categories of the ISTH bleeding assessment tool. Minor differences – all within the established ROTEM reference ranges – were noted for some MBD: mild haemophilia (MCF EXTEM, MCF INTEM, MCF FIBTEM), definite vWD type 1 (MCF FIBTEM), anticoagulation treatment (CT EXTEM), and systemic disorders (CT EXTEM).

Conclusions: Our data do not support the utility of thromboelastometry analysis for diagnosis, prognosis or management in patients with mild bleeding disorders, particularly in the perioperative setting.

**FM291**

**Establishment of a patient-derived myelofibrosis xenograft mouse model**

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Introduction: A growing number of patient-derived xenograft (PDX) mouse models have been developed over the past few decades that allow engraftment of human hematopoietic stem cell (HSC) malignancies in order to study the evolution of HSC and leukemia stem cells, as well as disease heterogeneity. Myelofibrosis (MF) in a HSC disorder characterized by bone marrow fibrosis that has the potential to transform into acute myeloid leukemia. However, the engraftment of MFSCs in PDX models is poor (Wang et al., JCI 2012) presumably due to the lack of supportive factors in the bone marrow (BM) microenvironment. We hypothesized that the constitutive expression of human cytokines and growth factors in a PDX model...
may promote the development of the human MF clone in vivo. Therefore, we used next-generation mice that express human M-CSF, IL-3, GM-CSF, TPO, and SIRPα-Tg (MISTRG) in order to develop a pre-clinical MF PDX model.

Methods: Purified peripheral blood stem and progenitor (CD34+) cells were collected from MF patients and intrahepatically transplanted into sublethally irradiated newborn MISTRG mice. 5–9 weeks after transplantation mice were sacrificed and analyzed for human engraftment using flow cytometry and immunohistochemistry.

Results: Engraftment was seen from four out of seven patient samples transplanted in MISTRG mice with an overall total median of 16.1% in the BM and 71.1% in the peripheral blood (PB) of human CD45+ cells. Over 60% of engrafted cells were of myeloid origin in the BM and PB, 18.55% and 50.85% were monocytes in the BM and PB respectively. In addition, a significant frequency of human CD45+ hematopoietic stem and progenitor cells (HSPCs) was observed in engrafted mice. Overall, the results suggest that the next-generation MISTRG mice support human MF engraftment.

Conclusions: MISTRG mice support unprecedented myelo-monocytic differentiation of human MF SCs in 57% of patient samples investigated so far. Immunohistochemistry will also be performed on the human CD34+ cells and some progenitor cells to confirm the human MF clone's identity. In conclusion, the MISTRG model may present a promising anti-leukemia treatment strategy.

The tumor suppressor protein p53 is inactivated in a large variety of cancer cells including acute myeloid leukemia (AML). While TP53 gene mutations are rarely observed in AML cells at diagnosis, p53 protein function is commonly suppressed by overexpression of the cellular p53 inhibitor MDM2. In addition, other growth factor signaling pathways such as the MAPK cascade (RAS-RAF-MEK-ERK) are often active in AML cells. Consequently, combined administration of MDM2 antagonists and MEK inhibitors may present an exciting therapeutic strategy.

Methods: The aim of this study was to identify AML subgroups with specific somatic mutations promoting human MF engraftment in PDX models next-generation sequencing will be performed on transplanted patient samples.

Results: We found a considerably differing anti-leukemia efficacy across various AML cell types depending on the molecular background. AML cells with maximum sensitivity to single compound treatment as well as to the combined treatment with both Idasanutlin and Cobimetinib were characterized by wildtype status of the TP53, FLT3 and NPM1 genes. Remarkably, combined treatment with Idasanutlin and Cobimetinib together was more effective than the single compound treatment. In contrast, AML cells with FLT3-ITD or with mutated NPM1 were less sensitive. Finally, TP53mut cells were largely resistant to both compounds as well as to the combined treatment.

Conclusion: Our data indicate that AML cells derived by the wildtype status of the TP53, FLT3 and NPM1 genes accounting for up to 25% of AML patients emerge to be most sensitive to the combined treatment with Idasanutlin and Cobimetinib. In contrast, AML cells with mutations in FLT3 or NPM1 are less sensitive, whereas AML cells with mutated TP53 are largely resistant. These results propose that the combination of an MDM2 and a MEK inhibitor may be an effective and specific treatment to target AML subtypes with wildtype status of the TP53, FLT3 and NPM1 genes.
Applying 3D quantitative microscopy to study global topography and cellular interactions in the bone marrow
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Introduction: During adulthood, bone marrow (BM) cavities are the primary sites of production of vast amounts of blood cellular components from a rare population of hematopoietic stem cells (HSCs). Beyond their hematopoietic function, BM tissues host immune responses and maintain immunological memory. In addition to hematopoietic cells, the BM is populated by a heterogeneous mixture of endothelial, mesenchymal and neural stromal cells, which provide the necessary infrastructure for hematopoiesis to unfold and play essential regulatory roles. A thorough understanding of the spatial distributions, structural dynamics and interactions established by diverse cellular components within the complex landscape of the BM, is key for the generation of comprehensive models of healthy and pathological hematopoiesis.

Methods: In our laboratory we have recently developed advanced microscopy protocols that enable the 3D visualization of large volumes of BM tissues at an organ-wide level and with cellular and subcellular resolution. Here we report the generation of customized computational tools, which allow the generation of quantitative spatial information in an automatic and unbiased fashion, and enable the extraction of spatial statistics for rigorous analysis of cellular interactions.

Results: We have employed this newly developed software suite to describe for the first time the spatial distribution of key components of the HSC niche, namely sinusoidal vessels and mesenchymal stromal cells. Our data demonstrate that in general the quantitative contribution of BM stromal cells to the total BM cellular asset is substantially underestimated by widely employed flow cytometric techniques. Detailed topological analysis reveals that the highly branched sinusoidal vessel network occupies on average 18% of the BM volume, subsequently constraining the space available for cells to distribute. Using rigorous spatial statistics we estimate that 95% of the BM space is contained within a distance of 22 μm from the nearest sinusoid. Nonetheless, mesenchymal stromal cells are significantly enriched in pervascular locations, pointing to a preferential interaction between these two key stromal components. Collectively our analyses provide quantitative measurements defining microarchitectural organization of BM stroma in homeostatic conditions. We anticipate that the tools developed will be instrumental to investigate the microarchitectural alterations underlying pathological hematopoiesis.

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Introduction: Patients (pts) relapsing with CML after allogeneic hematopoietic stem cell transplantation (alloHSCT) may be treated with TKI and/or DLI. As nowadays the majority of CML pts would have received at least imatinib prior to transplantation, we were interested in analyzing a) the type of TKI used after alloHSCT, b) the indication for TKI treatment, c) the outcome of this treatment and d) the temporal relationship with DLI if given.

Patients and methods: 435 pts received TKI after first allo HSCT for CML. The indications for TKI were the same as for transplantation (n = 25), for relapse/progression/persistent disease (n = 248), for prophylaxis/pro-emptive (n = 147), planned (n = 5), others (n = 8) and missing (n = 4).

Results: Median follow-up from start of TKI was 55 (1–171) months. The median time interval from transplant to TKI was 6 (0.2–165) months. It was longer for TKI given for relapse/progression with 15 (1–108) months and shorter for TKI given for prophylaxis/pro-emptive with 16 (0.2–43) months. It was longer for imatinib with 11 (0.2–121) months vs 3.8 (0.2–165) months for other TKI. Best response after TKI was complete molecular remission in 17.7%, cytogenetic remission in 44.4%, hematological response in 20.2% and no response/response/relapse in 57.7% of pts. 50% of pts treated with imatinib had a response (molecular/ cytogenetic/hematological) vs 34% with nilotinib, 33% with dasatinib and 33% with bosutinib/ponatinib, p = 0.014. In univariate analysis, OS, RFS and RI were better for imatinib vs other TKI (table).

In multivariate analysis for OS, imatinib vs other TKI post-transplant did not show anymore an effect, HR 1.19 (0.85–1.67), p = 0.317. Factors influencing OS were time from diagnosis to transplant, HR 1.01 (1.00–1.01), p = 0.009, AP vs CP1, HR 1.80 (1.11–2.91), p = 0.017 and BC/>CP1 vs CP1, HR 2.3 (1.58–3.33), p <0.0001. In multivariate analysis for RFS imatinib vs other TKI did not have an effect. Other factors having a tendency or influencing RFS were time from diagnosis to transplant, HR 1.00 (1.00–1.01), p = 0.054, AP vs CP1, HR 1.52 (1.00–2.31), p = 0.050, BC/>CP1 vs CP1, HR 2.11 (1.55–2.88), p <0.001. In multivariate analysis for OS imatinib vs other TKI did not have an effect. Other factors having a tendency or influencing RFS were time from diagnosis to transplant, HR 1.00 (1.00–1.01), p = 0.054, AP vs CP1, HR 1.52 (1.00–2.31), p = 0.050, BC/>CP1 vs CP1, HR 2.11 (1.55–2.88), p <0.001.

Conclusion: These data suggest that TKI after alloHSCT induce a response in about 42% of pts regardless of the type of TKI used and that time from diagnosis to transplantation as well as the phase of disease at transplant remain the main factors influencing the outcome of CML patients relapsing after alloHSCT.

Long-term clinical outcomes of patients with CYP2C9 and VKORC1 variants treated with vitamin K antagonists: a prospective, multicenter cohort study of elderly patients with venous thromboembolism
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Targeting the p53 inhibitor MDM2 enhances specificity and efficacy of the FLT3-inhibitor midostaurin in FLT3-ITD acute myeloid leukemia (AML)

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Introduction: Prognosis of acute myeloid leukemia (AML) patients with FLT3-ITD is poor, particularly in FLT3-ITD AML patients in relapse or refractory to conventional induction treatment or in FLT3-ITD AML patients unfit for intensive treatment, thus highlighting an unmet need for novel therapeutic approaches. The combined use of compounds targeted against the mutated FLT3 receptor and against cellular inhibitors of the master tumor suppressor p53 might propose an effective treatment option for this poor risk group of AML patients.

Methods: In this study, we assessed the protein kinase inhibitor Midostaurin (PKC412) and the MDM2 inhibitor HDM201 as well as the cytochrome P450 enzyme gene (CYP2C9) and long-term clinical outcomes in a prospective, multicenter cohort study of elderly patients treated with vitamin K antagonists for venous thromboembolism.

Results: Overall, 774 patients were followed for a median duration of 30.1 months. The mean age of 334 patients (43.2%) and 119 patients died (15.4%). Major bleeding occurred in 100 patients (12.9%), clinically relevant non-major bleeding in 167 patients (21.6%), and recurrent VTE in 100 patients (12.9%). After adjustment, the presence of CYP2C9 polymorphisms was significantly associated with any clinical event (hazard ratio [HR] 1.34; 95% CI 1.08, 1.66), death (HR 1.74; 95% CI 1.19, 2.52), and clinically relevant non-major bleeding (sub-hazard ratio [SHR] 1.38; 95% CI 1.01, 1.55), but not with major bleeding (SHR 1.03; 95% CI: 0.68, 1.55) and recurrent VTE (SHR 0.95; 95% CI 0.62, 1.44). The presence of VKORC1 variant was not associated with any clinical event. No relevant differences in the percentage of time spent within the therapeutic range were observed in patients with and without CYP2C9 variants [DAI].

Conclusions: In conclusion, we document a significant association between CYP2C9 polymorphisms and deaths, probably because of effects independent from quality of anticoagulation and major bleeding.

Conjoint high anti-C1q and anti-ADAMTS13 autoantibody titers mark the immune response in lupus nephritis and concurrent SLE/ITP patients

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Introduction: Thrombotic events such as microvascular occlusions – a hallmark of immune-mediated thrombotic thrombocytopenic purpura (ITP), are the main cause of mortality and morbidity among systemic Lupus erythematosus (SLE) patients with a prevalence of 10%. Renal thrombotic microangiopathic symptoms (TMA) are observed frequently together with an overactivated classical complement system with high anti-C1q antibodies (Abs) which have been shown to be strongly linked to the severity of active lupus nephritis. Given the considerable overlap of clinical symptoms between SLE and ITP, we evaluated if ADAMTS13 activity, anti-ADAMTS13 and/or anti-C1q antibodies (Abs) titers serve as additional blood markers to distinguish primary ITP from conjoint (secondary) ITP/SLE.

Method: ADAMTS13 activity (FRETs-VWF/F3 assay) and presence of circulating anti-ADAMTS13 and/or anti-C1q titers (commercial ADAMTS13 INH ELISA or C1q ELISA, respectively) were assessed in blood samples of a SLE cohort (n = 93; 40/93 with active lupus, 13/93 in remission and 40/93 with complement-mediated complications only) and compared to a cohort of acute ITP (n = 92; 67 first episode, 25 with a relapse) and 41 healthy controls.

Results: ADAMTS13 activity was severely decreased (<5%) in 96% (88/92) ITP patients and the 5 ITP/SLE patients. Anti-ADAMTS13 Abs were found in 43% (40/93) of SLE patients (titer >15 AU/ml, range: 16-945 AU/ml) compared to 21% (9/41) in ITP patients with a median of 62.8 AU/ml (range 5 to >104 AU/ml) and only 5% (2/41; 16 and 26 AU/ml) in healthy controls. Anti-C1q Abs were positive (15 IU/ml) in patients suffering from more than 1 autoimmune disease (n = 16) in both the SLE and ITP cohort, lupus nephritis (SLE cohort, 22/40), TMA-associated nephritis (5/40) or concurrent SLE/ITP (5) were marked by high dual positive Ab titers with the anti-C1q and anti-ADAMTS13 titers of 130 IU/ml, respectively.

Conclusions: Our findings show that SLE patients presenting with a TMA-like picture (lupus nephritis) or ITP patients with renal TMA constitute a specific sub-group marked by high dual positive C1q and anti-ADAMTS13 titers and anti-C1q Ab titers. Evaluation of larger patient cohorts with well documented clinical courses will allow to confirm dual Ab positivity as a marker for secondary complications in SLE and ITP.
Results: The coverage of the Swiss population by the CCRs increased from 55.3% to 65.1% during the observation time. 3684 new AML cases were registered, corresponding to an extrapolated number of 6226 new AML cases in the Swiss population during the observation time. The extrapolated mean annual case frequency increased from 235 to 299 AML cases (+27%). Age-standardized incidence rates ranged from 3.3–3.6 in males, and 2.5-2.8 in females per 100'000 patient-years, respectively, and remained stable throughout the observation time. Median age at diagnosis was 66 years for males in all time periods and ranged from 67-70 years in females. Age-standardized mortality rates ranged from 1.1–2.4 in males, and 0.8–1.7 in females. Mortality rates were lowest in the earliest time periods, indicating a reporting bias for 1989-2000. The fraction of unclassified AML decreased from 78% to 39% during the observation time. However, the proportion remained high (50% and 1.4%) in the older compared to younger patients in 2008–2012 (age cut-off: median age).

Discussion: AML incidence remained stable during the observation period, indicating that the 27% rise in case-frequency is related to population growth and ageing and not to an increase of age-specific risk. Elderly AML patients are more frequently not further subclassified, suggesting that diagnostics and reporting is less accurate in elderly patients. As previously reported for MDS patients, the currently available data is also insufficient for detailed health services research in AML patients. Further collection of longitudinal data on treatment, side effects and outcomes is warranted.

FM300

GPR56, a novel stem cell marker in CD34 negative acute myeloid leukemia?
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Objectives: Although considered a curable disease, acute myeloid leukemia (AML) leads to death in a considerable percentage of patients. The main obstacle to cure is relapse after apparent remission, which, from a cellular perspective, is thought to occur from so-called leukemic stem cells (LSCs). Several reports have documented that surface expression of the HSC marker CD34 can identify subpopulations of leukemic blasts with LSC properties and stem cell molecular signature within AML. However, ~30% of AML do not express CD34 on the cell surface, mainly in NPM-mutated AML that show low CD34 expression, and no other reliable marker for LSC isolation has been reported in this disease subtype. Recently, the G-coupled protein receptor 56 (GPR56), a molecule regulating cell adhesion, has been implicated as LSC marker in CD34 positive AML. Here, we aim to analyze whether surface expression of GPR56 can be used as LSC marker in CD34 negative (NPM-mutated) AML, where the LSC compartment has not yet been characterised.

Methods: CD34 negative AML patient samples were screened for GPR56 surface expression by flow cytometry using an anti-human GPR56 PE antibody, followed by subsequent FACS to separate GPR56-negative and positive leukemic blasts that were either used for in vitro colony forming unit (CFU) or in vivo xenotransplantation assays in immunosuppressed NSG mice.

Results: Flow cytometric assessment of GPR56 surface expression revealed heterogeneous but distinct GPR56 expression in each of the analysed samples (n = 6 CD34-negative AML patient blasts). Pilot data indicate that only GPR56+ (and not GPR56-) cells indeed induce CFU and in vivo leukemogenicity, indicating that clonogenicity and in vivo leukemogenesis are confined to GPR56+ cells in CD34- AML. We are currently awaiting further results from additional patient samples.

Conclusion and outlook: Our preliminary data suggests that GPR56 might indeed be used as a novel stem cell marker in CD34 negative AML. In order to solidify these results, we will perform RNA sequencing experiments to retrieve the LSC signature in GPR56+ vs. GPR56- sorted AML blasts. Since it has been recently shown that GPR56 expression promotes migration and adhesion of healthy HSCs to the BM niches, we furthermore plan to functionally characterize the role of GPR56 in CD34 negative AML by analysing the adhesion capacity of GPR56+/- cells in in vitro co-culture experiments with M5 stromal cells and in in vivo homing assays.
The bone marrow microenvironment is a target of graft-vs-host reactivity following allogeneic hematopoietic cell transplantation in mice

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Allogeneic hematopoietic cell transplantation (HCT) is the only curative treatment for many malignancies of the blood. Graft T cells (Tc) are critical to control malignant cells but can also induce graft-vs-host disease (GVHD), in which donor Tc target and destroy host tissues. Little attention has been paid to effects of alloreactive Tc on the bone marrow (BM) and how structural damage of its microenvironment affects hematopoietic recovery and function. Here, we studied in an MHC-matched, minor antigen mismatched mouse model the effects of lethal irradiation and HCT of purified hematopoietic stem cells (HSC; ckit+Sca1+Lin-) +/- Tc on the hematopoietic and non-hematopoietic BM compartments. At 1, 2, 3, and 4w post-HCT bones and marrow were analyzed by FACS and 3D-confocal microscopy. Post allo-HCT there was a transient weight loss in both groups (HSC and HSC+Tc), but no overt GVHD. Total BM cell counts dropped, but at 2w mice given HSC had significantly higher absolute BM counts compared with HSC+Tc recipients. Strikingly, B-cell recovery occurred promptly in HSC recipients but was severely impaired in the HSC+Tc group. Likewise, granulocyte recovery at 2, 3, and 4w was significantly better in HSC vs. HSC+Tc recipients. Regarding the non-hematopoietic compartment CD45-Ter119+CD31+ endothelial cells (EC) were significantly reduced in both groups compared with wildtype controls (WT) at 1, 2, and 3w post-HCT but recovery was superior in the HSC vs the HSC+Tc group with significantly higher EC counts at 2-3w. The most pronounced effects were observed for CXCL12-abundant reticular (CAR) cells (CD45-Ter119-CD31-CD140B-), which were initially reduced in HSC recipients but normalized at 4w post-HCT. In HSC+Tc recipients CAR cells were significantly lower and remained reduced at 4w. 3D-confocal microscopy confirmed these observations and revealed rapid recovery of extracellular matrix and vascular structures, with simultaneous disappearance of adipocytes at 2w post-HCT in the HSC group. In contrast, in recipients of HSC+Tc severe disruption of the extracellular matrix (Figure) led to a reduction in the entire area occupied by adipocytes. In clinical HCT delayed hematopoietic reconstitution presents a major problem contributing to increased morbidity and mortality. Our data show that alloreactivity has a major impact on the non-hematopoietic compartment of the BM in terms of both damage and reconstitution of the microarchitecture and ultimately hematopoietic recovery.

Intrinsic and extrinsic factors control aging of hematopoietic stem cells

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Life-long self-renewing hematopoietic stem cells (HSCs) repetitively contribute to replenishment of mature blood cells. Aged HSCs show reduced self-renewal, less efficient bone marrow (BM)-homing capacity, and myeloid-skewed differentiation. We demonstrated a cell-intrinsic drive towards dormancy in HSCs impaired by increased divisional history (ExpMed 2011). Here, we tackle the questions what extrinsic and intrinsic factors determine HSC behaviour at the cellular and molecular level. We have established in vivo single HSC divisional tracking with CFSE (5(6)carboxyfluorescein diacetate N-guccinimidyl ester), and subsequent isolation of different divisional classes of HSC-containing cell fractions (LKS) based on CFSE dilution for in vivo HSC functional readout. CFSE-labeled young (8–12 week old) and aged (>2 year old) LKS were transferred into non-irradiated young or aged recipients, respectively. To test biological function of HSC with distinct divisional histories, quiescent or cycling LKS were isolated and transplanted into lethally irradiated mice. The transplanted mice were monthly bled to follow long-term donor engraftment and lineage repopulation. To dissect aging-associated extrinsic factors, we performed antibody based protein arrays and transcriptome analysis.

Functional and structural dynamics of the bone marrow stromal microenvironment after cytoreductive therapies

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Introduction: Hematopoietically active bone marrow (BM) tissues are highly sensitive to cytoreductive treatments such as ionizing irradiation and chemotherapeutic agents, which are the treatment of choice for multiple malignancies and employed as conditioning regimens in BM transplantations. The cytotoxic damage and killing of rapidly cycling hematopoietic progenitors induced by myeloablative therapies has been extensively characterized. However, it is still largely unknown whether and to what extent these treatments target BM stromal cells of endothelial and mesenchymal origin, which critically regulate hematopoiesis. Here, we analyse the impact of BM stroma upon myeloablation, the resulting microarchitectural effects on BM and the kinetics of regeneration of BM tissues post-injury.

Methods: In this study we employ advanced flow cytometric protocols to analyze quantitative changes in cellular populations. Structural effects on the murine BM microenvironment are in turn visualized and quantified by using advanced 3D-confocal microscopy in combination with newly developed computational tools for image-based analysis.

Results: As previously reported, ionizing irradiation and 5-FU treatment led to a severe loss of hematopoietic stem and progenitor cells (HSPCs). Notably, a similar profound decrease in endothelial and mesenchymal stroma was observed. Decline in stromal cell numbers was apparent 7 days after treatment and encompassed a major loss of structural integrity of the BM microenvironment. 3D imaging revealed massive sinusoidal dilation followed by appearance of ruptures in vessel walls. Structural effects and cellular effects were partially reversed 14 days post treatment in a regenerative process that culminated 4 weeks after treatment. In addition, massive de novo differentiation of mesenchymal progenitors into adipocytes lead to adipogetic infiltration of large regions of the BM. Of note, this process was fully reversible as virtually almost all adipocytes were cleared from BM tissues 56 days after treatment. To characterize the functional role of BM function, reversible extramedullary hematopoiesis was prominent at time points of maximal BM damage.

Conclusion: Our observations demonstrate that the stromal BM microenvironment is highly sensitive to myeloablative therapies. Of note, BM tissues are endowed with an intrinsic regenerative and self-organizing capacity that enables rebuilding of a fully functional tissue microenvironment after severe damage.
Results:
mice. Therefore we performed a detailed analysis of metabolism in these
that VF and Ex12 mice display markedly decreased body fat and
unknown, since hemorrhagic and thrombotic complications are
exon 12 (Ex12). These mice exhibit all features of MPN and result in
oncogenic mutations such as JAK2-V617F. MPNs are characterized
disorders of hematopoietic stem cells (HSC) driven by activation of
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Introduction: In classical Hodgkin lymphoma (cHL) the low
representation (1–5%) of Reed-Sternberg cells (RS) challenged tumor genotyping on the diagnostic tissue biopsy. Cell free DNA (cfDNA) is
shed into the blood by tumor cells undergoing apoptosis and can be
used as source of tumor DNA for the identification of somatic mutations. This study aims at providing the evidence that the genetic profile of the cHL can be accurately tracked by using plasma cfDNA.

Genotyping of hodgkin lymphoma on the liquid biopsy
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Hypoglycemia and energy crisis contribute to early
lethality in JAK2 mutated models of myeloproliferative
neoplasm
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Background: Myeloproliferative neoplasms (MPN) are clonal disorders of hematopoietic stem cells (HSC) driven by activation of oncogenic mutations such as JAK2-V617F. MPNs are characterized by elevated plateau and/or erythrocyte production or development of myelofibrosis. We studied several mouse models of MPN that are driven by mutant JAK2-V617F (VF) or by an activating mutation in exon 12 (Ex12). These mice exhibit all features of MPN and result in early mortality. The causes of death in these mice are largely unknown, since hemorrhagic and thrombotic complications are relatively rare and leukemic transformation is not observed. We noticed that VF and Ex12 mice display markedly decreased body fat and therefore we performed a detailed analysis of metabolism in these mice.

Results: Hematopoietic specific activation of VF or Ex12 mutations in mice caused global metabolic changes including adipose tissue atrophy due to increased adipocyte lysis in white and brown fat tissues, systemic metabolic changes, and resistance to high-fat diet (HFD) induced obesity in mice. In addition, these mice under normal dietary conditions were severely hypoglycemic and showed almost no increased glucose tolerance despite normal insulin levels. These metabolic changes were also present in recipients transplanted with bone marrow from VF or Ex12 donors, indicating that the changes are caused by the mass of mutant hematopoietic cells. Intriguingly, HFD treatment significantly ameliorated early mortality of MPN mice. This effect was not due to reduction in elevated platelet and erythrocyte numbers, implying that altered energy homeostasis likely attributable for early mortality of MPN mice. Integrated transcriptomics, and metabolomics analysis together with metabolic functional assays identified increased reliance of mutant HSPCs on fatty acid oxidation, glycolysis, and amino acid metabolism causing clonal expansion of MPN initiating HSPCs. Pharmacological targeting of JAK2 activation with classical JAK2 inhibitor, Ruxolitinib, reduced MPN associated hypoglycemia, MPN clonal expansion, and disease burden.

Conclusion: Hypoglycemia and energy crisis are likely to contribute to lethality of MPN mice. Maintaining energy homeostasis and adipose tissue depots by high fat diet improved survival of MPN mice. Targeting the metabolic dependencies of the mutant MPN clone is a novel potential strategy for MPN treatment.
Heparin-induced thrombocytopenia (HIT) diagnosis in 30 minutes! A prospective evaluation of a rapid diagnostic work-up

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Introduction: The laboratory gold standard for diagnosing HIT is a functional assay, e.g., the Heparin Induced Platelet Aggregation (HIPA) test. We assessed 3 quantitative immunoassays (qIAs) detecting anti-PF4/heparin antibodies for their ability to predict the HIPA result. Our aim was to prospectively evaluate a rapid algorithm able to confirm or exclude HIT with a laboratory turn-around-time of 30 minutes.

Methods: We conducted a retrospective (05.2014–08.2015; n = 220) and a prospective (09.2015–08.2016; n = 234) study in patients with HIT suspicion. 46 plasma samples of the retrospective study and all samples of the prospective one were analyzed by 3 IAs (ELISA Zymutest HLA monospecific IgG; AccuStar HIT IgG; ID-/HP/F4-PaGIA). ROC analysis let us compare the areas under the curve (AUC) and determine cut-offs with 100% negative (NPV) and positive (PPV) predictive values for a positive HIPA.

Results: HIT diagnosis was confirmed by a positive HIPA in 10% of patients (22/220) in the retrospective and in 9.4% (22/234) in the prospective study. AccuStar showed an AUC of 0.98 both in the retrospective (p = 0.02 compared to Zymutest and p = 0.59 to PaGIA) and in the prospective study (p = 0.06 compared to Zymutest and p = 0.52 to PaGIA). A 100% PPV was observed with a result >1.37 U/ml (identifying 18/22 HIPA-positive samples) and with a result >0.77 U/ml (identifying 20/22 HIPA-pos samples) in the retrospective and prospective studies, respectively. A 100% NPV was observed with a result of ≤0.12 U/ml and ≤0.18 U/ml (overall identifying 218/236 HIPA-negative samples). PaGIA showed an AUC of 0.99 and 0.97 in the two studies. A test had a 100% PPV and a titer <2 had a 100% NPV (identifying 210/236 HIPA-negative cases). Applying conservative cut-off values of ≤0.12 (= negative) and ≥1.50 (= positive) for AccuStar results, only 13% of samples (36/280) were between these values (“grey zone”). Among them, 17 (47%) were correctly solved by PaGIA. Eventually, 7% of all samples (19/280) remained unclear until HIPA result. The in house cut-off produced no false positive or negative results.

Conclusion: The sequential application of two rapid immunoassays (AccuStar HIT IgG and ID-/HP/F4-PaGIA) with in-house determined cut-off values with 100% NPV and PPV enables a reliable and conclusive diagnostic work-up for ~95% of patients with clinical suspicion of HIT, in a laboratory turn-around-time of 30 minutes. We are now conducting a prospective validation of this rapid diagnostic algorithm.

Risk factors for recurrence in deep vein thrombosis patients with a tailored anticoagulant treatment based on residual vein thrombosis: contemporary data

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Background: Finding the optimal duration of anticoagulant treatment following an acute event of deep venous thrombosis (DVT) is challenging. Residual thrombosis has been identified as risk factor for recurrence, but data on management strategies based on residual clinical care pathways (CCP) are lacking.

Objective: To investigate the long-term clinical outcomes and predictors for VTE recurrence in a contemporary cohort of patients with proximal deep vein thrombosis (DVT) managed according to the presence of residual vein thrombosis.

Methods: All patients treated at Maastricht University Medical Center with an established clinical care pathway from June 2003 through June 2013 were prospectively followed for up to 11 years. Treatment duration was tailored based on residual vein thrombosis. Recurrence rates were determined. A Cox proportional hazards model employing anticoagulation treatment as time-varying covariate was used to define risk factors for recurrence.

Results: Out of 479 patients diagnosed with proximal DVT, 474 completed the two-year CCP (99%), and 457 (94.7%) the extended follow-up (2231.2 patient-years; median follow-up 4.8 years; median age 58.0 years; 50.4% females). Overall VTE recurrence was 2.9 per 100 patient-years, 1.3 if provoked by surgery, 2.1 if a non-surgical transient risk factor was present, and 4.0 if unprovoked. Residual thrombosis was present in 141 patients (29.8%). Duration of anticoagulation was 3 months in 75 patients (15.7%), 6 months in 230 (48.0%), 12 months in 95 (19.8%) and indefinite in 79 (16.5%). DVT was provoked by surgery in 95 patients (19.9%), by a transient non-surgical risk factor in 107 patients (22.3%) and unprovoked in 265 (55.3%). Significant predictors of recurrent events were unprovoked VTE (adjusted hazard ratio [HR] 4.6; 95% CI 1.7, 11.9), elevated d-dimers one month after stop treatment (HR 3.3; 1.8, 6.1), male sex (HR 2.8; 1.5, 5.1), high factor VIII (HR 2.2; 1.2, 4.0) and use of contraceptives (HR 0.1; 0.0, 0.9).

Conclusions: Patients with DVT managed within an established clinical care pathway according to the presence of residual vein thrombosis had low incidences of VTE recurrence. In accordance with other clinical settings, unprovoked VTE, male sex, elevated D-dimers one month after stop treatment, inflammation, and high FVIII were identified as major predictors for recurrent VTE.

Calcium monitoring in platelets: tool for diagnosing platelet function defects

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Introduction: Laboratory tests currently used to investigate a bleeding diathesis may fail to reveal the underlying hemostatic disorder. Flow cytometry (FC) improved our tools for exploring platelet (PLT) function and profiling defects associated with a bleeding diathesis. Our aim is to home standard FC analysis by extending investigations to intracellular signaling. In this work, we assessed free intracellular Ca²⁺ upon PLT activation.

Method: Platelet-rich plasma was obtained from citrate-anticoagulated whole blood. PLTs were activated with increasing concentrations of thromboxane analogue U-46619, ADP, thrombin, the two selective thrombin receptor agonists TRAP6 (PAR-1 agonist) and AYPGKF (PAR-4 agonist), convulxin (agonist of the GPVI collagen receptor), and ionopore. Activation end-points were secretion of alpha-granules (detected by P-selectin expression) and activation of the fibrinogen receptor (visualized by PAC-1 binding). Intracellular free Ca²⁺ was detected by its indicator Fluo-3 AM. After measurement of a stable baseline, PLTs were activated with various agonists, and Fluo-3 fluorescence was continuously acquired over time, up to 10 minutes, on a BD Accuri C6 flow cytometer.

Results: Optimal dose-response concentrations were determined for each agonist and Ca²⁺ monitoring following PLT activation was performed. Maximal and sustained cytosolic Ca²⁺ increase was observed after PLT activation with ionophore. Very strong and sustained increase was also observed by activation with convulxin and thrombin. While convulxin was able to induce a strong Ca²⁺ spike followed by a plateau, thrombin induced an initially strong Ca²⁺ response, which subsequently declined. Both selective PAR agonists, TRAP6 and AYPGKF, demonstrated a strong increase with rapidly declining intracellular Ca²⁺, but their combined action was not able to fully replicate thrombin effect. Finally, although a similar weak Ca²⁺ mobilization was observed with U-46619 and ADP, these agonists differently affected convulxin and thrombin responses when employed in combination.

Conclusion: The present work highlights the use of continuous calcium monitoring to complement FC analysis of PLT function. We demonstrate characteristic Ca²⁺ mobilization patterns following PLT activation with various agonists. This technique will sharpen the ability to detect PLT signaling defects in bleeding patients investigated for platelet function disorders.
Effect of complete lack of protein S on pregnancy outcome in mice

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Introduction: Complete protein S (PS) deficiency is a rare fatal thrombophilic syndrome. It is caused by a lack of protein C activator (PCa) and by a lack of protein S (PS). The aim of the present study was to examine the effect of complete lack of PS on pregnancy outcome in mice.

Results: Vaginal plugs were observed in all F8⁺Pros1⁺ females (n = 19), independently of the male breeder genotype, no litters were produced. Embryos collection revealed embryonic mortality at E11.5-12.5 (58% dead embryos; n= 41/71), E13.5-16.5 (69%; n= 44/64). Most of dead embryos were macerated but some of them showed hemorrhages and thrombosis but no PF. Among embryos collected before E9.5–10.5, there was a lower number of embryos carrying the F8⁺Pros1⁻ genotype than expected (33% vs 50%) and no live embryos collected after E12.5 were F8⁺Pros1⁻. All embryos collected from F8⁺Pros1⁺ and F8⁻Pros1⁺ pregnant mice were alive. Recurrent pregnancy loss never affected F8⁺Pros1⁺ mice survival. Between E12-16 and in comparison to F8⁺Pros1⁺ gravid mice, F8⁻Pros1⁻ pregnant mice displayed reduced platelet count (559 ± 79 vs 829 ± 92 G/L; P <0.05) and fibrinogen (1.0 ± 0.1 vs 2.4 ± 0.3 g/L; P <0.001), and increased TAT complexes (25.4 ± 2.8 vs 12.6 ± 4.3 ng/L; P <0.05). After auto-HSCT, the expression level of miR-21 was significantly different in responders compared to non-responders. Responders had a lower expression of miR-21 compared to non-responders. Further, serum VEGF levels were increased in PCM patients (477 ± 145 pg/ml versus 178 ± 78 pg/ml in normal controls; p <0.01). After auto-HSCT, the expression level of miR-21 was significantly different in responders compared to non-responders. VEGF expression was increased in the supernatant from miR-21 mimic transfected human PCM cell lines H929 and RPMI-8226 compared with the negative control, while VEGF was decreased in the miR-21 inhibitor transfected cell lines. The angiogenic ability of HUVECs was increased under pretreatment with the supernatant from H929 and RPMI-8226 cells transfected with miR-21 mimic compared with negative controls and decreased when pretreated with miR-21 inhibitor transfected cells.

Conclusions: This study demonstrated that miR-21 was upregulated in PCM patients. Responders to auto-HSCT had a decrease of miR-21 expression and VEGF levels. Further, miR-21 regulated angiogenesis. Therefore inactivation of miR-21 or activation of its target gene may be a potential therapeutic approach in PCM.

Overexpression of miR-21 involved in plasma cell myeloma-associated angiogenesis

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Introduction: Angiogenesis plays an important role in the pathophysiology of hematological malignancies including plasma cell myeloma (PCM). MicroRNA-21 (miR-21) is overexpressed and displays oncogenic activity in cancers. The aim of the present study is to examine the expression level of peripheral miR-21 in PCM patients and to determine its role in angiogenesis.
Free Contributions: Clinical Hematology

**FD311**

**Dynamics of expression of Programmed cell death protein-1 (PD-1) on T cells after allogeneic hematopoietic stem cell transplantation**

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**Introduction:** Blockade of the programmed-death 1 (PD-1) immune checkpoint represents a promising strategy to enhance anti-tumor immune responses after allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, observational studies suggest that PD-1 blockade can be complicated by the development of severe graft-versus-host disease (GvHD). A better knowledge of the dynamics of PD-1 expression by T cells after allo-HSCT is necessary in order to optimize PD-1 targeting therapies and limit toxicities.

**Methods:** We analyzed by flow cytometry 124 freshly drawn blood samples isolated from 98 allo-HSCT recipients. 23 healthy blood donors served as controls (HC).

**Results:** We observed a strong increase in PD-1 expression at the surface of CD4 and CD8 T cells isolated from allo-HSCT recipients compared with HC (Fig 1A). Importantly, we observed the significant increase of PD-1 expressing cells in all CD4 and CD8 T cell subpopulations studied (fig. 1B). We observed an inverse correlation between the time since allo-HSCT and PD-1 expression at T cell surface (fig. 1C). PD-1 expressing cells were higher than normal already at one month after allo-HSCT (fig. 1D). Thereafter, proportions of CD4 PD-1+ T cells remained higher than in HC up to more than 5 years after HSCT, while PD-1 expression on CD8 T cells started to normalize at 1 year after transplantation (fig. 1D). The stem cell source (BM vs PBSC), conditioning regimen (RIC vs MAC), use of total body irradiation and disease status at HSCT did not impact PD-1 expression. We observed higher proportions of PD-1+CD4+ but not of PD-1+CD8 T cells in patients receiving grafts from haploidentical donors displayed higher proportions of PD-1+ T cells than patients receiving grafts from matched related (p = 0.0049) or unrelated donors (p = 0.0049). No association was found between PD-1 expression on T cells and post-transplant complications, including acute or chronic GvHD, disease relapse and CMV reactivation.

**Conclusion:** We report here an early and long lasting increase of PD-1 expression on CD4 and CD8 T cells after allo-HSCT. Several factors, including TCD and transplantation from haploidentical donors, are associated with a further increase in PD-1 expression on T cells. These results will help harnessing the potential of PD-1 blockade after allo-HSCT.

**FD312**

**Defibrotide shows efficacy in the prevention of sinusoidal obstruction syndrome (SOS) after allogeneic hematopoietic stem cell transplantation: a retrospective study on 237 patients**

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**Introduction:** Sinusoidal obstruction syndrome (SOS) is frequent after HSCT and may have a mortality rate of up to 85%. Defibrotide has shown efficacy not only in the treatment of established SOS but also in SOS prevention in a prospective study in children as well as in adults (several retrospective studies).

**Patients and methods:** Between 1999 and 2009, we gave defibrotide intravenously to 237 successive patients transplanted (248 transplantations) for hematological diseases starting at day –7 up to day +20 post-transplantation (dose range 800–2400 mg/d) in combination with heparin. The control group did not receive defibrotide as prophylaxis anymore (2011–2015, total 241 patients with 248 transplantations).

**Results:** Median follow-up for the study group was 10 (range 2–16) years and for the control group 2.7 (range 1–18) years. None of the 237 patients in the defibrotide group developed SOS (Baltimore criteria). The 100 day cumulative incidence (CI) of SOS was 0% in the defibrotide group as compared to 4.8% (95% CI 2.6–8%) in the control group, p = 0.00046. The day 100 event free survival (EFS) was not significantly different with 60% (95% CI 54–66%) in the defibrotide group vs 53% (95% CI 47–59%) in the controls, p = 0.165, but the one year EFS was statistically different with 36% (95% CI 32–44%) vs 28% (95% CI 22–34%), p = 0.00096. The 100 day CI of acute GvHD was not significantly different between the two groups [27% (95% CI 22–33%) in the defibrotide group vs 29% (95% CI 24–35%) in the control group, p = 0.707] while the 1 year acute GvHD CI was significantly reduced in the defibrotide group [31% (95% CI 25–37%)] compared with the control group [42% (95% CI 36–48%), p = 0.026]. The one year overall survival (OS), relapse incidence (RI) and non-relapse mortality (NRM) were not statistically different. Multivariate analysis, performed taking into account clinical factors known to influence the risk of SOS, confirmed the favorable impact of defibrotide on 100 day SOS CI [HR 7.5×10^{-10} (95% CI 1.8×10^{-7}–3.2×10^{-4}), p <0.00001] (table).

<table>
<thead>
<tr>
<th>SOS incidence at 1 year</th>
<th>Hazard ratio</th>
<th>Lower 95%CI</th>
<th>Upper 95%CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&gt;50 vs &lt;50 years)</td>
<td>0.147</td>
<td>0.032</td>
<td>0.685</td>
<td>0.0150</td>
</tr>
<tr>
<td>AST/ALT (high vs normal)</td>
<td>34.410</td>
<td>5.813</td>
<td>203.700</td>
<td>0.00010</td>
</tr>
<tr>
<td>Bilirubin (high vs normal)</td>
<td>31.660</td>
<td>1.886</td>
<td>531.500</td>
<td>0.0160</td>
</tr>
<tr>
<td>HSCT Year (&gt;2007 vs &lt;2007)</td>
<td>0.009</td>
<td>0.000</td>
<td>0.180</td>
<td>0.00210</td>
</tr>
<tr>
<td>Conditioning (RIC vs MAC)</td>
<td>0.077</td>
<td>0.008</td>
<td>0.703</td>
<td>0.02300</td>
</tr>
<tr>
<td>Busulfan use (Yes vs No)</td>
<td>22.810</td>
<td>6.079</td>
<td>85.580</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>TBI (Yes vs No)</td>
<td>2.758</td>
<td>0.564</td>
<td>13.490</td>
<td>0.21000</td>
</tr>
<tr>
<td>HSCT Number (2nd vs 1st)</td>
<td>2.501</td>
<td>0.468</td>
<td>13.370</td>
<td>0.28000</td>
</tr>
<tr>
<td>Defibrotide use (Yes vs No)</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

Conversely, multivariate analysis failed to confirm the impact of defibrotide on 1 year EFS or acute GvHD CI.

**Conclusion:** To the best of our knowledge, this is the largest study on SOS-prophylaxis with defibrotide and it suggests that this drug may benefit the prevention of this liver complication. Our retrospective study needs to be confirmed in a prospective randomized trial.
Reactive hemophagocytic syndrome after hematopoietic stem cell transplantation: a multicenter retrospective study on behalf of the francophone society of stem cell transplantation and cellular therapy (SFGM-TC)


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Introduction: Reactive hemophagocytic syndrome (HS) is a rare complication that may occur after both autologous and allogeneic hematopoietic stem cells transplantation (HSCT). Only about sixty cases of post-HSCT HS have been reported in the literature so far.

Methods: We performed a multicenter retrospective study on behalf of the SFGM-TC, including adult HSCT recipients diagnosed with HS after HSCT. The recently reported HScore was applied for confirmation of HS diagnosis.

Results: Among the 33 patients reported, 2 patients were excluded because of insufficient data and 1 patient for an HScore less than 169. We included in the final analysis 27 patients in which the HS diagnosis was confirmed (median HScore 218 and HS probability of 97%). Median age was 45 years. 3 patients underwent autologous HSCT for non-Hodgkin lymphoma (NHL). 24 patients received allogeneic HSCT for hematological malignancies (n = 23) or severe aplastic anemia (n = 1) from HLA-identical siblings (n = 4), HLA-matched (n = 10) or mismatched (n = 8) unrelated donors, haploidentical donors (n = 2) or cord blood (n = 2). Median time from HSCT to HS diagnosis was 66 days (range 6–326). Fever was present in almost all patients (93%) while we observed splenomegaly in 13 (48%), hepatomegaly in 11 (41%) and lymphadenopathy in 8 (30%) patients. We found pancytopenia in 14 patients (52%). All patients displayed elevated ferritin levels. 11 patients (41%) had triglyceride levels at >4 mmol/l, while only 7 patients (26%) had fibrinogen <2.5 g/L. Aminotransferases were elevated in half of the patients (n = 14). Bone marrow hemophagocytosis was found in 15 patients (56%) (fig. 1A). 20 patients (74%) had pharmacological immune suppression at time of HS diagnosis. Infections were the most frequent triggering events (48%) followed by cancer (30%) and GvHD (15%) (fig. 1B). Median survival after HS diagnosis was 58 days and the 1-year overall survival (OS) was 22% (fig. 1C). Treatments most frequently employed, either alone or in combination, were steroids (n = 16), IVIG (n = 7) and Etoposide (n = 7). Etiological anti-infectious or anti-cancer agents were employed alone in 7 patients. Three patients underwent a second allogeneic HSCT that provided long-term rescue in one patient.

Conclusion: Our study, which is to the best of our knowledge the largest series of HS following HSCT reported so far, provides a description of HS as a rare but devastating complication of HSCT associated with an extremely high mortality.

Changes of telomere length reflect the clonal suppression seen with the telomerase inhibitor imetelstat in patients with essential thrombocythemia

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Background and aims: Myeloproliferative neoplasms (MPN) are characterized by cellular proliferation due to a dominant clone defined by a driver mutation, with or without subclones with additional mutations and/or polyclonal hematopoiesis. Due to the loss of telomere sequences with each cell division, in neoplastic cells with a high mitotic rate neoplasms are typically short. In the study with the telomerase inhibitor imetelstat (IM) we demonstrated rapid and durable hematologic and molecular responses (Baerlocher et al. N Engl J Med 2015) and suppression of clones with non-driver mutations in patients (pts) with ET. Our aims were to evaluate telomere length variations (TLV) in MPN pts and in ET pts treated with IM (IM-ET) as well as correlation with hematologic and molecular responses.

Patients and methods: 17 IM-ET pts who were resistant or intolerant to prior therapies and 63 MPN pts (16 ET, 34 PV, 13 MF) untreated or treated with standard of care (SOC-MPN) were analyzed. TLV were measured by automated multicolor flow-FISH.

Results: All IM-ET pts showed low TLV at baseline, with 12 pts below the 10th percentile, and TLV of SOC-MPN pts were around the 90th percentile. The median difference in TLV to the age-related 50th percentile (dTLV) in IM-ET pts was significantly lower than in SOC-ET pts and similar to dTLV of pts with MF. In IM-ET pts with shorter baseline TL, driver mutation burden at baseline was significantly higher (p = 0.03) and best reduction in driver mutation burden was significantly lower (p = 0.03). In 10/13 IM-ET pts, dTLV were higher at best response, reflecting the reduction of neoplastic clones in relation to normal hematopoietic cells. This change of dTLV correlated significantly with the maximum reduction of the JAK2V617F burden (p = 0.0003). Of interest, the 3 IM-ET pts with lower or steady TLV had similar to dTLV of pts with MF. In IM-ET pts with shorter baseline TL, driver mutation burden at baseline was significantly higher (p = 0.03) and best reduction in driver mutation burden was significantly lower (p = 0.03). In 10/13 IM-ET pts, dTLV were higher at best response, reflecting the reduction of neoplastic clones in relation to normal hematopoietic cells. This change of dTLV correlated significantly with the maximum reduction of the JAK2V617F burden (p = 0.0003). Of interest, the 3 IM-ET pts with lower or steady TLV had similar to dTLV of pts with MF.
A prognostic tool for predicting prognosis in early stage chronic lymphocytic leukemia patients

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Introduction: The natural history of Binet A chronic lymphocytic leukemia (CLL) is highly variable, including patients showing progressive disease requiring treatment and cases with an indolent disease for whom a watch and wait approach is recommended. Recently, two prognostic scores (MDAAC-score and CLL-IPI) have been developed to predict prognosis of CLL, though they do not inform the outcome of patients with Binet A CLL. The aim of our study was to perform and validate a model retaining its prognostic value in the subgroup of Binet A patients.

Methods: 637 patients affected by Binet A CLL were included into the study. The dataset was divided into training and validation series. The training cohort included 229 patients prospectively enrolled at the University of Eastern Piedmont (UPO). The validation cohorts included 90 patients retrospectively observed at Oncology Institute of Southern Switzerland (IOSI) and 318 individual patient’s data from the multicenter observational study O-CLL1.

Results: In the UPO training cohort, three independent prognostic variables predicting disease progression (PFS) were identified by the multivariate analysis: IGHV mutational status (HR = 3.6), palpable lymph nodes (HR = 2.4) and lymphocyte count (HR = 2.1). By recursive partitioning, patients concomitantly harboring unmutated IGHV genes and palpable lymph nodes had the highest risk of progression (median PFS, 2.5 years; 5-year PFS, 7%). The model correctly discriminated PFS in 73% of cases (c-index: 0.732) and showed a positive (PPV) and negative predictive (NPV) values for the identification of patients progressing within 5 years of 81% and 80%, respectively. The accuracy of the model was higher than that of the MDAAC-score (c-index = 0.593) and of the CLL-IPI score (c-index = 0.687). The model was validated in the IOSI (c-index = 0.712) and in the O-CLL1 (c-index = 0.660) series.

Conclusion: The presence of unmutated IGHV genes and palpable lymphadenopathy identifies Binet A CLL patients showing a high risk of progression and treatment requirement within 5 years from diagnosis. For this subset of CLL patients, enrollment into early interventional studies may be beneficial.

Disclosures: None.

Pharmacokinetics and pharmacodynamics of LSD following oral administration in healthy subjects

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Background and objective: Lysergic acid diethylamide (LSD) is used recreationally and in clinical research. The aim of the present study was to characterize the pharmacokinetics and exposure-response relationship of oral LSD.

Methods: We analyzed pharmacokinetic data from two published placebo-controlled, double-blind, cross-over studies using oral administration of 100 and 200 µg LSD in 24 and 16 subjects, respectively. Plasma concentrations of LSD, subjective effects, and vital signs were repeatedly assessed. Pharmacokinetic parameters were determined using compartmental modeling. Concentration-effect relationships were described using pharmacokinetic-pharmacodynamic modeling.

Results: Geometric mean (95% confidence interval) Cmax values of 1.3 (1.2-1.9) and 3.1 (2.6-4.0) ng/ml were reached 1.4 and 1.5 h after administration of 100 and 200 µg LSD, respectively. The effects of LSD were related to plasma concentrations of LSD, subjective effects, and vital signs were repeatedly assessed. Pharmacokinetic parameters were determined using compartmental modeling. Concentration-effect relationships were described using pharmacokinetic-pharmacodynamic modeling.

Conclusions: The present pharmacokinetic data are important for the evaluation of clinical study findings (e.g., functional magnetic resonance imaging studies) and the interpretation of LSD intoxication. Oral LSD presented dose-proportional pharmacokinetics and first-order elimination. The data are not applicable to changes in plasma concentrations over time, with no evidence of acute tolerance. The studies were registered at ClinicalTrials.gov (NCT02308999, NCT01878942).

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GABA$_{A}$ subtypes-selective modulation: a novel mechanism-based approach to the treatment of neuropathic pain

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Introduction: Neuropathic pain (NP) affects about 7% of the general population in European countries. Meta-analyses indicate that only a minority of NP patients has adequate response to drug therapy and management of NP is still an unmet medical need. New insights into the contribution of defined subtypes of GABA$_A$ receptors (GABA$_A$ Rs) to the different clinical effects of benzodiazepine (BDZ)s, including analgesia, have suggested that 1-sparing selective BDZs, such as N-desmethylclobazam (NDMC), may be a new realistic alternative for the treatment of NP.

Method: Healthy volunteers, proof-of-concept RCT assessing antihyperalgesic and sedative effects of BDZs on a UVB-induced pain model of central sensitization [1]. Human cell electrophysiology (recombinant GABA$_A$ Rs) and mice behavioral experiments based on a chronic constriction injury model comparing diazepam (DZP), clobazam (CBZ) and NDMC activity profiles [2].

Results: In healthy volunteers, at the time of maximum effect, CBZ and clobazam (CLN) antihyperalgesic effect was greater (vs. placebo) by respectively 15.7% (95% CI 0.8–30.5) and 28.6% (95% CI 4.5–52.6), p < 0.05. Difference (vs. placebo) in sedation (VAS) was only significant for CLN 26.3 mm (95% CI 15.0–37.7), p < 0.001 [1]. In receptor assays, NDMC had a nearly 4-fold over GABA$_A$Rs activity ratio than CBZ and DZP. Unlike DZP, NDMC caused no or modest sedation at antihyperalgesic doses in two strains of wild-type mice [2]. Conclusion: NDMC 0.2/1 mg in 1 vitro activity profile and long term clinical experience from its marketed parent compound (CBZ) make it an advisable clinical candidate for further proof-of-concept assessment in human. Therefore the HUG has manufactured a new chemical entity and initiated a drug development program for NDMC starting with a phase-I trial comparing analgesic and sedative effects of NDMC 20 mg and 60 mg with clonazepam 1.5 mg in healthy volunteers and two phase-I single and repeated dose pharmacokinetic studies.

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Population pharmacokinetics analysis of dolutegravir in HIV-1 infected individuals

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Introduction: Dolutegravir (DTG), the latest integrase inhibitor (INIs) approved for HIV treatment is coformulated in a single tablet regimen with abacavir and lamivudine. DTG has demonstrated potent antiviral activity and a very good tolerability and is widely prescribed in HIV-infected patients (1). DTG is primarily metabolized via UDP-glucuronosyltransferase (UGT 1A1) with a minor component of CYP3A4 (2). The aim of this observational study was to characterize DTG pharmacokinetic profile, to quantify interpatient variability and to identify potential factors that influence drug exposure.

Methods: All dolutegravir concentrations data were collected as part of routine therapeutic drug monitoring performed in our hospital, between June 2014 and December 2015 from HIV treatment-naïve and experienced patients. A population PK analysis was performed by comparing various structural models using NONMEM. The effect of relevant demographic factors and co-medications were on dolutegravir disposition was explored.

Results: A total of 594 plasma levels were measured in 514 HIV-positive patients under stable state regimen conditions. Plasma concentrations ranged between 31 and 7971 ng/mL. A one-compartment model with first order absorption and elimination best characterized dolutegravir pharmacokinetics. Average DTG clearance was 0.93 L/h, volume of distribution 18.9 L, and mean absorption time 1.27 h$^{-1}$. The inter-subject variability on CL was estimated at 27%. Among the demographic covariates tested, body weight and age influenced positively and moderately DTG CL (25% and 24% respectively) as well as smoking status (17%). Coadministration of atazanavir decreased DTG clearance by 38% and the association of darunavir increased the clearance of DTG (14%).

Conclusion: The variability in DTG pharmacokinetics appears lower than for other INIs. Several covariates were identified impacting DTG exposure however their effect appears to be relatively modest and seems not to be clinically significant except for atazanavir coadministration.


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Cost-effectiveness of extended screening and treatment with sofobuvir and ledipasvir using systematic rapid antibody saliva and dried blood spot testing in custodial setting

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Introduction: HCV prevalence amongst prisoners is typically high due to the large proportion of high-risk groups. We explored the cost-effectiveness of expanding hepatitis C virus (HCV) screening and subsequent treatment in Swiss custodial settings, given the availability of rapid antibody saliva tests (Oraquick®) and dried blood spots (semi-quantitative viremia and viral genotype), and recent therapeutic advances which have higher cure rates and shorter treatment courses [1].

Methods: A comprehensive strategy offering screening to all detainees was compared to the current setup of screening high-risk individuals (e.g. from endemic countries, active or former injecting drug users [IDUs]). A decision tree simulated the diagnosis pathway, and results from a Markov model were included to predict treatment effects based on ledipasvir and sofobuvir regimen, and natural progression over a lifetime time-horizon [2].

Deterministic and probabilistic sensitivity analyses were performed to explore parameter uncertainty and whether key input variations changed the cost-effectiveness of comprehensive screening.

Results: At a willingness-to-pay threshold of CHF 100,000 per quality-adjusted-life-year (QALY), comprehensive screening had an 84% probability of being cost-effective, with a corresponding NMB of CHF 33,451,972 and ICER of CHF 7,168/QALY. Results were most sensitive to the respective HCV prevalence in the current and comprehensive screening populations, treatment initiation rates, and screening offer acceptance rates.

Compared to the current practice of screening high-risk individuals, comprehensive screening is likely to be cost-effective due to the increase in testing rates, where we conservatively estimated in this study. Furthermore, comprehensive HCV screening of prisoners may prove more cost-effective in countries where prisoners are not routinely screened.

Conclusions: Comprehensive screening programmes could be considered in prison units with a large proportion of high-risk individuals and where detainees are incarcerated for enough time to complete a treatment course during their sentence.

References

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Novel genetic variants in carboxylesterase 1 predict early-onset capecitabine-related toxicity

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Background: Capecitabine (Cp), an oral prodrug of 5-fluorouracil, is commonly prescribed to treat gastrointestinal and breast tumors. However, dose-limiting adverse effects occur in 20–35% of patients at standard doses, in particular hand-foot syndrome and diarrhea. The aim of this study was to evaluate, for the first time, the association of genetic variability in all enzymes of the Cp activation pathway with early-onset toxicity from Cp-based chemotherapy.

Patients and methods: The coding and exon-flanking regions of the cytidine deaminase gene (CDA) were sequenced in 144 Cp-treated patients, in whom Cp-related toxicities in the first two chemotherapy cycles were recorded. For the other investigated genes (CES1, CES2, TYMP, UPP1, and UPP2), sequencing of coding and exon-flanking regions was performed in a discovery subset of 48 patients (24 with severe Cp-related toxicity, 24 with no or mild toxicity, and 12 non-CD536 carriers) and associated candidate variants were subsequently genotyped in the full cohort.

Results: We identified a haplotype in the carboxylesterase 1 gene (CES1) associated with Cp-related toxicity (OR = 4.3, 95% CI: 1.3-14.2, P = 0.017; and c.1-92A>G: OR = 4.4; 95% CI 1.3-14.5, P = 0.014) with increased risk of Cp-induced diarrhea was replicated.

Conclusions: This is the first study to identify an association of genetic variation in CES1 with Cp-related toxicity. Given that a variant (rs2244613) of the same CES1 haplotype was previously associated with trough concentrations and bleeding from the CES1-metabolized anticoagulant dabigatran, this finding provides evidence for the existence of a common regulatory CES1 variant with possible clinical relevance for carboxylesterase-metabolized drugs.

References

P500

Genetic variants of cytochrome P450 influence pharmacokinetics and pharmacodynamic effects of MDMA in healthy subjects

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Introduction: In vivo and in vitro studies respectively showed that cytochrome P450 (CYP) CYP2D6, CYP2C19, CYP2B6, and CYP1A2 contribute to the metabolism of 3,4-methylenedioxyamphetamine (MDMA, “ecstasy”), but the role of genetic polymorphisms in MDMA metabolism in humans is widely unknown. Therefore, we characterized the effects of genetic variants in the involved CYP enzymes on the pharmacokinetics and pharmacodynamic effects of MDMA.

Methods: The genetic variants in these CYP enzymes were characterized in 139 healthy subjects (69 male, 70 female, aged between 18–45 years) in a prospectively designed pooled analysis of eight double-blind, placebo-controlled, crossover studies. MDMA was administered orally in a single dose of 75 or 125 mg (dose range of 0.8–2.7 mg/kg; mean = 1.7 mg/kg). Blood samples and pharmacodynamic measures were taken repeatedly up to 6 h after drug administration. Subjective effects were assessed using Visual Analog Scales (VAS) including “any drug effect” and “drug liking”. Genomic DNA was extracted from whole blood. Genotyping was performed using TaqMan SNP genotyping assays.

Results: CYP2D6 poor metabolizers (PMs) exhibited increased maximum plasma levels of MDMA (+15%) and of its active metabolite 3,4-methylenedioxyamphetamine (MDA, +50%) compared with extensive metabolizers (EMs), and decreased levels of the inactive metabolite 4-hydroxy-3-methoxyamphetamine (HMMA, –50%). Blood pressure and subjective drug effects increased more rapidly after MDMA administration in CYP2D6 PMs than in EMs. MDMA-EMDA conversion was positively associated with genotypes known to convey higher CYP2C19 or CYP2B6 activities. Additionally, CYP2C19 PMs showed greater cardiovascular responses to MDMA compared with other CYP2C19 genotypes. Furthermore, the maximum concentration of MDA was higher in tobacco smokers that harbored the inducible CYP1A2 rs762551 A/A genotype compared with the non-inducible C/C-carriers.

Conclusion: The findings indicate that genetic polymorphisms in CYP2D6, CYP2B6, CYP1A2, but mainly CYP2D6 contribute to the metabolism of MDMA in humans. Additionally, genetic polymorphisms in CYP2D6 and CYP2C19 may moderate the pharmacodynamics effects of MDMA.

References

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Determination of plasma levels for serotonin, melatonin and their metabolites: analytical validation, normal ranges and circadian variations

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Introduction: Serotonin (5-hydroxytryptamine; 5-HT) is a monoamine derived from tryptophan, best known as an autacoid and neurotransmitter that modulates a wide range of physiological processes. Its multi-step metabolism, including its interconversion into melatonin (involving the pineal gland), has been poorly studied. In this work we developed an analytical method to determine plasma concentrations of 5-HT and of its metabolites: serotonin (5-HT), N-acetylserotonin (NAS), 6-hydroxymelatonin (6-OH Mel), 5-Methoxytryptamine (5-MT), 5-Hydroxyindole acetic acid (5-HIAA),...
5-Methoxyindole acetic acid (5-MIAA), 5-Hydroxytryptophol (5-HTP), 5-Methoxytryptophol (5-MTP). Additionally, these molecules can be sulfo- or and glucuro-conjugated. Our first aim was to determine the physiological range and circadian variability of plasma levels of these metabolites.

Methods: An LC-MS/MS assay for the measurement of free 5-HT and its 8 metabolites in plasma was developed and fully validated. The determination of conjugate forms is underway. In a preliminary study, free 5-HT and its metabolites were measured in 21 healthy volunteers (aged 20 to 54 years, 12 males), over 24 hours. Blood samples were collected every hour between 10 PM and 6 AM in complete darkness, and every 2 hours the rest of the day.

Results: A calibration curve ranging from 0.25 to 400’000 pg/ml was established for each analyte. The assay was found linear within this concentration interval. The sensitivity of the LC-MS/MS assay was dependent on the analyte investigated (0.25 to 390 pg/ml). No carryover was found. Intra- and inter-run coefficients of variation were acceptable (0.5% to 22.7%). Free 5-MT, 5-HTP and 5-MTP remained below the quantification limit. Mean values and SDs were determined for the remaining metabolites at each time point. All metabolites exhibited significant circadian variations over 24 hours, as already known for melatonin, but of less amplitude.

Conclusion: We developed and validated a robust method for measuring serotonin and 8 metabolites in human plasma. The determination of these concentrations will afford a valuable tool for our understanding of pineal and digestive physiology, effects of drugs modulating serotonergic transmission and paraneoplastic manifestations of neuroendocrine tumors. Circadian variations preclude the definition of single normal ranges.

Cross-species comparison study of the in vivo metabolism of the novel investigational anti-tuberculosis agent PBTZ169

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Introduction: PBTZ169 is a drug candidate for treating tuberculosis (TB) with a new and unique mode of action, i.e., it covalently inhibits DprE1, a flavo-enzyme essential for the biosynthesis of key cell wall components of M. tuberculosis [1]. A remarkable in vitro effectiveness has been demonstrated with minimum inhibitory concentration (MIC) values below 0.0005 μg/ml, together with no general anti-bacterial activity [2]. In vitro metabolism studies demonstrated that PBTZ169 undergoes primarily hepatic phase I biotransformation into several metabolites. Moreover, hydroxy- and oxo-metabolites of PBTZ169 have been shown to also possess anti-TB activity in vitro, with apprecicable MIC values. For a comprehensive pharmacokinetic-pharmacodynamic analysis, it is therefore necessary to fully characterize the in vivo profiles of active (and inactive) metabolites of PBTZ169, in various human and non-human species.

Methods: A bioanalytical method employing ultra-high pressure liquid chromatography coupled with tandem mass spectrometry (UHPLC-MS/MS) was developed for the accurate and sensitive quantitation of PBTZ169 together with 6 currently known metabolites (5 active and 1 inactive) in biological fluids (e.g., plasma) from several species (e.g., rodent, dog, human, etc.). Secondly, an untargeted analysis approach using liquid chromatography hyphenated to high-resolution mass spectrometry (LC-HRMS) was applied to in vivo samples for the comprehensive analysis of the metabolites profile of PBTZ169.

Results: Quantitative assays highlighted distinct cross-species differences in the pattern of metabolites profiles of PBTZ169. Moreover, targeted analysis using UHPLC-MS/MS reveals additional chromatographic peaks with consistent kinetics over the dosing interval in the monitored selected reaction monitoring traces. These newly identified PBTZ169 metabolites are additional oxidized species which, together with phase II biotransformation products, are currently being characterized in detail by LC-HRMS.

Conclusion: Overall knowledge about the behavior of PBTZ169 is currently being expanded through this comprehensive characterization and quantification of the in vivo phase I and II metabolite profiles of PBTZ169, in several relevant species, by using a combination of targeted and untargeted LC-MS-based approaches.

References:

Use of antiepileptic drugs during breastfeeding: what do we tell the mother?

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Introduction: Epilepsy affects nearly one in a hundred persons. Its treatment is effective but not without side effects. Epileptic mothers are faced with the question of the possibility of breastfeeding under treatment. Knowledge about the passage of various antiepileptic drugs into breast milk and its consequences for the infant is limited. Faced with this uncertainty, breastfeeding is often discouraged for these patients. The aim of this work is to comprehensively review the available data regarding antiepileptic drugs during breastfeeding, to compare these data with the information provided by the summary of product characteristics (SmPCs), and to provide recommendations for the use of these drugs in breastfeeding women.

Methods: The 23 antiepileptic agents available in Switzerland were included in this study. We performed a systematic review of the literature using Medline and Lactmed. In Medline, the generic name of each antiepileptic drug was associated with the terms ‘Breastfeeding’ or ‘Lactation’ or ‘Milk, Human’. A breastfeeding compatibility score was developed and validated (1 = compatibility established; 2 = likely; 3 = uncertain, requiring surveillance; 4 = rather discouraged; 5 = clearly contra-indicated). The estimated score based on the literature review was compared with the estimated score based on the recommendations provided by the SmPCs.
Results: 75 articles were identified as containing exposure and safety data for 15 antiepileptic agents during breastfeeding. The comparison between the score values based on the literature review and on the SmPCs revealed a very low degree of concordance (weighted kappa: 0.08).

Conclusion: Phenobarbital, primidone, carbamazepine, valproate, and levetiracetam are probably compatible with breastfeeding. Treatment with phenytoin, ethosuximide, clonazepam, oxcarbazepine, vigabatrin, topiramate, gabapentin, pregabalin, lamotrigine, zonisamide may be authorized during breastfeeding. However, breastfed infants should be carefully monitored for side effects. Data on use of mesuximide, clobazam, rufinamide, felbamate, lacosamide, sulfiame, perampanel and retigabine are insufficient to adequately assess the risk for the breastfed infant. The reliability with which the current state of knowledge is reflected in the SmPCs should be improved.

A posteriori percentiles for Therapeutic Drug Concentration Monitoring (TDM)
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Introduction: A population pharmacokinetic model allows reconstructing the predictive distribution of drug concentrations in a population of patients, as a function of time and the dosing regimen. We propose to calculate a posteriori percentiles (i.e. percentiles from the posterior predictive distribution of concentrations) for the rendering of TDM results in a patient for whom past measurements are available. We illustrate the clinical usefulness of such a posteriori percentiles to:
- determine the probability that future concentrations lie within a pre-specified therapeutic range, under either the current or a modified dosing regimen
- detect significant changes in drug disposition, e.g. following drug-drug interactions or malfunction of elimination organs
- identify patient adherence issues

Methods: Considering a population pharmacokinetic model of Voriconazole (Pascal & al. Clin Infect Dis, 2012;55:381-90), a set of 1 to 10 simulated trough concentrations was generated for a fictive patient under different dosing regimens. The distribution of predicted concentrations over the next dosing interval was reconstructed using the model while taking into account past values. This enabled us to assess the expectedness of future measurements in the patient, and the probability of the next trough concentration to lie within the therapeutic range, under different dosing regimens.

Results: Based on 10'000 fictive patients, simulated TDM improved from 50% to 71% the chance of reaching the target therapeutic range of 1.5–4.5 mg/L. Using simulations, we show how the incremental change in percentiles (i.e. percentiles from a posteriori percentile curves) may depict the clinical usefulness of such a posteriori percentiles to:
- assess the expectedness of future measurements in the patient, and
- determine the probability that future concentrations lie within a pre-specified therapeutic range, under either the current or a modified dosing regimen

Conclusions: The financial incentive to market patent-protected drugs is well documented. However, the use of therapeutically equivalent products may be a further step towards individualized drug dosage adaptation.

Experiences and optimisation strategies of medication supply after hospital discharge
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Introduction: The hospital-to-home transition is a vulnerable stage in patient care. Patients might experience problems with medication supply, which possibly lead to therapy interruptions. The objectives of this study were to investigate medication supply after hospital discharge, and patients' and physicians' opinions about optimisations.

Methods: A telephone interview was conducted with 100 discharged patients from the surgical and internal medicine's wards from the cantonal hospital in Baden. Inclusion criteria were: ≥50 years old, patients from the surgical and internal medicine's wards from the cantonal hospital in Baden. Patients were recruited by telephone between the 2nd and 6th day after discharge, and a pitchboard, structured interview on experienced optimisations in the medication supply process took place. Semi-structured interviews were conducted with five physicians. Results from patient interviews and the general discharge process were discussed.

Results: Patients were 65.6 ± 17.4 years old, 39% female, and 53% from the internal medicine's ward, and 97% regularly visit the same pharmacy. At the time of the interview, 77 had their prescription filled. Of these, 78% visited the pharmacy on the day of discharge, but it took up to six days until they received all medication. Supply problems were encountered by 14 of 77 patients (18%), mainly because of medication not being on stock at the community pharmacy. Four patients experienced therapy interruptions for a maximum of three days. Patients discharged from internal medicine's wards had more supply problems compared to surgical wards (relative risk = 5.56, p = 0.007). Patients experiencing supply problems had statistically significant more daily medication intakes (8.0 ± 4.32 vs. 4.9 ± 3.04, p = 0.010). Physicians were surprised about the late prescription filling and worsened about disease outcomes. However, interruptions were interpreted as rare. The strategy to transfer prescriptions from hospital to community pharmacy prior to discharge was refused by 71% of patients and not favourable for the physicians, mainly because of a questionable benefit. But both groups found that bridging supply would be welcome.

Conclusion: This study showed that patients discharged from a Swiss hospital encounter supply problems, but therapy interruptions are rare. Bridging supply was found to be an acceptable intervention. Interventions should consider these opinions and focus on internal medicine patients with a high number of medication.
Due to GI bleeding. Half of the patients (n = 43, 50%) agreed to
admitted to a tertiary hospital and to calculate costs associated with
as it is one of the most often observed ADE. The aim of the study is to
costs. For the present study gastrointestinal (GI) bleeding was selected
are related to ADE and are associated to considerable increases in
Introduction: The oral EGFR tyrosine kinase inhibitor erlotinib is
pharmacokinetics and pharmacodynamics of erlotinib.
Methods: We prospectively included 36 patients with advanced
NSCLC receiving oral erlotinib 150 mg once daily. On day 1 and after
an overnight fast, 2 mg oral midazolam and 100 mg oral caffeine were
administered. Plasma and DBS were collected to determine concentrations of erlotinib, midazolam, caffeine and their metabolites (OSI-420, 1-hydroxymidazolam, paraxanthine) up to 6 hours. Plasma and DBS samples were analyzed using UPLC-MS-MS, and PK data were processed using population modeling.
Results: A high correlation was found between plasma and DBS concentrations for erlotinib (R² = 0.960, P < 0.0001), OSI-420 (R² = 0.971, P < 0.0001), midazolam (R² = 0.995, P < 0.0001) and caffeine (R² = 0.968, P < 0.0001). Individual caffeine clearance was significantly correlated with erlotinib clearance (R² = 0.33, P = 0.048), but midazolam clearance was not (R² = -0.09, P = 0.596). There was a trend for lower erlotinib clearance in patients experiencing grade 2 or 3 skin rash as compared to patients experiencing grade 0 or 1 rash (3.15 vs. 3.93 L/hr, P = 0.086).
Conclusions: Probe drug phenotyping is unlikely to substitute therapeutic drug monitoring of erlotinib in patients with advanced NSCLC, but capillary blood sampling may replace more invasive venous blood sampling to monitor erlotinib concentrations.

Enzymatic pathways metamizole metabolism in humans
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Introduction: Metamizole (dipyrone, Novalgin®) is an analgesic drug used increasingly due to its favorable gastrointestinal and renal tolerability. The major metabolites of metamizole are the non-enzymatically generated methylaminoantipyrine (MAA), aminooantipyrine (AA), formylaminoantipyrine (FAA) and non-enzymatically generated methylaminoantipyrine (MAA), formylaminoantipyrine and methylaminoantipyrine. It is assumed that the metabolism of metamizole takes place in the liver but the CYPs involved are not known. The only identified enzyme in this pathway is N-acetyltransferase 2, which is known to N-acylate AA to AAA. The aim of the present study was to identify the enzyme responsible for the demethylation of MAA to AA.

Methods: MAA was incubated with human liver microsomes (HLM) over 6 hours. Inhibition assays were conducted by adding selective CYP450 inhibitors. CYP substrates were used to proof specific CYP inhibition. Induction assays were performed using HepaRG cells in the basal state and after induction with rifampicin (20 µM for 2 days). Moreover, the metabolism of MAA was investigated in human liver homogenate (HHL). Additionally, MAA was incubated in buffer containing oxidizing enzymes (horseradish peroxidase (HPO), soybean lipoxidase (SLO), human myeloperoxidase (MPO)). Drug concentrations were quantified by LC-MS/MS.

Results: HLM displayed a minor formation of AA (<1%) over 2 hours. Inhibition assays did not reveal a specific CYP for the demethylation. However, the inhibition cocktail reduced the metabolic microsomal activity by half. HepaRG cells treated with rifampicin (inducing CYP3A4, CYP2C8 and CYP3A7) did not show an increase in MAA metabolism compared to basal conditions. Demethylation could also be shown in HHL, whereby the calculated reaction velocity was comparable to the reaction velocity in HLM. Extrapolation of MAA metabolism in HLM or HHL to the entire liver revealed that hepatic metabolism could explain only a minor portion of metamizole metabolism in humans. Interestingly, in the presence of HPO, SLO or MPO, MAA was rapidly metabolized, depending on the peroxidase used and the hydrogen peroxide concentration. Under these conditions, approximately 20% of MAA was demethylated to AA.

Conclusions: Comparison of the in vitro metabolism of MAA with the in vivo pharmacokinetics of metamizole suggests that the liver is not the main location of metamizole metabolism in humans. Our data imply that extrahepatic peroxidases might play an important role in MAA metabolism.
Smarter Medicine Hospital: quantified self
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Introduction: Based on the choosing wisely initiative, corresponding top-five Smarter Medicine Recommendations SMR for Swiss hospitals were published. MIQ data exist with regard to adherence to these key values, however. Tools like big data analytics / data mining based on clinical information systems help to quantify, understand and influence our institutions' processes and thus achieving continuous improvement.

Methods: Retrospective, anonymized, quantitative analysis of all inpatients (Internal medicine) in 2016 concerning key values linked to the top-5 list.

Results: 3’930 inpatients (41% female, average length of stay 6.6 days, mean age 71.3 years) were analyzed. Blood tests: in a cumulative amount of 20’024 inpatient days, 19’116 phlebotomies were performed. This results in 5 blood tests per patient stay (including phlebotomy on admission/ED) or an average of 0.8 blood samples per patient and day. Urinary catheter (UC): 607 (15.4%) received a UC, 41 (1%) already had it on admission. Mean duration of maintenance was 4.8 ± 3.8 days. In 1% of UC patients, nosocomial urinary tract infection was documented. Blood transfusions BT: 408 BT where performed. On average, hemoglobin level prior to transfusion was 74.0 ± 10.3 g/l and 1.6 ± 0.6 red blood cells RBC units were administered. Bed rest: in 3’505 inpatients formal assessments were performed; 159 (4.5%) were initially under bed rest, additional 128 (0.4%) during hospitalization. On average, bed rest was lasted for 2.9 days in patients of causes.

Benzodiazepines: 3’427 patients had at least one drug prescription, both on admission and discharge. 365 (10.7%) had benzodiazepine prescriptions on admission, 373 (10.9%) on discharge. During hospitalization, 1473 (5.3%) out 27’886 on demand prescriptions were benzodiazepines. 628 (43%) where second line prescriptions (given a first line non-benzodiazepine prescription) for sleep disorders. Only 28 (1.9%) had benzodiazepines as first-choice on demand prescription for sleeping disorders.

Conclusion: For a first time, this quantitative assessment with regard to SMR offers both, deep insight into (selectively excellent) adherence to key values as well as a launching point for benchmarking with other institutions and further quality improvements. Information management will play a key role (including correlated data, e.g. diagnoses, co-morbidities, indications) in order to achieve precise decision support, process improvements and increased quality of care at lower costs.

The role of GPs in hospital admissions of terminally ill patients: results from a survey of Swiss GPs
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Background: Hospital admissions of palliative care patients at the end-of-life are considered inappropriate and should be avoided. This study aimed to evaluate the frequency and type of GPs self-reported end-of-life hospital referrals. Further, the association between frequent hospital referrals and referral reasons, confidence in end-of-life care and regional palliative care network were assessed.


Methods: Main outcome measure was GPs assessment of the type and frequency of end-of-life referrals 1–3 weeks before death. The association between hospital admissions frequency and GP characteristics was tested using logistic regression models, controlling for age, gender and regional characteristics.

Results: The questionnaire was completed by 579 Swiss GPs (Response Rate 31%). Thirty-seven percent of GPs reported frequent hospital admissions shortly before death. Logistic regression analysis indicated GPs were less likely to report frequent hospitalizations shortly before death when they felt confident in crisis anticipation (OR = 0.76, 95% CI = 0.60, 0.96), in coping with patient’s wish to die (OR = 0.74, 95% CI = 0.60, 0.91) and in handling spiritual needs (OR = 0.80, 95% CI = 0.68, 0.94). Furthermore, GPs were twice as likely to report frequent hospitalizations because of relatives’ wish (OR = 2.39, 95% CI = 1.90, 3.05), difficult symptom control (OR =2.26, 95% CI = 1.84, 2.81), missing resources of GPs (OR = 2.16, 95% CI = 1.68, 2.80) or small or missing caring network (OR = 2.11, 95% CI = 1.71, 2.63). Intriguingly, GPs were more likely to transfer their patients often to the hospital if GPs used palliative councils often (OR = 1.93, 95% CI = 1.22 3.10).

Conclusions: GPs reporting frequent hospital admissions of palliative care patients at the end-of-life were shown to be less confident in non-somatic palliative care skills, irrespective of age, gender and regional characteristics. Thus, favoring the acquisition of these skills through continuous medical education and providing alternative options to hospitalisation might reduce hospital admissions shortly before death.

Elegibility for PCSK9 inhibitors in the general population
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Introduction: PCSK9 inhibitors are new lipid-lowering drugs recommended for very high-risk patients such as those with familial hypercholesterolemia or cardiovascular disease (CVD) not reaching optimal LDL-cholesterol levels despite maximum dose of statins. Because these news drugs are 40 times more expensive than statins, the societal impact of using these drugs in the general population is uncertain.

Aims: We aim to assess the proportion of patients potentially eligible for PCSK9 inhibitors in the Swiss general population according to the latest 2016 European and American guidelines.

Methods: We studied 4,905 adults aged 35–75 years from the CoLaus study, a prospective population-based cohort in Switzerland, with available lipid measurements both at baseline and at the 5-year follow-up visit. At baseline, the prevalence of patients at very-high risk of CVD was assessed. After 5-years, according to 2016 European Society of Cardiology (ESC) and 2016 American College of Cardiology (ACC) guidelines, we assessed eligibility for PCSK9 inhibitors, defined as unmet LDL-cholesterol goals despite use of rosuvastatin 20 mg, atorvastatin 40 mg or simvastatin 40 mg, assuming a 20% additional reduction of LDL-cholesterol with addition of ezetimibe.

Results: The prevalence of very high-risk patients at baseline was 16.3% (n = 715) respectively 12.3% (n = 604), and after 5 years only 12% (n = 58), respectively 18% (n = 87) reached optimal lipid targets according to ESC, respectively ACC guidelines. Most of very high-risk patients would first need initiation or intensification of statins or ezetimibe, before prescription of PCSK9 inhibitors (see figure).
According to ESC respectively ACC guidelines, 0.2% (n = 9) respectively 4.9% (n = 243) of the general population would be eligible for PCSK9 inhibitors. If initiation or intensification of statins at 5-year would not be possible because of statin intolerance, 1.4% (n = 70) respectively 9.6% (n = 471) would be eligible for PCSK9 inhibitors according to ESC respectively ACC guidelines.

**Conclusion:** A large number of patients at very high-risk for CVD had sub-optimal statin therapy and did not reach optimal lipid targets after 5 years. Although there are large differences of eligibility between European and American guidelines, the amount of prescription of PCSK9 inhibitors in the general population will also depend on the ability to intensify statin use and dosage.

The “Rösti”-Study: a time motion study comparing the allocation of time of internal medicine residents in two Swiss hospitals, a comparison of a Swiss German Cantononal teaching hospital with a university hospital in the French speaking part

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**Background:** Several factors, such as cultural habits, type of hospital (university vs. non-university), local organization and practice (number of patients per resident) and resident characteristics may influence residents’ time allocation. We thus actualised and work role transition frameworks.

**Methods:** Two different time motion studies were performed in the departments of internal medicine of CHUV and KSB. Trained observers recorded residents’ activities during day shifts. To ensure comparability, the same study protocol, tablet-based software and instruction manual were used. Out of 22 recorded activities, we selected for comparison: activities directly related to patients, documentation, supervision, personal time and direct patient contact.

**Results:** The time spent per patient per day was calculated based on patient-equivalents. One patient-equivalent was defined as the presence of a patient during the whole observed shift of an individual resident. We compared mean values using the two-sided, unpaired t-test.

**Results:** Comparison of time spent in different activities.

<table>
<thead>
<tr>
<th>Activity</th>
<th>CHUV</th>
<th>KSB</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total time spent with patients</td>
<td>94.9</td>
<td>91.3</td>
<td>0.015</td>
</tr>
<tr>
<td>Activities directly related to patient*</td>
<td>332.0</td>
<td>321.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Time with communication</td>
<td>29.1</td>
<td>30.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Delivery of results, decision</td>
<td>9.9</td>
<td>9.3</td>
<td>0.0007</td>
</tr>
<tr>
<td>Communication with family</td>
<td>15.8</td>
<td>15.9</td>
<td>0.84</td>
</tr>
<tr>
<td>Documentation</td>
<td>100.9</td>
<td>100.5</td>
<td>0.97</td>
</tr>
<tr>
<td>Writing in EMR</td>
<td>72.5</td>
<td>72.2</td>
<td>0.93</td>
</tr>
<tr>
<td>Discharge letter</td>
<td>4.5</td>
<td>5.6</td>
<td>0.0007</td>
</tr>
<tr>
<td>Transmission</td>
<td>32.4</td>
<td>31.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Supervision</td>
<td>60.3</td>
<td>58.1</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Results:** Baseline characteristics of residents are shown in table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CHUV</th>
<th>KSB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.9</td>
<td>30.9</td>
</tr>
<tr>
<td>Months postgraduate training</td>
<td>21.2</td>
<td>20.9</td>
</tr>
<tr>
<td>Months experience in internal medicine</td>
<td>16.6</td>
<td>16.1</td>
</tr>
<tr>
<td>Swiss diploma</td>
<td>66.7%</td>
<td>68.5%</td>
</tr>
<tr>
<td>Female gender</td>
<td>57.3%</td>
<td>61.5%</td>
</tr>
</tbody>
</table>

**Results:** KSB residents had a shorter post-graduate training (21 vs 31 months, p < 0.001). Residents were observed during 486.4 hours (43 shifts) in KSB vs 568.9 h (49 shifts) in CHUV. Mean shift duration was similar (11.3 ± 1.1h in KSB vs 11.6 ± 1.3h in CHUV, p = 0.19). Mean patient-equivalent was 7.4 ± 1.0 in KSB vs 7.8 ± 2.3 at CHUV (p = 0.27).

**Results:** How well are Swiss French-speaking physicians prepared for independent practice in ambulatory general internal medicine?

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**Introduction:** Moving from training to independent practice represents a major transition in professional life. The aim of this study was to explore the extent to which Swiss general internists who recently set up private practice felt prepared to work as independent physicians.

**Methods:** We conducted focus groups among a sample of physicians practicing as general internists (FMH) for 5 years in different working contexts of the French speaking part of Switzerland. Questions focused on positive and negative aspects of setting up a practice, degree of preparedness, strengths and weaknesses of postgraduate training. Transcripts were analysed according to dimensions described in organisational socialisation frameworks.

**Results:** 28 physicians from 5 cantons participated in 7 focus groups: 1/3 trained exclusively in academic settings, most worked in an urban or suburban area and predominantly in small group practices. Most positive reported elements of setting up practice referred to notions of freedom, autonomy and mastery, and physician patient relationships while negative reported elements referred to feelings of stress and loneliness related to non-clinical tasks such as administrative, financial and time management as well as medico-legal issues for which all participants felt both incompetent and unprepared. Although physicians felt adequately prepared to perform most medical tasks, they reported discomfort in dealing with common problems in rheumatologic, minor traumatology, ENR, skin and psychiatric problems in all contexts and in paediatrics, gynaecology, as well as surgical skills if working in rural areas. Several participants reported not having anticipated the importance of having a network of specialists once in independent practice. They also described several practice-based ethical dilemmas opposing professional values to reality of practice (freedom, autonomy, altruism versus work-life balance, practice business management and patient accountability) which forced them to clarify their professional roles and expectations.

**Conclusion:** Postgraduate training in ambulatory general internal medicine could be further improved to better support the reality of transition. More emphasis should be put on learning and teaching in the environment for which physicians are being prepared, especially during the last years of training.
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Undernutrition is associated with increased financial losses in hospitals

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**Background and aims:** Undernutrition is associated with increased hospital costs. Whether these increased costs are totally compensated by third-payer systems has not been assessed. We aimed to assess the differences between actual and reimbursed hospital costs according to presence/absence of nutritional risk, defined by a Nutritional risk screening-2002 (NRS-2002) score ≥3.

**Methods:** Retrospective study using administrative data for years 2013 and 2014 from the department of internal medicine of the Lausanne university hospital. Total and specific costs (i.e. related to treatments, medical interventions, imaging, laboratory analyses, food, intensive care units…) were obtained. Reimbursed costs were based on the Swiss Diagnosis Related Group (DRG) system and we considered 1 DRG point = 10’500 CHF (average value for 2014). Coverage of the costs was computed as the ratio costs/reimbursements and expressed as percentage, and further categorized as complete (≥100%) or less than complete (<100%).

**Results:** 2200 admissions with NRS-2002 data were included (mean age 76 years, 53.9% women), 1398 (63.6%) of which were considered nutritionally ‘at-risk’. After multivariate adjustment, patients nutritionally ‘at-risk’ had higher costs (multivariate-adjusted difference ± standard error: 34’206 ± 1246 vs. 22’214 ± 1666 CHF, p <0.001) and higher reimbursements (26’376 ± 1105 vs. 17’783 ± 1477 CHF, p <0.001) than patients ‘not at risk’. Still, reimbursements failed to cover the costs, leading to an average deficit of 7831 ± 660 CHF in patients ‘at-risk’. vs. 4431 ± 881 in patients ‘not at-risk’ (p <0.003). Being nutritionally ‘at-risk’ also led to a lower likelihood of complete coverage of costs: multivariate-adjusted odds ratio and 95% confidence interval 0.77 (0.62–0.97), p <0.05. Patients ‘at-risk’ had lower percentage of total costs in medical interventions, food, imaging and “other”, but the absolute differences were less than 2%.

**Conclusion:** Hospital costs of patients nutritionally ‘at-risk’ are less well reimbursed than of patients ‘not at-risk’. Better reporting of undernutrition in medical records and better reimbursement of undernourished patients is needed.

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Should thyroid tests be performed to investigate the causes of anaemia? A large population-based study

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**Introduction:** A relationship between overt thyroid dysfunction and anaemia is commonly mentioned, but limited data are available on the association with subclinical thyroid dysfunction. In a large population-based cohort, we aimed to quantify the effect of thyroid function on haemoglobin concentration (Hb) and to study the association with anaemia.

**Methods:** We analysed participants from the EPIC-Norfolk cohort with thyroid stimulating hormone (TSH), free thyroxine (FT4) and Hb measured at baseline and follow-up. Hypothyroidism was defined as TSH ≥4.40 mIU/L, either subclinical (SHypo) with normal FT4 or overt (OHypo) with low FT4. Hyperthyroidism was defined as TSH <0.45 mIU/L, either subclinical (SHyper) with normal FT4 or overt (OHyper) with elevated FT4. Euthyroidism was the reference category (normal TSH, normal FT4). Anaemia was defined as Hb <12 g/dl for women and <13 g/dl for men. In the cross-sectional analysis, we used multiple linear regression to compare Hb across the TSH categories and logistic regression to analyse the association between thyroid dysfunction and anaemia.

**Results:** In the cross-sectional population (n = 12,337), the mean age was 59 years and 53.1% were women. 11,174 (90.6%) participants were euthyroid and had a mean Hb of 13.9 g/dl. No relevant differences in Hb were observed among TSH categories. In multivariable analyses, Hb was 0.23 g/dl (95% CI: 0.40 to 0.06) lower in OHypo, and 0.40 g/dl (95% CI: 0.78 to 0.01) lower in OHyper than in euthyroidism. In the logistic regression, OHypo was associated with anaemia (adjusted OR 1.89, 95% CI 1.23–2.88), OHyper showed a borderline association (adjusted OR 2.16, 95% CI 0.94–4.95) whereas no association was found in SHypo/SHyper. In the longitudinal analysis, 460 of 7031 participants (6.5%) developed anaemia during a follow-up of 55,733 person years (median 4.7 years). When we compared SHypo/SHyper to euthyroidism, the adjusted hazard ratio of anaemia was 1.01 for SHypo (95% CI 0.68–1.51) and 0.52 for SHyper (95% CI 0.23–1.18). Results were similar in all sensitivity analyses.

**Conclusion:** Considering the minimal changes in Hb among the TSH categories and the lack of prospective association between thyroid dysfunction and anaemia, in our study subclinical thyroid dysfunction does not seem to be an independent risk factor for the development of anaemia.

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Introduction of an organised programme and social inequalities in mammography screening: a 22-year population-based study in Geneva, Switzerland

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**Introduction:** Generalisation of mammography screening contributed, at least in part, to the decrease in breast cancer mortality in developed countries. The implementation of an organised programme has been suggested to increase screening participation and reduce social disparities in screening access. We aimed to describe the evolution of socioeconomic inequalities in mammography screening before and after the introduction of an organised programme in Geneva, Switzerland.

**Methods:** We included 5345 women with no past history of breast cancer, aged 50–74 years and who participated in the cross-sectional Bus Santé study, between 1992–2014. Outcome measures were:

- a) never had a mammography (1992–2014) and b) never had a mammography or not in the two years before survey (subgroup analysis, 2007–2014).

We divided educational attainment in 3 groups.
(primary, secondary and tertiary) and considered two periods - before the introduction of screening programme in 1999 and after. We calculated the relative (RII) and slope (SII) indexes of social inequality, which measure the relative and absolute inequalities between the different educational levels, respectively. We used Poisson models to compare screening prevalence before and after screening programme implementation.

Results: We observed a decrease in the proportion of unscreened women during the study period from 30.5% to 3.6%. Lower educated women more probably never had a mammography (RII = 2.39, p < 0.001; SII = 0.10, p < 0.001). Implementation of an organised screening programme coincided with a decrease in the proportion of unscreened women independently of educational attainment (prevalence ratios were reduced; however, vs. after: RII = 4.41, p < 0.001). However, both absolute and relative inequalities persisted (RII = 2.11, p = 0.01; SII = 0.04, p = 0.01).

Conclusion: Introduction of an organised programme increased participation but was not sufficient to eliminate socioeconomic disparities in breast cancer screening.

Diagnosis of acute myocardial infarction in patients presenting with left bundle branch block

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Introduction: Patients with suspected acute myocardial infarction (AMI) in the setting of left bundle branch block (LBBB) present an important diagnostic and therapeutic challenge to the clinician, highlighted by divergent recommendations given by the respective guidelines in the United States and Europe. It is currently unknown, whether patients presenting with acute chest pain and new/ presumably new LBBB should also receive immediate coronary angiography and/or thrombolysis such as those with clear ST-segment elevations.

Methods: We aimed to prospectively evaluate the incidence of AMI, and the diagnostic performance of selected ECG criteria and high-sensitivity cardiac troponin (hs-cTn) T and I among 8830 patients presenting with symptoms suggestive of AMI to the emergency department. Presence of LBBB, ECG criteria (Sgarbossa, Smith, Selvester), and final diagnoses were adjudicated by independent cardiologists. Findings of the derivation cohort (n = 4015) were validated in two external cohorts.

Results: In the derivation cohort, LBBB was present in 140 patients (3.5%). AMI was the adjudicated final diagnosis in 32% of patients with LBBB, with similar incidence in those with known LBBB versus those with presumably new LBBB (29% vs 35%, p = 0.42). ECG criteria had modest accuracy (64–71%), low sensitivity (2–18%), and high specificity (94–100%) for AMI. Diagnostic accuracy of hs-cTnT and hs-cTnI at presentation as quantified by the area under the receiver-operating characteristics curve was very high (0.91; 95%CI 0.85-0.96).

Conclusion: Guidelines calling for immediate invasive procedures in patients with LBBB should be reevaluated. Specific ECG criteria and suggested (h)s-cTn thresholds allow an accurate and immediate triage to coronary angiography in patients with LBBB and symptoms suggestive of AMI (fig. 2).

Interventions recommended to prevent, manage and treat compassion fatigue: a systematic review of the literature

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Background: In healthcare and social professions, compassion fatigue (CF) is a term used to refer to a state of advanced and profound exhaustion and distress resulting from the repeated empathic and compassionate engagement with traumatised and suffering populations. This study provides a critical appraisal and review of the existing recommendations to prevent, manage and treat CF.

Methods: Five electronic databases (Medline/Pubmed, Embase, Web of Science, CINAHL plus and PsycINFO) were consulted. Because of the conceptual ambiguity of CF, the first search strategy was to identify articles published between January 1980 to March 2016, in English or in French, using the term “CF” and the terms that were used interchangeably with it in the literature (namely “secondary traumatic stress” and “vicarious traumatisation”). The second search strategy was to identify and review published articles containing suggested strategies and interventions for combating CF. The literature search was completed by hand searching reference lists. Each of the articles was analyzed in detail using an evaluation form. Duplicate papers, papers which did not provide an abstract, and papers that were not related to the topic of this study were removed (see fig. 1).
Results: Fifty published original articles met the inclusion criteria: three articles were systematic literature reviews, seven were experimental studies, six were descriptive studies, seven were qualitative studies, two were mixed method studies, and twenty-five were evidence based on the authors’ opinion. The analysis of the articles suggested that CF can be combated among helping organisations and professionals, which requires increasing their (self-) awareness of occupational hazards through education, debriefings and supervisions, and equipping them with adequate knowledge and skills that will enhance their coping and resiliency resources. It also requires developing and nurturing self-care and self-management strategies, and promoting organisational and structural changes that will mitigate work environment constraints (see fig. 2).

Conclusions: CF can be combated among helping organisations and professionals. Additionally, combating successfully CF may also require redefining our own perceived role and missions as a helping professional, including changes in our ways and levels of expectation to fulfil them.

No association between grip strength and cardiovascular risk; the CoLaus population-based study
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Background: Low grip strength (GS) is predictive of cardiovascular (CV) disease but whether it improves CV risk prediction over existing CV risk scores has not been evaluated. We assessed the predictive value of low GS on incident CV events taking into account several CV risk equations in a Swiss population-based study.

Methods: 2707 adults (54.8% women, age range 50–75 years) were followed for a median time of 5.4 years. GS was assessed using a hydraulic hand dynamometer. Low GS was defined according to Fried criterion. CV absolute risk at baseline was assessed using recalibrated risk equations in a Swiss population-based study.

Results: 188 incident CV events occurred during follow-up. The unadjusted positive association between low GS and incident CV events disappeared after adjusting for CV absolute risk (table).

Conclusion: Low GS is not predictive of incident CV events when taking into account CV absolute risk.

Table: Association grip strength and CV events.

<table>
<thead>
<tr>
<th>Hazard Ratio [95%CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.76 [1.13–2.76]</td>
</tr>
<tr>
<td>Adj. for SCORE</td>
<td>1.23 [0.79–1.94]</td>
</tr>
<tr>
<td>Adj. for Framingham 2001</td>
<td>1.34 [0.86–2.10]</td>
</tr>
<tr>
<td>Adj. for PROCAM 2007</td>
<td>1.47 [0.94–2.31]</td>
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POSTERTOUR 1: MÉDECINE INTERNE GÉNÉRALE II / ALLGEMEINE INNERE MEDIZIN II

Try hard to reconcile the medication upon admission in a tertiary internal medicine department
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Background: Medication discrepancies largely arise due to communication issues at transition steps. Up to 70% of patients have at least one discrepancy between regularly taken drugs and hospital-prescribed drugs. A lack of accuracy in medication history is responsible for 50% of medication errors and for 20% of adverse drug effects occurring in hospitals. We aimed to assess the feasibility of a medication reconciliation process upon admission.

Methods: Within the national initiative of Patient Safety Switzerland, we developed our process from own expertise and literature. Interns were trained to collect two different sources of information (medical and practical) and confront them within a structured interview with the patient, which included questions about allergies and over-the-counter drugs. We developed a electronic medical record (EMR) form to support the process. The nurses provided the practical source (i.e pillbox). We included all consecutive patients admitted in two unit of the internal medicine during one year. Exclusion criteria were age <65 years and not being directly admitted from home. Interns were asked if the reconciliation would have clinical significance (yes or no) and to assess the time spent on a 5-step scale.

Results: Starting November 2015, 1,155 admitted patients were screened. 621 were excluded because of age (n = 369), not directly admitted from home (n = 243), or lost follow-up (n = 9). Of the 534 included patients, 62% were females. Average age was 80.4 (SD ± 8.0) years. Interns performed 302 reconciliations (56.9%). Average delay until completion was 37.7 (SD ± 59.2) hours after admission. Interns assessed 54% of reconciliations as useful (116/213 answers);

Conclusions:

1) the difficulty to get information from partners delays the reconciliation; 2) a high rate of reconciliation needs training and support of interns; 3) a good EMR is the key tool for an efficient reconciliation.
Conclusions: Despite subjective benefit, medication reconciliation performed by the physicians alone is time-consuming and barely feasible without added resources. Wide implementation is desirable but needs to be supported by good IT tools, active participation of other caregivers, and might have to be restricted to high-risk patients.

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Integrative hospital treatment in older patients to benchmark and improve outcome and length of stay – the In-HospiTOOL study – a quasi-experimental, multicenter comparative effectiveness health care research trial

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Introduction: Health care costs are high and rising also due to an aging, polymorbid population, why resource allocation becomes a priority. There is lack of evidence-based tools namely for polymorbid patients to improve integrative in-hospital care and transition process in an acute care hospital setting. Also, there is no reference standard for quality benchmarking in Switzerland which is mandatory to compare quality of care of different institutions. To address these issues, we propose a multicenter “before-and-after” trial to study the effect of an inter-professional inpatient management tool on length of stay and other patient-centered outcomes.

Methods: In-HospiTOOL combines several patient discharge measures and was developed involving multiple professions. An electronic monitoring and reporting system enables clinical user oriented benchmarking to assess hospital processes, quality, delays in hospital transition and barriers for discharge stratified by profession. For external multicenter validation, In-HospiTOOL will be implemented in five Swiss secondary and tertiary care hospitals. We will use a quasi-experimental approach and compare length of stay before and after hospital-wide implementation of the tool in relation to changes in length of stay in hospitals not using the tool (time-trend analysis with data from other Swiss hospitals provided by the Swiss Federal Office of Health serving as controls).

Expected results: We expect a total inclusion rate of 45'000 patients across all three 6-month study periods (observation, implementation, intervention). Based on our monocentric experience we expect the In-HospiTOOL to have a strong effect on inter-professional team work in this polymorbid setting which results in reduction in length of stay of at least 1 day. We also expect that patient outcomes are not negatively affected by the intervention (e.g. intensive care unit admission, mortality, unplanned readmission, patient satisfaction). A safe reduction of length of stay will have positive implication on overall hospital costs.

Conclusion: The trial will yield concise information on whether and how the “In-HospiTOOL” improves inter-professional team work and thereby reduces length of stay without negatively impacting subjective and objective markers of patient outcomes. The large amount of collected patient data will enable comparison of transition processes within different hospitals and establish a benchmarking for patient care quality.

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Students’ implication in faculty development programs contributes to their development of professional identity

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Background: Medical students develop their professional identities through various activities and relationships within different settings. As students are being increasingly involved as simulated learners in their actual and projected professional identity development (PID).

Methods: A Faculty development program was developed at the Geneva University Hospitals (Switzerland) to train faculty members from five departments (including hospital and ambulatory general internal medicine) in clinical teaching skills on domains such as clinical reasoning, communication, professionalism, and inter-professional collaboration. Medical students who participated in OSTEs were invited to take part into focus groups. They were asked about what they learnt and how this experience influenced their vision of being a student, resident, and supervisor. Discussions were analysed using a framework based on personality and social structure perspectives (PSSP model).

Results: Focus groups took place with 25 medical students from 4th to 6th years. PID emerged at three levels. On the institutional level, having the opportunity to take part into clinical supervisors’ training helped students develop a professional identity outside the clinical settings and allowed them to enter further into the community of practice. On the interactional level, students realised they could become actors of change by actively seeking or giving feedback. On the personal level, they discovered that mistakes could become sources of learning rather than blaming and felt better prepared to cope with faculty feedback. Finally, they realised that being a medical supervisor was about mastering medical and teaching competences.

Discussion: Taking part in OSTEs can have a positive impact on students’ perceptions regarding the institution as a learning environment, their role as actors of change and their own position towards mistakes. Including students’ participation in OSTEs seems to be a way to support their PID while sustaining faculty development.

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Frequency of use and acceptability of clinical prediction rules for pulmonary embolism among Swiss general internal medicine residents

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Background: Whether the Revised Geneva Score (RGS) and the Pulmonary Embolism Severity Index (PESI), two well validated and recommended clinical prediction rules (CPRs) for pulmonary embolism, are used in clinical practice is unknown.

We evaluated the frequency of use, the acceptability among clinicians, and which factors drive the use of the RGS and the PESI.

Methods: We conducted an online survey among Swiss general internal medicine residents from five university and non-university hospitals in July 2016 to examine the frequency of use of the RGS and PESI. We assessed rule acceptability using the 12-item Ottawa Acceptability of Decision Rules Instrument (OADRI). Each item is rated on a 6-points scale, 0 points indicating a low and 6 points a high acceptability. We further explored the association between physician and educational factors and rule use using a mixed logistic regression model.

Results: The response rate was 433/859 (50.4%). Overall, 61% and 35% of the residents indicated that they always or regularly use the RGS and the PESI, respectively. The mean overall OADRI score was 4.3 points for the RGS and 4.1 points for the PESI, indicating good overall rule acceptability among practitioners. The OADRI suggests that both the RGS and the PESI to be easy to use (mean score for the RGS 5.4 points; mean score for the PESI 4.7 points) and to have a clear wording (RGS 5.1; PESI 4.7), but not to be easy to remember (RGS 3.8; PESI 3.0), Rule acceptability (odds ratio [OR] 5.71 per score point, 95% confidence interval [CI] 3.34–9.76), prior training in the emergency department (OR 4.96, CI 2.09–11.76), number of years since graduation (OR 1.37 per year, CI 1.04–1.80), availability of internal guidelines recommending RGS use (OR 4.15, CI 2.05–8.36), and your education (OR 0.83 per one-year increase, CI 0.72–0.96) increased the odds of using the RGS. Rule acceptability (OR 6.27 per score point, CI 4.04–9.73), learning of the rule during medical school (OR 2.06, CI 1.22–3.48), and younger age (OR 0.83 per one-year increase, CI 0.72–0.96) increased the odds of using the PESI.
Use of strong opioids in cancer and non-cancer pain in a Swiss population

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Oscar Reich1, Johann Steurer4, Jakob M. Burgstaller5
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Introduction: Globally, opioids are increasingly used for non-cancer pain. In Switzerland, the use in strong opioids more than doubled between 2006 and 2013. Studies suggest that the use of opioids in a daily morphine equivalent dose (MED) of 100 mg or more is associated with an increased risk of potential serious side effects. The objectives of this study were twofold: 1) to assess the use of opioids for cancer and non-cancer pain in a Swiss population; 2) to assess in non-cancer pain patients the proportion of opioid use at a daily MED dose of 100 mg or more.

Methods: Analysis of insurance claims for opioids between 2006 and 2014 from one of the major health insurers in Switzerland covering 1.2 million individuals (approximately one-sixth of the Swiss population). Included were patients with at least one opioid prescription claim. Strong opioids used in drug substitution programs were excluded. All opioids were converted into mg MED. Opioid use was divided into cancer and non-cancer diagnosis using the Anatomical Therapeutic Chemical (ATC) drug classification and predefined Tarmed positions.

Results: Overall, we analyzed 597,536 episodes (94% non-cancer diagnoses, 6% cancer diagnoses) of opioid use in 576,664 patients. In 207,344 episodes (152,493 patients) more than one opioid claim was reimbursed: 90.8% of these were used for non-cancer diagnosis, in 9.2% for cancer diagnoses. More than one opioid claim for strong opioids was found in 78,431 episodes (66,440 patients); in 17.2% for cancer diagnoses, 82.8% for non-cancer diagnoses. In non-cancer episodes, treatment duration was mostly less than 90 days (82%) and mostly at a dose of less than <20 mg MED. In 15% of the episodes a chronic opioid use was found. Of the patients taking opioids at a maximum dose of 100 mg and more, 56% were chronic opioid users (fig. 1).

Conclusion: The analysis of opioid use in a Swiss population showed that opioids were mainly used for non-cancer diagnoses. Further, a small population potentially at risk for opioid related serious adverse events was identified.
Methods: We conducted 62 semi-structured interviews with randomly selected residents, fellows, nurses, nurse managers, and nursing assistants across four departments of the Geneva University Hospitals: internal medicine, family medicine, pediatrics, and surgical units. Interviews focused on sources, consequences, and responses to conflicts. Content analysis enabled us to identify features characterizing conflicts. Descriptive and inferential statistics were used to compare the features between intra- and interprofessional situations.

Results: Of the 130 situations of conflicts shared by participants, 57% were intra-professional and 43% were interprofessional. Regarding sources of conflicts, relationship difficulties caused more intra- than interprofessional conflicts (62% vs 41%, P = 0.02), whereas disagreements on patient-related tasks (27% vs 48%, P = 0.02) and general perceptions of a group vis-à-vis another group (3% vs 27%, P < 0.001) generated more interprofessional conflicts. There were no significant differences between intra- and interprofessional conflicts for most consequences, except for professional mobility, which tended to be affected by inter-professional conflicts (20% vs 9%, P = 0.09). Individuals involved in intra-professional conflicts tended towards denial and avoided actively managing conflicts (47% vs 30%, P = 0.07). For other responses, differences between intra- and interprofessional conflicts were not significant.

Conclusion: There are differences between intra- and interprofessional conflicts, particularly for conflict sources. These differences suggest that interprofessional education would benefit from integrating situations that focus on collaborative patient care. The similarities we observed between intra- and interprofessional conflicts in terms of consequences and responses to conflicts evidence the need to focus on a variety of situations, relationships, and professional roles that reflect clinical settings when designing educational interventions.

Caring for chronic wounds: a pilot survey of knowledge, attitude and beliefs of internal medicine house staff

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Objective: Assess house staff (HS) knowledge, attitude and perceptions regarding chronic wounds and their treatment.

Methods: Pilot study among 171 HS in general internal medicine post-graduate training who were invited by email to complete an online web-based questionnaire in January 2017. Results: We received 50 responses (29% participation rate). Nearly all responders (92%) had managed chronic wounds during the prior month. 64% had dealt with issues related to wounds at least 10 times since graduation and all felt this would recur in their future careers. For 56% of them, this represented a major real public health issue. 52% of responders did not feel confident managing chronic wound, specifically with regards to choice of dressing, pressure relief, debridement, probe to bone test, arterial assessment or restraint use. They were more comfortable recognizing etiology, infection and factors that may delay healing. 59% reported lack of practical training and 4% lack of interest. 92% received less than 10 hours of undergraduate teaching about chronic wounds and 90% wished for further training. 61% of HS felt that the choice of dressing was "very important" and 35% considered it to be "vital". Nearly all (98%) trusted nurses to select local treatment. 77% of HS were in favor of using a smartphone application to support wound management and 90% felt telemedicine could also be helpful. Potential wound management barriers were, by decreasing frequency: lack of training, the diversity of wounds, lack of consensus, multidisciplinary approach, the workload, the off-putting appearance of wounds and discouraging prognosis.

Conclusion: Our data suggest that many junior house staff in internal medicine do not feel confident with chronic wound management and wish for more training in this area which they consider a frequent problem and a major public health issue. This statement of needs, paves the way for a larger study designed to confirm these preliminary findings and to identify ways to improve the training in chronic wound management.

Cardiovascular disease risk factors among male youths in Southern Switzerland: a transversal study

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Introduction: Cardiovascular diseases, first cause of death in Switzerland, are frequently attributable to risk factors already present in children and adolescents. The aim of this study was therefore to describe the prevalence of cardiovascular disease risk factors in 18- to 20-year-old males undergoing medical examination to assess fitness to be affected by intra-professional conflicts (20% vs 9%, P = 0.09). Individuals involved in intra-professional conflicts tended towards denial and avoided actively managing conflicts (47% vs 30%, P = 0.07). For other responses, differences between intra- and interprofessional conflicts were not significant.

Conclusion: There are differences between intra- and interprofessional conflicts, particularly for conflict sources. These differences suggest that interprofessional education would benefit from integrating situations that focus on collaborative patient care. The similarities we observed between intra- and interprofessional conflicts in terms of consequences and responses to conflicts evidence the need to focus on a variety of situations, relationships, and professional roles that reflect clinical settings when designing educational interventions.

Methods: We conducted 62 semi-structured interviews with randomly selected residents, fellows, nurses, nurse managers, and nursing assistants across four departments of the Geneva University Hospitals: internal medicine, family medicine, pediatrics, and surgical units. Interviews focused on sources, consequences, and responses to conflicts. Content analysis enabled us to identify features characterizing conflicts. Descriptive and inferential statistics were used to compare the features between intra- and interprofessional situations.

Results: Of the 130 situations of conflicts shared by participants, 57% were intra-professional and 43% were interprofessional. Regarding sources of conflicts, relationship difficulties caused more intra- than interprofessional conflicts (62% vs 41%, P = 0.02), whereas disagreements on patient-related tasks (27% vs 48%, P = 0.02) and general perceptions of a group vis-à-vis another group (3% vs 27%, P < 0.001) generated more interprofessional conflicts. There were no significant differences between intra- and interprofessional conflicts for most consequences, except for professional mobility, which tended to be affected by inter-professional conflicts (20% vs 9%, P = 0.09). Individuals involved in intra-professional conflicts tended towards denial and avoided actively managing conflicts (47% vs 30%, P = 0.07). For other responses, differences between intra- and interprofessional conflicts were not significant.

Conclusion: There are differences between intra- and interprofessional conflicts, particularly for conflict sources. These differences suggest that interprofessional education would benefit from integrating situations that focus on collaborative patient care. The similarities we observed between intra- and interprofessional conflicts in terms of consequences and responses to conflicts evidence the need to focus on a variety of situations, relationships, and professional roles that reflect clinical settings when designing educational interventions.

Figure 1: Confidence range regarding chronic wound.

Conclusions: Our data suggest that many junior house staff in internal medicine do not feel confident with chronic wound management and wish for more training in this area which they consider a frequent problem and a major public health issue. This statement of needs, paves the way for a larger study designed to confirm these preliminary findings and to identify ways to improve the training in chronic wound management.
Detection of atrial fibrillation with a smartphone-App – study design and methods of DETECT AF pro trial

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“Preventicus,” Jena; “Department of Internal Medicine, University Hospital Regensburg, Regensburg; “Department of Internal Medicine, University Hospital Greifswald, Greifswald, Germany

Introduction: Detection of silent atrial fibrillation (AF) is challenging but of pivotal importance particularly in stroke prevention. Recent studies confirmed the merits of long-term monitoring. Nevertheless, currently available diagnostic tools are burdened with disadvantages in that they are inconvenient, costly and/ or invasive. The prospective DETECT AF pro trial aims to verify the accuracy of a new diagnostic tool using a smartphone-App (“Preventicus®”) Heartbeats. In a predecessor study (DETECT AF) we tested the same App employing photoplethysmographic (PPG) signals of a smartphone camera to distinguish between AF and sinus rhythm (SR). In that retrospective study the App reached a sensitivity and specificity of 95% (Krivoshei et al., Europace 2016).

Study design: Prospective, blinded, multicenter, international study, inclusion criteria: Subjects of legal age, with SR or AF, informed consent – exclusion criteria: Legally incompetent persons, pacemaker rhythm AF Group: Group of patients with atrial fibrillation SR Group: Age- and gender-matched patients with sinus rhythm Data is blinded to the analysing researcher and will be evaluated and monitored externally. 660 subjects will be recruited until February 2017.

Methods: The subjects place the camera of a smartphone (iPhone 4s, Apple, CA, USA) on their index finger for 5 minutes to allow the recording of a PPG signal (pulse wave). During this recording the finger is illuminated by the integrated LED-light. A single lead ECG is recorded (Kardia, AliveCor, USA) as a reference. Per-relevant data including comorbidities and medication are collected. The pulse wave curve data are coded with the patient’s ID and analysed by “Preventicus®” in a blinded fashion; files of the patients will be assigned to the App or AF. The ECGs will be analysed by cardiologists other than the researcher in a blinded fashion and assigned to SR or AF as well. Results will then be aggregated, unblinded and merged under monitoring. Primary target parameters are the App’s sensitivity and specificity for detecting AF compared to a standard ECG interpreted by a cardiologist. Secondary target parameters include the proportion of non-vascular abnormalities in the overall study.

Conclusion: The DETECT AF pro trial provides clinical level evidence evaluating an App for automatic detection of AF with a smartphone camera. Data will be available for the SSGIM Meeting.

Bedside mobility app: improving the bedside workflow process

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Introduction: Clinical documentation in the electronic medical records (EMR) is a complex task at the time of a patient’s hospital stay. The current tools used at the bedside in our hospital are paper supports (task list printouts or personal notes) and portable computers on wheels (COWs). Although the printouts can guide tasks and the personal notes can support handoffs, they are a potential source of error (e.g., prescriptions made after printing, transcription errors in delayed data entry from annotations). COWs facilitate data entry (e.g., vital signs, or clinical scores) but are not always available (two COWs per unit). Our project aims at developing a prototype of a smartphone app that can optimize the bedside workflow process to improve the efficiency, quality and safety of patient care.

Method: After studying the bedside work process of nursing teams, an interdisciplinary group of nurses, physicians and pharmacists developed a prototype smartphone application with nurses from internal medicine and surgery. The iterative development process also included a usability test in a lab with twelve nurses.

Results: In the specifications for the prototype, we included existing EMR or paper functionalities (e.g., task lists, clinical data entry for vitals), as well as new functionalities to support team communication (e.g., support for handoffs, team chat). After selecting one’s assigned patient for the shift, the view of patients’ charts is opened; nurses can support the handoffs, as well as a multi-patient view of tasks and needed materials per room. At the bedside, scanning the patient’s identity bracelet opens their chart (identito-vigilance): users can validate tasks by one swipe and/or add explanatory notes. Data can be entered directly at the bedside, and is integrated in the EMR. Finally, an informal team chat can help improve team communication.

Conclusion: Our prototype was designed to fill a gap in the nursing bedside workflow process and was developed iteratively with nurses to provide optimal usability. A proof of concept test will be conducted in two wards shortly (internal medicine and surgery) to study the app’s efficiency, its integration in the workflow process, and its effect on patient safety. Based on this prototype, future mobile support tools can also be developed for physicians.

How asthma, nose polyps and myocardial infarction finally led to the diagnosis of an eosinophilic granulomatosis with polyangiitis

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Innere Medizin, Spital Zollikerberg, Zürich, Switzerland

Background: The eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss) is a systemic vasculitis of small and medium blood vessels, characterised by asthma, nose polyps and serum eosinophilia. The most affected organ is the lung. There are three typical phases (prodromal, eosinophilic and vasculitic phase). Diagnosis is made by clinical findings and in 40–60% by positive antineutrophil cytoplasmatic antibodies (ANCA).

Case presentation: A 49-year old female presented with chest pain, dyspnea and ecg changes, suspicious for an infarction. The patient has a 4-month history of cardiac attacks, starting with an infarction caused by a spontaneous coronary artery occlusion. There was no significant narrowing of the coronary arteries in the angiography. Since then, the patient had more attacks, once leading to reanimation. The last angiography due to a non-stemi showed vasospasm of the coronaries, reversible to local application of nitroglycerin. Under these circumstances, a single coronary etiology seemed implausible. The patient has a history of allergic asthma, well controlled until her early 30ties. Lately, the patient suffered of poor control and of nose polyps. A recent spirometry showed severe obstruction and decreased diffusion capacity with partial atelectasis of the lower lobe in a CT-scan. The biopsy showed negative cytology and bacteriology but proliferation of the eosinophilic granulocytes, also documented in the blood analysis (with elevated total IgE). Repeated vasculitis screening was negative. While we started a systemic steroid therapy, the patient was asymptomatic with normal eosinophilic blood count. Two weeks later the patient suffered another cardiac attack in combination with elevated eosinophilic granulocytes. In diagnosis of poorly controlled asthma, nose polyps and vasculitic phase, elevated IgE, serum eosinophilia (eosinophilic phase) and cardiac vasospastic attacks (vasculitic phase), we diagnosed EGPA despite negative ANCA screening. We started a systemic therapy with steroids and cyclophosphamide. The eosinophilia normalised quickly. Follow up showed a well controlled asthma without cardiac symptoms and a high quality of life.

Conclusions: The diagnosis of a EGPA can often be missed because of diverse symptoms, differential diagnosis and negative ANCA tests (in cardiac involvement up to 40%). Heart involvement is a leading cause of mortality in EGPA, the more important it is to think of EGPA with patients having cardiac symptoms and a history of asthma.
Nightlife Switzerland: prevalence of violence and violence-linked injuries in major cities on weekend nights

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Policlinique Médicale Universitaire, Lausanne, Switzerland

Introduction: Observed over a week, 78% of night disturbance, 74% of verbal conflicts and violence-linked injuries and 73% of violent acts were associated to alcohol consumption, mostly on Friday and Saturday nights in neighborhoods with active nightlife. The consumption of alcohol and recreational drugs may be linked to the opening hours of bars and clubs on Friday and Saturday. Comparing the prevalence of violent acts with the amount of clubs different Swiss cities count and analyzing the number of violent incidents stratified per hour over a week could help establishing recommendations for a safer nightlife. This includes advice for teenagers and young adults, their parents, as well as public health professionals, medical teams and police corps.

Methods: Literature research concerning years 2014 to 2016 and communication with five public health institutions and research groups, as well as with three nightlife organizations. Consulting of statistical evaluations in cooperation with the Federal Statistics Office concerning the type and timeframe of violence-linked injuries and municipal and cantonal police reported violent acts. Graphical representation of nighttime offer in Switzerland 2016 and number of violent acts (yearly from 2009 to 2015) stratified per hour.

Results: Violence-linked injuries incidence increases up to eight-fold on weekend nights compared to nights on workdays. Police reported infractions against penal code concerning violence were clearly more numerous on Friday and Saturday night compared to the other ones. Lausanne leading the list of club offer with 6.2 clubs per 100 000 inhabitants is also the Swiss city with the highest reported infractions against penal code in general and ranging in top-three positions of increase of violence-linked injuries (8.6-fold increase; 8.8 in Lucerne, 8.7 in Geneva) in weekend nights compared to the remaining ones.

Conclusion: Cities presenting a broad offer of nightlife activities such as clubs are prone to sharp increases in violent act incidence on Friday and Saturday nights, be it measured on the amount of violence-linked injuries or on the amount of reported infractions against penal code. Recommendations for “high-risk” hours on weekend nights could be made through the results of this study. Public health professionals and policy makers should be aware of the issue linked to late-night violent acts, and establish and support the corresponding medical resources and safety disposures.
by oral fluconazole for a total of six months. CRP, haemoglobin, serum creatinine, proteinuria and vasculitic skin lesions resolved during the treatment. However, the LS/S1 intervertebral disc remained destroyed by the Candida infection requiring spinal surgery in the near future. **Conclusion:** A frequent problem turned out to have a rare cause. Candida spondylodiscitis is a very uncommon cause of low back pain, especially in an immunocompetent patient without other risk factors for fungal infections. Despite the typical symptoms (fever, back pain), apparently normal MRI scans initially misguided our diagnostic work up. In specific situations, PET/CT may help to distinguish between inflammatory and degenerative disease.

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**P343**

2-year results of a critical incident reporting system in a service of internal medicine

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**Introduction:** In 2015 a computer-based critical incident reporting system (CIRS), accessible to all staff members, was implemented in our hospital. In the service of internal medicine all events are addressed to a single CIRS coordinator who sorts them into two groups: those to be analysed within the service versus those necessitating external interlocutors. The latter are sent to the CIRS coordinators of the concerned departments and of other specific directorates. Internal events are submitted to different CIRS multi-professional specialists who may work alone or in groups (fig. 1).

Here we report the first summary of this implementation.

**Methods:** We collected data about the total number of incidents and the profession of reporters. We categorised the incidents into 22 subtypes derived from the OMS classification and examined the feedback modalities used for these incidents’ analysis.

**Results:** Between 2015 and 2016 we collected 1224 reports with a constant reporting rate of about 1 report/100 hospitalisation days, corresponding to about 1.7 reports a day. All events were analysed and categorised (fig. 2).

Nurses reported most incidents (89%), notably falls, medication administration errors and equipment problems. Doctors reported 9% of the declared events, mostly related to clinical situations. Clinical-related incidents increased from 5% in 2015 to 14% in 2016, in contrast to other subtypes whose incidence remained stable. Here we report the first summary of this implementation.

Conclusion: In our service CIRS participation (and satisfaction!) is excellent. While all incidents are analysed, the current challenge is to transform these analyses into daily improvements. Major limitations include the still complicated organisation, the need to prioritise, as well as the lack of personal and financial resources available to analyse the more complex incidents.

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**P344**

Evaluation of a multicomponent childhood obesity counseling program in primary care using the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework

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2Ostschweizer Kinderspital, St. Gallen, Switzerland

**Background:** Primary care providers can use behavioral lifestyle interventions to effectively treat overweight and obese children, but implementing these interventions is challenging. Most childhood obesity intervention evaluation studies focus on effectiveness. Few studies describe implementation. We evaluated critical components of a childhood obesity intervention, so stakeholders could implement it in other settings.

**Methods:** We evaluated a pilot implementation study of an existing structured lifestyle intervention in the Canton of Bern, Switzerland. The intervention was aimed at children 6-8 years old, whose BMI was over the 90th age-adjusted percentile. It was led by a primary care physician and consisted of 10 sessions, spread out over a year-long period. We used the Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) evaluation framework to describe the pilot implementation study. We stratified description of RE-AIM components at the patient- and physician-level. For Reach, at the patient-level, we counted the number of children screened for BMI. At the physician-level, we counted the number of physicians invited to participate in the study. For Effectiveness, at the patient-level, we measured change in BMI z-score. We determined Adoption at the patient-level by the number of children included and, at the physician-level, by the number of participating physicians. For Implementation, we counted the number of consultations held per patient. For Maintenance, at the patient level, we counted the number of children who discontinued the intervention; at physician-level, we counted the physicians who still used components of the intervention two years after the study ended.

**Results:** Reach: 864 children were screened; of these, 65 were overweight or obese. A total of 384 physicians were invited to participate in the study. Effectiveness: BMI z-score significantly decreased (−5.6%, p = 0.01). Adoption: 14 participating physicians treated 26 patients. Implementation: the mean number of consultations was 8. Maintenance: 9 (35%) children discontinued the intervention; 6 (50%) physicians we contacted continued to apply at least one component of the intervention.

**Conclusions:** The intervention effectively reduced BMI z-score. The RE-AIM framework helped us summarize critical components of the implementation study so others could more easily implement the program in other settings.
Challenging fever – case report of a patient with fever of unknown origin

Introduction: Fever of unknown origin (FUO) is still a diagnostic challenge. The list of disorders causing FUO is very long. We report the case of an 81 year old woman where after numerous investigations only splenectomy provided the diagnosis.

Case report: While the female patient presented to the hospital, she reported general weakness, fatigue and loss of weight during the last month. Past medical history was remarkable for monoclonal gammopathy of undetermined significance (MGUS) and chronic inflammatory demyelinating polyneuropathy (CIDP). For the latter she regularly received intravenous immunoglobulins. At admission no outstanding clinical features were registered. Important laboratory findings are specified in table 1. Chest radiograph was unremarkable. Blood cultures remained without bacterial growth. An abdominal ultrasound and CT scan showed no explanation for the clinical situation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>89</td>
<td>120–160 g/l</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>6.2</td>
<td>4–12 G/l</td>
</tr>
<tr>
<td>Thrombocytes</td>
<td>327</td>
<td>150–300 G/l</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>261</td>
<td>&lt;8 mg/l</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>66</td>
<td>&lt;12 mm/h</td>
</tr>
<tr>
<td>Free light chains lambda</td>
<td>23.5</td>
<td>5.7–26.3 mg/l</td>
</tr>
<tr>
<td>Free light chains kappa</td>
<td>17.3</td>
<td>3.3–19.4 mg/l</td>
</tr>
<tr>
<td>Kappa/lambda ratio</td>
<td>0.74</td>
<td>0.26–1.65</td>
</tr>
<tr>
<td>IgM</td>
<td>0.9</td>
<td>0.4–2.4 g/l</td>
</tr>
</tbody>
</table>

During the hospitalisation the temperature was repeatedly elevated up to 39 °C and the state of the patient declined gradually over the next weeks. An empirical trial of antibiotics and the probatory administration of steroids had no effect, considerably elevated markers of inflammation and fever persisted. Based on the patients history with MGUS of the type IgM a lymphoproliferative disorder was discussed. $^{18}$F-FDG PET/CT showed a slightly increased uptake in the spleen and an enhancement in the ascending colon. But even with the biopsies of the colon the suspicion of a lymphoma could not be confirmed. Because of further deterioration of the patient and despite only slightly increased glucose uptake in the marginally enlarged spleen, splenectomy was performed with immediate disappearance of the fever. Histologically the diagnosis of a diffuse large B-cell lymphoma (DLBCL) was made and chemotherapeutic treatment was started. After twelve days fever recurred and the patient died because of a sepsis with staphylococcus aureus.

Conclusion: This case demonstrates the difficulties to find the underlying disease of fever of unknown origin. Beside thorough history-taking, repeated physical examinations, laboratory tests and basic imaging procedures, $^{18}$F-FDG PET/CT scan can add important clues for further investigations of lymphoproliferative or infectious disease. In this case only splenectomy provided finally the diagnosis of the lymphoma. The diagnosis of primary splenic diffuse large B-cell lymphoma is often made by core-needle biopsy, but splenectomy seems to improve survival.
10 Jahre informatikbasierte CIRS-Erfassung an einer mittelgrossen internistischen Klinik
Philipp Rochat, Beat Frauchiger
Kantonsspital Frauenfeld, Frauenfeld, Switzerland


### Table 2: Causes of 6-month unplanned readmissions.

<table>
<thead>
<tr>
<th>Diagnosis category</th>
<th>TUG test duration ≥15 seconds (n = 66)</th>
<th>TUG test duration &lt;15 seconds (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease, n (%)</td>
<td>10 (21.7)</td>
<td>12 (19.7)</td>
</tr>
<tr>
<td>Infection, n (%)</td>
<td>9 (19.6)</td>
<td>7 (11.5)</td>
</tr>
<tr>
<td>Oncological disease, n (%)</td>
<td>7 (15.2)</td>
<td>11 (18.0)</td>
</tr>
<tr>
<td>Respiratory disease, n (%)</td>
<td>6 (13.0)</td>
<td>7 (11.5)</td>
</tr>
<tr>
<td>Neuropsychiatric disease, n (%)</td>
<td>5 (10.9)</td>
<td>7 (11.5)</td>
</tr>
<tr>
<td>Gastro-intestinal disease, n (%)</td>
<td>3 (6.5)</td>
<td>6 (9.8)</td>
</tr>
<tr>
<td>Osteoarticular disease, n (%)</td>
<td>2 (4.4)</td>
<td>5 (8.2)</td>
</tr>
<tr>
<td>Endocrine or metabolic disease, n (%)</td>
<td>2 (4.4)</td>
<td>3 (4.9)</td>
</tr>
<tr>
<td>Other, n(%)</td>
<td>3 (6.6)</td>
<td>5 (8.2)</td>
</tr>
</tbody>
</table>

Conclusions: In this prospective cohort study, functional impairment at discharge of an acute medical hospitalization was associated with higher risk of death, but not with unplanned readmission within 6 months after discharge. Objective and simple performance-based assessment may represent a better prognostic measure for mortality than for readmission.

Figure: Kaplan-meier curve for time until first visit to the general practitioner. HF-patient discharged to home. There was no difference between hospitalizations followed by a readmission (dashed line) or not (solid line, p-value 0.978).

Conclusions: The majority of HF-patients go back to their GP in the 30 days following their discharge. Unexpectedly, many refused to book an appointment during their hospitalization. Reason remains unclear. Further studies should identify reasons of this delay and determine if some are modifiable. We also should assess whether a shorter delay reduce readmissions: current recommendations about appropriate time to follow-up are based on expert opinions and limited literature.

Medical collaboration during ICU admission decisions: a qualitative study of interns’ and ICU physicians’ perceptions

Monica Escher, Patricia Hudelson, Mathieu Nendaz, Barbara Ricou, Thomas Fenernegg, Stéphane Cullati

Background: Intensive care (ICU) admission decisions are complex particularly for seriously ill patients. They involve collaboration between the referring internists and ICU physicians. Good collaboration is associated with patient health-related outcomes and healthcare providers’ satisfaction with the decision making process. How physicians perceive each other roles can influence the quality of collaboration.

Aims: Explore internists’ and ICU physicians’ perceptions of their roles and how perceptions relate to experience of collaboration during admission decisions.

Methods: In-depth interviews with ICU physicians (n = 12) and internists (n = 12) working in a Swiss tertiary care hospital. Interviews were analyzed using an inductive thematic approach.

Results: Internists and ICU physicians had the same perception of their various respective roles. Both groups of physicians estimated that their colleagues usually performed their roles satisfactorily. Shortcomings were reported in complex situations involving seriously ill patients and gave rise to tensions. Sources of tension related to: 1. Imparting information about the patient: ICU physicians complained that internists did not provide the relevant information, thus making the decision more difficult. Internists complained that ICU physicians did not trust them and expected to be convinced of the appropriateness of intensive care. 2. Choosing comfort care: ICU physicians felt that internists did not take their responsibility and let them make a comfort care decision. 3. Misunderstanding about ICU physicians’ expected role: Internists reported they sometimes only wanted ICU physicians’ advice, whereas ICU physicians assumed the internists wanted the patient to be admitted to intensive care.

Conclusion: ICU admission decisions involving seriously ill patients can give rise to tensions between internists and ICU physicians. Further research should determine if physicians’ dissatisfaction leads to inappropriate admission decisions.

Funding: Swiss National Science Foundation, NPR 67 “End-of-life”

Medical residents working with vulnerable patients improve their psychosocial skills: a Swiss pilot study

Pau Mota, Francis Vu, Jeremie Blaser, Elodie Dory, Patrick Bodemann, Monika Escher, Marielle Ricou, Béatrice Gavalchin, Thomas Perneger, Stéphane Cullati

Background: Scientific literature has shown that patients at high risk of vulnerability are involved in more encounters perceived as difficult by physicians. Physicians involved in difficult encounters denoted worse psychosocial outcomes. Practice and physicians who experience many of their patients as difficult are more likely to end in burnout. This study aims to take advantage of a specific setting, the Department of Ambulatory Care at the University of Lausanne, in which medical residents frequently work with patients holding high levels of vulnerability. The main objective of this study was to assess the medical resident beliefs about psychosocial aspects of health care, both, before and after, working in a university setting dealing with patients at high socioeconomic risk.

Methods: This is a prospective pilot study with a 6 months follow-up. To assess medical resident beliefs about psychosocial aspects of health care we used the Physician’s Belief Scale (PBS). We compared the PBS score of medical residents both before and after having worked 6 months in the outpatient clinic. A second wave of medical new residents (n = 16) is currently under study (final results are expected in march-april 2017), with which we will be able to extend the sample size to a total of 27 to perform a similar analysis.
The role of hepcidin in iron homeostasis in inflammation – an exploratory pilot subgroup analysis in medical inpatients

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1Medizin, Universitätsspital Basel; 2Blood Transfusion Centre, Swiss Red Cross; 3Clinical Trial Unit, Universitätsspital Basel, Basel; 4Medizin, Luzerner Kantonsspital, Luzern, Switzerland

Introduction: Iron metabolism depends on hepcidin in terms of absorption, transmembrane transport in the small intestine and recycling of iron in macrophages including iron release and sequestration. Especially inflammatory states and diseases including infections decrease iron availability. The primary aim was to analyze the correlation between hepcidin and iron-dependent laboratory markers (neutrophil granulocytes, procalcitonin, erythropoietin, IL-6, TNF-α, IL-3, hemoglobin, serum transferrin receptor, transferrin, transferrin saturation, ferritin, free iron, CRP, GFR, MCH, MCV).

Methods: Study design: Prospective, cross-sectional, observational, exploratory pilot subgroup analysis. Primary endpoint: Correlation of hepcidin with neutrophil granulocytes, procalcitonin, erythropoietin, IL-6, TNF-α, IL-3, hemoglobin and serum transferrin receptor, transferrin, transferrin saturation, ferritin, free iron, CRP, GFR, MCH and MCV levels. Inclusion criteria: Age ≥18, medical inpatient (hospitalization >24h), CRP >5 mg/l. Exclusion criteria: History of dialysis-dependent chronic kidney disease, use of erythropoiesis-stimulating agents, pregnancy, history of allogeneic stem cell transplantation. Two venous punctures: 1. after admission 2. >5 days of hospitalization. Pearson product-moment correlations for hepcidin and the mentioned laboratory parameters (see primary aim) were calculated. The cut-off level was set at p<0.05 +/−30% correlation due to multiple testing.

Results: Forty randomly selected medical in-patients with CRP >5 mg/l were analyzed. The mean age was 69.5 years (range 54–78), 50 percent were male. The Pearson correlation showed a positive correlation of hepcidin levels with TNF-α and procalcitonin levels whereas hemoglobin and GFR (CDK-EPI) showed an inverse correlation with hepcidin levels. The role of hepcidin in iron homeostasis in inflammation – an exploratory pilot subgroup analysis in medical inpatients

Conclusion: Procalcitonin and TNF-α showed a positive correlation with hepcidin levels, which could be well explained by inflammation and disease activity. GFR and hemoglobin were inversely correlated to hepcidin levels. Hepcidin is renally excreted, which could well explain higher hepcidin concentration in decreasing kidney function. Interestingly, several other well-known markers of inflammation including IL-6 showed a Pearson correlation below 0.30. The correlation of hepcidin with inflammation and its mediators needs further study, especially taking into account that the first anti-hepcidin drugs are being tested in clinical trials.

Pearson correlation coefficients for hepcidin and different laboratory parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pearson correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepcidin vs. laboratory parameter</td>
<td></td>
</tr>
<tr>
<td>Positive correlation</td>
<td>Heparidin vs. Procalcitonin</td>
</tr>
<tr>
<td></td>
<td>Heparidin vs. TNF-α</td>
</tr>
<tr>
<td>Negative correlation</td>
<td>Heparidin vs. GFR</td>
</tr>
<tr>
<td></td>
<td>Heparidin vs. Hemoglobin</td>
</tr>
</tbody>
</table>

Pearson correlation with hepcidin below r = 0.3: neutrophil granulocytes, erythropoietin, IL-6, TNF-α, IL-3, serum transferrin receptor (sTfR), transferrin, transferrin saturation, ferritin, free iron, CRP, GFR, MCH, MCV levels.

a. 1.0 equals full correlation, 0 equals no correlation
Evolution of medication in heart failure patients hospitalized in a Swiss university hospital
Davy Cabrio1,2, Pedro Marques-Vidal1, Gérard Waebel1
1Department of Medicine, Internal Medicine, Lausanne University Hospital (CHUV); 2Université de Lausanne, Lausanne, Switzerland

Background: Patients with heart failure (HF) patients are frequently on polypharmacy (5+ drugs), and subsequently at risk of potentially deleterious drug-drug interactions (DDI). Our objective is to study the trends and determinants in the number and classes of medicines prescribed and in the prevalence of polypharmacy among patients hospitalized for HF.

Methods: Retrospective analysis of discharge data in the department of Internal Medicine of the Lausanne university hospital between 2008 and 2015. DDIs were estimated according to the criteria of the Geneva hospital. DDIs were tested on significance by generalized estimation equations (GEE).

Results: Data from 3’666 hospitalizations (mean age 77.6 ± 12.4 years, 47.1% women) were analyzed. Almost all patients (3’527, 96.2%) were on polypharmacy at discharge, and 631 (17.2%) were discharged with 15+ drugs. The prevalence of polypharmacy remained stable at 96.5% in 2008 and 96.8% in 2015, but the prevalence of patients with 15+ drugs increased from 12.2% in 2008 to 21.2% in 2015 (p = 0.05) (table 1).

<table>
<thead>
<tr>
<th>Year</th>
<th>Polypharmacy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>96.5%</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>96.8%</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Almost all patients with HF are on polypharmacy. The prevalence of patients taking 15+ drugs is increasing, but no concomitant increase in DDIs was found.

Table 1: Polypharmacy.
The most frequently prescribed medicines were diuretics (79.0%), angiotensin-related drugs (angiotensin II receptor blockers or angiotensin-converting-enzyme inhibitors, 62.8%) and β-blockers (58.7%). Increased comorbidities, HF as a comorbidity and compliance to ESC guidelines were positively associated while being discharged home or increasing age were negatively associated with polypharmacy. Almost two thirds (2’327, 63.5%) of patients had at least one potential DDI. The prevalence of potential DDIs increased from 19.4% in patients taking less than 5 drugs to 83.7% in patients taking 15+ drugs. Conversely, the prevalence of patients with at least one potential DDI remained stable throughout the study period (66.8% in 2008 and 59.1% in 2015, p = 0.180) (table 2).

Table 2: DDI.

Progress! Medication Reconciliation: a national programme to improve medication safety at transitions in care
Andrea Niederhauser, Liat Fishman, Chantal Zimmermann
Stiftung Patientensicherheit Schweiz, Zürich, Switzerland

Introduction: Poor communication and information loss put patients at risk for medication discrepancies at hospital admission and discharge. Studies have shown that in up to half of patients the medication history at admission contains errors, potentially leading to unintended omissions, duplications or incorrect dosages of medications in hospital and post-discharge. Medication Reconciliation (MedRec) is an effective strategy for reducing such risks and is already a routine practice in many countries. The goal of the programme progress! Medication Reconciliation is to promote this practice in acute care hospitals in Switzerland.

Methods: The programme consisted of two main elements: a campaign to raise awareness and a pilot project conducted in eight hospitals. The pilot focused on a best possible medication history (BPMH) at admission as the basis for a safe prescribing process. Each hospital designed and tested its own BPMH process taking into account the quality standards for a BPMH as defined by the programme. For example, some hospitals conducted the BPMH solely with medicine interns, while others involved pharmacy staff such as pharmacists and pharmacy assistants. The evaluation focused on the practical experiences with these processes.

Results: The evaluation demonstrated that the participating hospitals laid the groundwork for further improving their medication process. Several challenges to sustainable implementation were identified, many of them revolving around the time needed to access and compare medication sources for the BPMH and to conduct the other steps such as systematically interviewing the patient and documenting the medication list. Important conditions of successful implementation are institutional support, electronic tools which are integrated into the workflow, ensuring continuous training and supervision of frontline staff and clearly defining roles and responsibilities while promoting a culture of interprofessional collaboration.

Conclusion: Medication Reconciliation is regarded as an important patient safety measure, however, at this time there are still many obstacles to widespread sustainable implementation. To further promote MedRec in Switzerland, tools developed by progress! will be made available to all Swiss hospitals and a position paper will be published. Researchers in Switzerland are encouraged to further investigate effective models for implementing MedRec, such as selection criteria for targeting high-risk patients.

Differences in the course of Italian- and German-speaking patients’ outcome after interdisciplinary pain program
Thomas Benz1,2, Felix Angst1, Roberto Broschi1, Susanne Lehmann1, Achim Elfering1, André Aeschlimann2
1Research Department, RehaClinic, Bad Zurzach; 2Institute of Psychology, University of Bern, Bern, Switzerland

Background: Management of chronic pain patients is a challenge in primary care. Available evidence shows that perception, coping, and treatment of pain varies among different populations and cultural regions. In particular, it is unknown how much migrants in Western European countries profit from pain management programs. The aim of this study was to quantify state and changes of health state and quality of life of immigrant native Italian-speaking patients with fibromyalgia or chronic back pain before and after a 4-week, interdisciplinary inpatient pain program and to compare the results with German-speaking patients.

Methods: The prospective cohort study with 62 Italian-speaking and 63 German-speaking patients measured health-related quality of life, pain, fear and depression comparing at baseline, after 4 weeks of pain program and at 1 year follow-up. Differences between the two groups were tested on significance by generalized estimation equations (GEE). This method modeled changes of health by multivariate logistic

POSTERTOUR 1: MÉDECINE INTERNE GÉNÉRALE I / ALLGEMEINE INNERE MEDIZIN I
Life and death: a comparison of ICU physicians’ and internists’ survival predictions for patients assessed for intensive care

Monica Escher1, Bara Ricou1, Mathieu Nendaz2, Fabienne Scherer1, Stéphane Cullat1, Patricia Hudelson1, Thomas Perneger1

1Hôpitaux Universitaires de Genève; 2Unité de Développement et de Recherche en Éducation Médicale, Faculté de Médecine, Geneva, Switzerland

Background: Expected improvement in survival is the main justification for admission to the intensive care unit (ICU). To make a decision, physicians must estimate the patient’s prognosis whether he is cared for on the ward or in the ICU. Contradictory estimations may explain the occurrence of disagreements between the referring physicians and the ICU physicians about the appropriateness of ICU admission. Physicians’ ability to accurately predict survival of a patient assessed for intensive care is not known.

Aims: Assess referring internists’ and ICU physicians’ accuracy in predicting patient survival on the ward and in the ICU, and determine whether the survival estimates correlate with the admission decision and with observed survival.

Methods: All consecutive requests for ICU admission made for patients hospitalized in the Division of General Internal Medicine of the Geneva University Hospitals were identified. The ward and the ICU physicians involved were contacted within 12 hours and asked to estimate patient survival using predefined categories of probabilities. The admission decision and the patient characteristics were collected. We used regression models for the analysis.

Results: 201 patients were included, of whom 140 (69.7%) were admitted into the ICU. Overall 58 patients (28.9%) died within 28 days. Physicians predicted a survival benefit from intensive care for most patients. Agreement between internists and ICU physicians was good (Spearman rho 0.5). Higher survival ratings by both groups of physicians were associated with higher proportions of admitted patients, but the admission decision was more strongly influenced by the ICU physicians’ estimates. Observed patient survival was strongly associated with predicted survival by both physicians. The internists’ prediction however was more accurate than the ICU physicians’, whether the patient stayed on the ward (areas under the ROC curves 0.74 vs 0.69) or was admitted into the ICU (area under the ROC curve 0.76 vs 0.63).

Conclusion: Internists more accurately predict survival for patients assessed for admission to intensive care than ICU physicians. However, ICU physicians’ estimates more strongly influence the admission decision.

Funding: Swiss National Science Foundation, NRP 67 “End-of-life”
Background: Autopsy rate has been declining for decades in Switzerland as well as all over the world. This negative trend might create important problems because autopsies ensure valid causes of deaths. Moreover medical training of physicians and quality of patients' care rely in part on the possibility to perform autopsies. An important obstacle for getting permission to autopsy seems to be the poor communication skills of physicians.

Methods: After performing a communication training with physicians in the Department of Medicine (DM), the new communication strategy was applied for the postmortem autopsy conversation with relatives. Moreover, we developed a structured questionnaire to find out the practical experience of the participating doctors in regard to their conversation skills.

Results: In the period from November 2014 to October 2015 489 patients died in the DM. 353 questionnaires could be evaluated. In 76% of all evaluated conversations, the new guide of the communication training was applied. In 86% of the cases, the conversation was felt as open and relaxed with the relatives. Seven % felt the conversation as oppressive and unpleasant and 7% did not answer the question. In 89% of all evaluated questionnaire the doctors could understand the decision of the relatives for performing an autopsy or not.

Conclusion: In summary, the majority of the physicians have accepted and used the new guide for optimized conversation skills. In most cases, the conversation was perceived as comfortable. We suggest, that the medical staff should receive regular training in communication skills for a confident and better conversation with patients and their relatives.

Trends and determinants of polypharmacy and potential drug-drug interactions at discharge from hospital, 2009–2015

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Lausanne University Hospital (CHUV), Lausanne, Switzerland

Introduction: Polypharmacy is increasingly common and associated with risk of drug-drug interactions (DDIs). We aimed to measure the trends and determinants of polypharmacy and DDIs among patients discharged from the department of Internal Medicine of the Lausanne university hospital.

Methods: Retrospective study including 18'075 adult patients discharged between 2009 and 2012. Polypharmacy and excessive polypharmacy were defined as [5–9], [10–14] and 15+ drugs, respectively. DDIs were defined according to the criteria of the Geneva University hospital.

Results: Polypharmacy decreased from 45% in 2009 to 41% in 2015, while excessive polypharmacy increased from 40% to 46%. In 2015, 13% of patients received 15+ drugs. age, coming from other health care settings, higher Charlson Index, number of comorbidities and quartiles of LOS to be significantly and independently associated with polypharmacy and excessive polypharmacy. The risk of having at least one DDI decreased from 66.9% (95% CI: 64.8–68.9) in 2009 to 59.3% (57.6–62.0) in 2015 (p <0.001). Multivariate analysis showed number of drugs [Odds ratio and 95% confidence interval: 3.69 (3.32–4.11); 9.39 (8.34–10.6) and 20.3 (17.1–24.0) for [5–9], [10–14] and 15+ drugs, respectively], gastrointestinal disease [3.16 (2.76–3.61)] and cancer [1.38 (1.19–1.59)] to be positively associated, and lung [0.82 (0.74–0.90)] and endocrinological [0.63 (0.53–0.74)] diseases to be negatively associated with risk of DDI.

Conclusion: Excessive polypharmacy is increasing among hospital patients, and is associated with an increased risk of DDI. The decrease in the overall risk of DDI could be due to an improved management of multidrug therapy.

Keywords: polypharmacy; excessive polypharmacy; drug-drug interactions; epidemiology; hospital

An almost fatal “Müsli” resulting in a superwarfarin intoxication

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1Kantonsspital Baden, Baden; 2Universität Zürich, Zürich, Switzerland

Background: Vitamin K antagonists are essential in the management of coagulation disorders through inhibition of vitamin K 2,3-epoxide reductase (VKOR). Superwarfarins are long-acting, high affinity VKOR inhibitors and used as rodenticides.

Case report: A 50-year-old woman with a schizoaffective disorder presented with severe acute neck and abdominal pain. Clinical examination showed multiple subcutaneous hematomas at the site of injection. Laboratory analyses revealed pathologic coagulation assays (INR >6) and severe anemia (Hgb: 5.8 g/dl). With a slightly elevated fibrinogen and normal factor V activity, acute liver failure was ruled out. A CT scan of the abdomen was performed detecting a hemorrhagic ovarian cyst without active bleeding sites. After the transfusion of one erythrocyte concentrate, the hemoglobin level increased adequately and remained stable. While the administration of 1000 IU 4-factor prothrombin concentrate and 30 mg Vit. K stabilized initial coagulopathy, a minimum of 30 mg Vit. K daily for another 50 days was required in order to keep the INR below 1.5 (fig. 1). Although repetitively denied by the patient, an intake of long acting warfarin was suspected. However, urine toxicological screening using a fast immunochromatographic assay and a wide range LC-MS screen for xenobiotics did not reveal any agent explaining the patient's symptoms. Furthermore, a subsequent serum LC-MS screen for anticoagulant agents was negative. Plasma mixing studies restored abnormal prothrombin time ruling out an acquired inhibitor problem. As clinical suspicion persisted, the patient's serum was specifically tested for the presence of superwarfarins. A specific LC-MS method identified the presence of difenacoum. After being confronted, the patient admitted rodenticide ingestion with suicidal intent. A bag with this substance ambiguously labeled with “Müsli” (intended for mice – and not “Birchermüesli”) was meanwhile found in the basement.
Conclusions: 1) This case illustrates the long-acting and high affinity anticoagulant effect of superwarfarins, widely available as rodenticides occasionally consumed with suicidal intent. 2) Due to the long-acting effect of superwarfarin (difenoacin 1/2; 128d), long term and high dose vitamin K treatment is essential along with continuous prothrombin-time monitoring (fig. 1). 3) Our report emphasizes the importance of staying persistent when high clinical suspicion is present despite so-called negative test results.

The minimal clinically important difference (MCID) raises the significance of outcome effects above the statistical level

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1Forschung, RehaClinic, Bad Zurzzach; 2Forschung, Psychiatrische Uniklinik Burghölzli, Zürich; 3Medizin, RehaClinical, Bad Zurzzach, Switzerland

Background: In measurement of outcome effects, the patient’s subjective perception to feel a change in health defines clinical effectiveness irrespective of statistical significance. The aim was to illustrate and discuss current and proposed new concepts of effect quantification and significance.

Methods: Different methods for determining minimally clinically important differences (MCIDs) are reviewed and further developed focusing on their characteristics and (dis)advantages.

Results: In controlled studies, empirical score differences between verum and placebo become statistically significant if sample sizes are sufficiently large. For example, a score difference of 5 points (scale 0–100) between the verum and the placebo effect becomes statistically significant, if the sample sizes are n >33 for each of both groups at a standard deviation = 10 of the score differences (baseline to follow-up). MCIDs by contrast, are defined by patients’ perceptions, which led to “anchoring” of effects by the “transition” item, where patients rate their change of health between baseline and follow-up in an evaluation study. The MCID for improvement by the “mean change method” is the difference of the mean change experienced by the “slightly better” group minus that of the “almost equal” group. The MCID can be expressed as absolute or relative score, as effects size (ES), standardized response mean (SRM) and standardized mean difference (SMD) (dissimilar). It can further be adjusted by multivariate regression modeling. In our example of knee osteoarthritis, the MCID for pain relief was 8.74 score points, 17.15% of the baseline score, ES = 0.407, SRM = 0.413, SMD = 0.469. This is consistent to the range of 0.30–0.50 for MCIDs reviewed in literature. After adjusting for potential confounders, the MCID was 2.20 score points or an increase of 2.9% per score point to feel better (logistic regression).

Conclusion: Absolute and relative MCIDs are easy to interpret and apply to data of investigative studies. MCIDs expressed as ES/SRM/ SMD reduce bias, which mainly results from dependency on the baseline score. Multivariate linear and logistic regression modeling further reduces bias by adjustment for possible confounders and increase validity. Anchor-based methods use clinical/subjective perception to define MCIDs and should be clearly differentiated from MCIDs reviewed in literature.

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Table 1: Factors associated with thrombophilia testing.

<table>
<thead>
<tr>
<th>Testing for FV Leiden and/or Prothrombin G20210A mutation</th>
<th>No (N = 2039)</th>
<th>Yes (N = 67)</th>
<th>P-value</th>
<th>OR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>68.7 ± 17.2</td>
<td>55.1 ± 16.3</td>
<td>&lt;0.001</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age ≥65 years (%)</td>
<td>1322 (64.6)</td>
<td>19 (28.4)</td>
<td>&lt;0.001</td>
<td>0.19 (0.11–0.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>1026 (60.5)</td>
<td>36 (53.7)</td>
<td>0.583</td>
<td>1.26 (0.77–2.07)</td>
<td>0.362</td>
</tr>
<tr>
<td>Swiss national (%)</td>
<td>1589 (77.9)</td>
<td>53 (79.1)</td>
<td>0.820</td>
<td>1.50 (0.81–2.77)</td>
<td>0.201</td>
</tr>
<tr>
<td>Coming from home (%)</td>
<td>1750 (85.8)</td>
<td>50 (74.6)</td>
<td>0.010</td>
<td>0.48 (0.27–0.85)</td>
<td>0.011</td>
</tr>
<tr>
<td>Private insurance (%)</td>
<td>197 (9.7)</td>
<td>10 (14.9)</td>
<td>0.154</td>
<td>2.00 (0.99–4.07)</td>
<td>0.054</td>
</tr>
<tr>
<td>NA: not assessable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients coming from home were less likely of having FV Leiden and/or prothrombin G20210A mutation testing. Patients with FV Leiden and/or prothrombin G20210A mutation testing had similar length of stay compared to VTE without such testing (median: 7.7 versus 9.9 days, p = 0.319); no statistically significant difference was found regarding in-hospital mortality.
Table 2: Outcome associated with thrombophilia testing.

<table>
<thead>
<tr>
<th></th>
<th>No (N = 2039)</th>
<th>Yes (N = 67)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In hospital mortality</td>
<td>142 (70)</td>
<td>1 (1.5)</td>
<td>0.085</td>
</tr>
<tr>
<td>Length of stay[^1]</td>
<td>9.9 (3.3–19.9)</td>
<td>7.7 (4.1–14.4)</td>
<td>0.319</td>
</tr>
</tbody>
</table>

[^1] Median and [interquartile range], between group comparison using Kruskal-Wallis test

Conclusion: FV Leiden and/or prothrombin G20210A mutation testing in hospitalized patients with a prior VTE was infrequently performed. Hence, 22 FV Leiden and/or prothrombin G20210A mutation testing were performed per year, which represents roughly 1% of the patients with VTE admitted in Lausanne University hospital each year. In the majority of cases, the practice of thrombophilia testing for patients with VTE in Lausanne University hospital complies with guidelines.

Adherence to recommendations for preventive care in primary care: a cross-sectional study in Switzerland and France

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Polyglobulie bei Anabolikamissbrauch

Michael Kuhn[^8], Sylvette Baldesberger[^9], Stefan Bilz[^10], Michael Brändle[^11]


Einleitung: Unterschiedliche Anabolen Androgene Steroide (AAS) werden nicht nur im professionellen Bodybuilding sondern zunehmend bei ambitionierten Hobbybodybuidlern oft in Kombination eingenommen.

Fallbeispiel: Wir präsentieren einen Fall von einem 55jährigem Mann, der wegen drei Wochen bestehender Kopfschmerzen, verminderter Antrieb sowie wiederholten Schwächezuständen ohne Bewusstseinsstörungen durch den Hausarzt zugewiesen wurde. Laborchemisch zeigte sich ein Hb von 210 g/l, HK 0.59 sowie Kreatinin von 132 µmol/l. Im Somatoscore war das überproportioniert muskulöse Erscheinungsbild bei einem BMI 33.3 kg/m² auffallend. Anamnestisch war zu erfahren, dass der Patient wiederholt die letzten Jahre verschiedene Anabolika zur Leistungssteigerung einsetzte hatte. Unter dreimaligem Adiuretika mit je 450 ml war das Hb mit 192 mg/l rückläufig. Da der Patient hierunter bereist beschwerdefrei war, drängte er auf raschen Austritt.


Baseline characteristics of individuals using a new online-tool assessing cardiovascular risk factors (www.swissheartcoach.ch)

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[^12] Centre for Primary Health Care; University of Basel, Liestal, Switzerland; 2VR Consult, Niederberg, Germany; 3Swissheart Foundation, Berne, Switzerland

Background: Controlling the epidemic of CVD requires a multifaceted strategy targeting modifiable cardiovascular risk factors. In 2012 the Swissheart Foundation – in cooperation with experts in the field – started to develop an online programme called www.swissheartcoach.ch. The project addresses the general population (primary prevention) as well as individuals with established CVD (secondary prevention). Computer-based education may be used as an effective strategy for transferring knowledge and skill development to patients. We undertook a survey to characterize the baseline data (e.g. cardiovascualar risk profile) of the registered users during the first six month since launching, potentially indicating the attractiveness and use of tool.

Methods and results: The project was launched by advertisement in lay press in March 2016 and since then users’ data have been systematically collected. From March to September 2016, a total of 1217 people registered their data on www.swissheartcoach.ch. Twenty-eight subjects (0.02%) were excluded from the analysis since only data of gender, age and BMI were available. The analysed sample’s (n = 1189) mean age was 58.6 years (SD = 12.3) and 46.2%
were women. Overall, 72% reported to be smokers and only 4% to suffer from diabetes type 2. From those who know their blood pressure (BP) (83.7%), only 6% have a BP ≥140/90 mm Hg.

**Conclusion:** Data analysis is ongoing and will be available in more details in May 2017. First results suggest that the registered users’ cohort is a rather healthy population. Therefore, the potential of lifestyle changes in this population might have only a small effect on their cardiovascular risk profile as it already seems to be low. Still we believe that the implementation of an internet-based educational system for lay persons and health care professionals is an innovative strategy in Switzerland to foster motivation and know-how regarding cardiovascular risk factors and lifestyle changes.

### Daily business or not – two cases of rare complications following bone marrow biopsy

Nicola Frei¹, Tobias Sitzlé², Christian Bucher³, Markus Diethelm¹

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**Introduction:** Bone marrow biopsy is a common procedure to diagnose several hematological disorders. Although an invasive procedure, it is a save intervention with a complication rate of 0.05%. Known complications are bleeding, local infection and nerve damage. Risk factors for adverse events include myeloproliferative disorder, treatment with aspirin (and other putative platelet dysfunction), warfarin, obesity or disseminated intravascular coagulation. We present 2 cases of serious complications following a bone marrow biopsy.

**Case report:** A 77-year-old man was referred for further evaluation of a thrombocytosis. Blood tests excluded an iron deficiency in the presence of a hyperchrome and macrocytic anemia while treated with dual platelet aggregation inhibition in the context of a coronary heart disease with stent implantation 4 months ago. To decide the further management of the platelet aggregation inhibition therapy in the case of a possible myeloproliferative disease, a bone marrow biopsy was performed. Shortly after the intervention the patient complained of pain in the gluteal area. The following computed tomography (fig. 1) with angiography showed a pseudoaneurysm of the left superior gluteal artery with active hemorrhage and intragluteal hematoma. Dual platelet aggregation inhibition was paused and 1 platelet concentrate was administered, the patient fully recovered without intervention. In the second case, a 40-year-old woman on hemodialysis treatment due to cardiovascular risk factors and lifestyle changes.

**Conclusion:** In general bone marrow biopsy is a safe procedure, independent of the examiners experience. Nevertheless in every case the indication for this examination is to verify thoroughly and paying attention to a technically correct procedure is essential.

### An unusual cause of severe recurrent gastroenteritis – a case report

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**Introduction:** An 82 years-old man known for ulcerative colitis and hypertension was hospitalized for the 5th time in 1 month with the same clinical characteristics: acute nausea, vomiting, diarrhea, low blood pressure, acute renal failure and leukocytosis. Following each episode he recovered quickly, but the day after returning home the symptoms reappeared, requiring another hospitalization. Various pathologies were considered instigating numerous investigations. At this 5th admission, a close look at the patient’s record showed that his hypertensive drug (olmesartan) had systematically been suspended at admission. At discharge, as blood pressure raised and renal function recovered, he was told to take his usual medication again. With 40 mg olmesartan, his BP could not be controlled, he suffered of nausea, vomiting and diarrhea. The symptoms disappeared within 4 hours. C4 complement and C1 esterase inhibitor function were normal as well as serum tryptase. We retained the diagnosis of visceral angioedema induced by olmesartan.

**Method:** We searched PubMed, UpToDate and Google Scholar with the keywords “angiotensin II receptor blocker” (ARB), “angioedema”, “visceral” and “intestinal”. As we retrieved very little literature, we extended our search with the key words “angiotensin converting enzyme inhibitor” (ACEI).

**Results:** We found sparse literature about ARB-induced intestinal angioedema, only case reports. ARBs and ACEIs are responsible for similar side effects, sometimes with cross-reactions. ACEI-induced visceral angioedema is better described (estimated frequency 0.1–0.2%). The diagnostic criteria are: timing with medication intake, abdominal pain/emesis/diarrhea, normal C1 esterase inhibitor and C4 levels, CT-scan showing segmental intestinal edema, and absence of alternative diagnosis. The pathophysiology is explained by bradykinin increase due to ACE inhibition with ACEIs and other less understood mechanisms with ARBs. Genetic predisposition, hormonal influence or inflammatory pathways may also be involved.

**Conclusion:** As a case report of ARB-induced intestinal angioedema reminds us of this rare but potentially life-threatening side effect. Delayed diagnosis can lead to unnecessary investigations and mistaken treatments. More generally, it reminds us that unexplained symptoms may be due to drugs. Careful anamnesis, sometimes with detailed retrospective medical record study, can be more helpful than repetitive blood sampling and extensive imagery.

### Pulmonary foreign body granulomatosis is an important differential diagnosis in patients with intravenous drug abuse and suspect radiological examination

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¹Allgemeine Innere Medizin; ²Pathologie; ³Pneumologie, Kantonsspital St.Gallen, St.Gallen, Switzerland

**Introduction:** Pharmaceutical tablets contain filler agents such as talc, microcrystalline cellulose or crospovidone. By intravenous injection of such pulverized tablets these filler agents accumulate in the pulmonary capillary bed and may cause foreign body granulomas. Granulomas can develop in the pulmonary arteries or in the interstitium of the lung. After repeated intravenous exposure this inflammatory process may lead to interstitial pulmonary fibrosis and emphysema.

**Case report:** A 32-year-old man with a long history of intravenous drug abuse (IVDA) was transferred by ambulance to our hospital in an overall bad condition, with fever (39 °C), chills and dyspnea. Clinical examination revealed crackles in the lower lung fields. Blood tests showed increased inflammatory values. The chest X-ray raised strong suspicion of miliary tuberculosis. Initially an empiric antibiotic therapy with ceftriaxone and clarithromycin was started to treat pneumonia. A computed tomography (CT) of the chest showed a micronodular pattern. For further diagnostics a flexible bronchoscopy was performed for a bronchoalveolar lavage. With the additional hypothesis of a foreign body granulomatosis a transbronchial biopsy was taken. This...
showed multiple granulomas within the alveolar walls. All granulomas contained amorphous birefringent polarizable foreign material. There were no signs of malignancy; biopsy and culture were negative for tuberculosis. The reason for the elevated inflammatory values was an influenza A infection; therapy with oseltamivir was started. The patient left the hospital after four days against medical advice.

A trial with prednisone 60 mg daily resulted in an explicit improvement of the symptoms with decrease of redness, pain, swelling and induration. Since the pain increased again after dose reduction to 30 mg prednisone daily, we raised prednisone to 50 mg/d. After complete recovery a new pacemaker was implanted on the contralateral side without any complications. Two months later, prednisone dose could be tapered to 20 mg/d.

**Conclusion:** After exclusion of bacterial infection, pressure dermatitis or postimplantation erythema must be considered in patients with local signs of inflammation around the pacemaker pocket. Histological examination of the affected skin can contribute to the diagnosis. In case of suspected contact hypersensitivity to implant material, allergological exploration should be performed (patch testing, in selected cases lymphocyte transformation test). Depending on the cause, cutaneous reactions are occasionally self-limiting (postimplantation erythema) or the pacemaker can translocate subpectoral or subcostal (pressure dermatitis). Corticosteroid may reduce skin symptoms of contact dermatitis, but recurrence is common. In many cases, however, removal of the pacemaker is inevitable. Special gold-plated or entirely polytetrafluoroethylene coating pacemaker systems are available for reimplantation. In our case the early consideration of pacemaker dermatitis eventually could have prevented the explantation and reimplantation of the pacemaker.

**Swimming induced pulmonary edema (SIPE) or immersion pulmonary edema is a rare form of non-cardiogenic pulmonary edema**

**Lorenz Bärlocher**, Ruth Gamio-Veis, Philipp K. Haager, Markus Diethelm, Michael Brändle

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**Introduction:** SIPE is a rare form of non-cardiogenic pulmonary edema. The frequency of SIPE is rising because of the increasing popularity of endurance sports competitions like triathlons.

**Case report:** We report on a 66 years old, sporty and healthy patient with acute dyspnea and chest pain while swimming in the Lake of Constance. Upon arrival of the emergency rescue service peripheral oxygen saturation was 85% (with an increase to 92% with 2 l oxygen), blood pressure 139/92 mm Hg with a pulse of 71/min. Clinical findings were normal except bibasilar crinkles on pulmonary auscultation. ECG showed negative T waves in I, II, III, aVF and V6 and chest X-ray revealed alveolar pulmonary edema (fig. 1a). Echocardiography showed a normal left ventricular ejection fraction without underlying dyskinesia. Although the symptoms dissolved spontaneously and quickly ashore, we performed coronary angiography. We found only slight coronary sclerosis with no relevant stenosis. Heart rhythm monitoring revealed no rhythm disturbances. Since the alveolar pulmonary edema resolved spontaneously on the X-ray (fig. 1b) and causes for cardiogenic pulmonary edema were excluded, we diagnosed a SIPE.

**Discussion:** SIPE has first described in divers and swimmers 1989. Nearly 300 cases have since been published. Incidence and prevalence is rising in endurance swimming competitions with a reported prevalence of 1.4% in triathletes. Pathophysiologically SIPE is not fully understood. It’s presumed to originate from exercise-induced elevation of pulmonary capillary pressure causing mechanical stress failure of the pulmonary capillaries. Other factors, which favour a SIPE are: immersion, elevation of the negative intrathoracic pressure and hypothermia. Also cold water, negative static lung load, exertion, fluid loading and low vital capacity are postulated risk factors for SIPE. In order to diagnose SIPE with typical acute symptoms (dyspnea,
haemoptysis appearing during swimming or shortly after, there must be an absence of other causes (laryngospasm, water aspiration) and complete disappearance of the alveolar pulmonary edema on the chest X-ray within 48h. First treatment measures include leaving water, stopping physical exercise and seeking medical care. Therapy is supportive with oxygen and possibly diuretics. Prognosis is good without any structural or functional lung damage. Patients suffered from SIPE are at increased risk of relapse in the same situation.

Aortic valve reconstruction with autologous pericardium instead of prosthetic replacement: new technique and preliminary results of the first 3 cases in Western Switzerland

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Introduction: For more than 10 years, a new technique of aortic valve reconstruction (AVR, stenosis as well as insufficiency) has now been described in Japan with more than 400 cases reported with a mean follow-up of 2–3 years (known as the Ozaki technique, cf. references). We report the first 3 cases in Western Switzerland.

Method: Review of medical records and case report of operated patients with the Ozaki technique for aortic valve reconstruction between November and December 2016 in a Western Switzerland private clinic.

Results: 3 patients have had AVR by the Ozaki technique for: 1. a 68 years old, indication: congenital unicupid aortic valve, small aortic annulus with high risk of prostheses-patient mismatch evaluated by effective orifice area in relation to body size; 2. a 47 years old, indication: 6 weeks post-endocarditis due to Streptococcus mitis oralis aortic valve insufficiency grade IV/IV; 3. a 47 years old, indication: aortic valve fibro-elastoma with severe regurgitation of 50–80% and relative contra-indication to long-term anticoagulants due to co-medication interactions. The hospital follow-up was favorable for all three, apart from the second case which was complicated by a right sided hemotothorax reoperated within 12 h but with uneventful recovery thereafter, with remarkable results on the early post-operative echocardiography follow-up for all 3 cases.

Conclusions: This new surgical technique needs to be known as it offers new perspectives and alternatives as to both classic surgical techniques (bioprosthesis, mechanical valve) and the new transcatheater aortic valve implantation (TAVI). The main interest of this technique is that the implantation of foreign material is no longer needed and the prescription of lifelong anticoagulants or anti-platelets beomes unnecessary, with the hope that the use of autologous pericardium will prove a durable alternative to biological valves. The only restriction to keep in mind is that this technique has no more than a 10 year follow-up since the first reported cases and a mean 2 to 3 years follow-up on the large series reported in 2014.


Vocal cord dysfunction: a forgotten differential diagnosis in acute dyspnea

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Introduction: Vocal cord dysfunction (VCD) is a clinical phenomenon describing an inappropriate episodic adduction of the true vocal folds. The prevalence for VCD is unclear but is estimated to be found in up to 5% of supposed asthmatic patients. Patients typically present themselves at the emergency department with acute upper airway obstruction. Concomitant psychiatric morbidity, gastroesophageal reflux disease and postnasal drip might observed as supplementary risk factors. Since internists are not familiar with VCD, diagnosis is often delayed and leads to unnecessary costs and treatment including intubation and tracheostomy.

Case report: A 61-year-old female patient with severe dyspnoe attacks for many years was considered to suffer from severe and therapy-resistant asthma culminating in admission to an intensive care unit few years ago. Patient history was further remarkable for multiple hospitalisations due to asthma attacks, suspicion of Morbus Widal, reflux, headache and depression. At presentation, the patient was suffering from an acute and severe dyspnoe attack, cough with white sputum and sore throat without fever. Arterial blood gas analysis (under 12 L supplementary oxygen) showed severe respiratory insufficiency (pH 7.44, PCO2 5.37 kPa, PO2 6.04 kPa). Chest X-ray showed no pulmonary infiltrate. The patient was diagnosed with infevorous exacerbation of asthmatic disease and antibiotic therapy (Ceftriaxon) was initiated. Further workup showed normal lung pathogens, while calprotectin was elevated (580 µg/g). Colonoscopy showed non-ulcerating pancolitis, and biopsy revealed chronic epitheloid, non-caseating granulomatous infiltration with low active inflammation, intact crypt architecture and no signs of ulceration. Gastroduodenoscopy also revealed diffuse epitheloid granulomatous infiltration, one granuloma appearing necrotic, while vascular involvement was absent.

Computer tomography showed thickened walls of the colon, small subpleural and peribronchial nodules of the lung with one enlarged hilar lymph node, interpreted as post-bronchitic and unspecific. Differential diagnosis included TB of the GI tract, autoimmune, and inflammatory bowel disease. Extensive tests for infectious diseases and interferon gamma stimulation test in blood were negative, as were TB cultures and PCR from biopsy. Rheuma factor, soluble interleukin-2 receptor and neopterin were elevated, serum angiotensin-converting enzyme level was within normal range. Corticosteroid treatment was started, under which inflammation normalized. Repeated colonoscopy showed a reduction of granulomas, CT scan of the lung resolution of nodules. Finally, histology from transbrachial biopsy confirmed epitheloid granulomas, and the diagnosis of sarcoidosis of the GI tract and lungs was made. Azathioprin was added to the treatment regime, under which symptoms of the patient improved.

Conclusion: Differential diagnosis of granulomatous disease is challenging in patients at risk for tuberculosis. Sarcoidosis of the GI tract is very rare (5–10% of overall cases), and primarily manifests with unspecific symptoms. Before establishing immunosuppressive treatment, infectious diseases, in particular TB must be excluded.
function, discordant with uncontrolled asthma activity. Subsequent detailed history including the use of a VCD screening checklist suggested the presence of vocal cord dysfunction. Following logopedic intervention and start of proton pump inhibitor therapy the patient was dismissed without symptoms. Close follow-up is planned.

Conclusion: This case report highlights the importance of detailed history taking also in patients with longstanding and established diagnoses. In addition, awareness of VCD, recognizing patients at risk and including this differential diagnosis in patients with severe resistant asthma might reduce unnecessary treatments and hospitalisations.

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**Wandering through a rock-garden – case report of Tracheobronchopathia Osteochondroplastica**

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Chronic cough is a very common symptom in general medicine. Sometimes CT and bronchoscopy may reveal an uncommon cause: Tracheobronchopathia Osteochondroplastica (TO). We present a case of this very rare disease. A 71 year old female patient presented with chronic cough for more than a year. She describes waking up from cough at night, especially having heavy attacks in the morning with some tough mucus. She also experiences being hoarse all day with foreign body sensation in the throat. Initial pneumological consultation showed bronchial hyperreactiveness, but inhalation therapy brought no relief. A trial with a proton pump inhibitor was also unsuccessful. A CT scan was performed demonstrating several small lesions adjacent to the tracheal wall mounting to the thyroid gland and beneath. Bronchoscopy then revealed impressive findings of TO. The entire tracheal wall showed multiple firm nodules with intact mucus membranes along the cartilaginous rings sparing the Pars Membranacea.

Since there is no causative therapy, aware of the benign course of the disease, we recommended using antitussive agents to control the patient’s chronic cough. TO is a very rare airway disease of unknown etiology characterized by accumulation of cartilaginous and osseous nodules. It was first described during autopsy by Rokitansky in 1855. TO is mostly incidentally detected in CT Scans, during intubation or bronchoscopy. Symptoms of patients are usually chronic cough despite adequate treatment trials, exertional dyspnea, hoarseness, occasional hemoptysis and recurrent pulmonary infections. Diagnosis is established via radiology and bronchoscopy demonstrating characteristic small submucosal nodules in the trachea sparing the posterior wall. It can affect the entire trachea ranging as far as the main bronchi, in some cases causing atelectasis. Lesions may be so numerous that the bronchoscopic aspect may appear as a “rock-garden”. Histopathology shows calcification, chondrification or lamellar ossification, with possible foci of bone marrow and hematopoiesis. The underlying etiology and pathology of TO are unclear. Differential diagnosis include tracheal neoplasms, calcificating tuberculosis, tracheobronchial calcinosi, Wegener granulomatosis and relapsing polychondritis. The course of TO is benign with only slow progression. Only few of the cases showed or developed more severe airway obstruction. Therapy focusses on symptom control using centrally acting antitussive agents.

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**Myocarditis associated with campylobacter enteritis**

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Introduction: Myocarditis in developed countries is very often associated with an infectious etiology, especially viral infections. An association with bacterial infections is much less frequent – especially the association with campylobacter enteritis is reported only in few cases.

Case report: A 24-year-old, healthy young man was admitted to our emergency department because of sudden chest pain, increasing with deep inspiration. Apart from transient fever and watery diarrhea for the last 3 days the clinical history as well as the actual vital signs were unremarkable, no cardiovascular risk factors were known, no drug intake. An ECG showed only non-specific findings. Initial blood tests showed elevated cardiac and inflammatory markers (Troponin-I 5297 ng/l (normal value <30 ng/l), C-reactive protein 201 mg/l (normal value <8 mg/l)). An echocardiography revealed only mildly reduced left-ventricular ejection fraction with an infero-lateral hypokinesia (fig. 1). While computed tomography coronary angiography could rule out coronary artery disease, cardiac magnetic resonance imaging showed extensive areas of late gadolinium enhancement in the basal segments of the interlateral wall (fig. 2). Diarrhea as well as chest pain ceased during the next days without specific treatment. Stool culture revealed campylobacter jejuni (retrospectively due to tartare ingestion 5 days before symptom onset). So we were able to make the diagnosis of campylobacter-associated myocarditis.
In an outpatient control 4 weeks later the patient described an uneventful course. The echocardiographic findings as well as laboratory findings were normalized.

**Conclusion:** Campylobacter jejuni-enteritis is a rare cause of myocarditis, a special feature is the short time interval of one to five days between the onset of enteritis and the onset of myocarditis.

To understand the relation between Campylobacter infection and myocarditis, and at least prevent co-accurrence, it might be important to identify the pathomechanism, which is not known yet.

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**Watch AF – Smartwatches for detection of atrial fibrillation**

**Introduction:** Detection of atrial fibrillation (AF) is of pivotal importance for stroke prevention. Recent studies confirmed the merits of long-term monitoring. Current wearable diagnostic tools are burdened with disadvantages of inconvenience, costs or invasiveness. In a previous study we tested an app that employed photoplethysmographic (PPG) signals of a smartphone camera to distinguish between normal sinus rhythm and AF based on the newly developed Preventicus® Heartbeats algorithm. That retrospective study has been shown to achieve a sensitivity and specificity of 95%. In the WATCH AF study, this algorithm is tested for the first time with PPG signals from a smartwatch (Samsung) and a wristband (Wavelet health). Our study aims to determine the accuracy of these applications compared to an ambulatory ECG system.

**Methods:** In this prospective, blind, international, multicenter-study, 600 subjects are being recruited until March 2017. Subjects must be of legal age. SR group is age- and gender-matched with the AF group. Pulse wave curves will be recorded for five minutes simultaneously with a smartwatch on one and a wristband on the other arm (sides randomized). At the same time, an ambulatory ECG system will record a synchronous ECG as reference. The pulse wave curve data will be analysed in a blinded manner off-line with the Preventicus® Heartbeats algorithm and will then be labelled as either SR or AF. Additionally, information about cardiovascular risk factors, concomitant disease and medication, are collected. Primary target parameters are the app’s sensitivity and specificity in correctly detecting AF compared to an automatically interpreted ECG. Secondary target parameters include the proportion of non-evaluable recordings in the overall study and differences between the two devices.

**Results:** The enrolment is expected to be complete in March 2017. Complete trial results are expected for in April 2017.

**Conclusion:** WATCH AF is the first study to validate PPG signals from the wrist to detect AF in a blinded, ECG controlled fashion.

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**Long term relapse of Whipple’s disease: a case report and literature review**

**Introduction:** Detection of atrial fibrillation (AF) is of pivotal importance for stroke prevention. Recent studies confirmed the merits of long-term monitoring. Current wearable diagnostic tools are burdened with disadvantages of inconvenience, costs or invasiveness. In a previous study we tested an app that employed photoplethysmographic (PPG) signals of a smartphone camera to distinguish between normal sinus rhythm and AF based on the newly developed Preventicus® Heartbeats algorithm. That retrospective study has been shown to achieve a sensitivity and specificity of 95%. In the WATCH AF study, this algorithm is tested for the first time with PPG signals from a smartwatch (Samsung) and a wristband (Wavelet health). Our study aims to determine the accuracy of these applications compared to an ambulatory ECG system.

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**Results:** The enrolment is expected to be complete in March 2017. Complete trial results are expected for in April 2017.

**Conclusion:** WATCH AF is the first study to validate PPG signals from the wrist to detect AF in a blinded, ECG controlled fashion.
dose of amiodarone (150 mg) was intravenously given. The AF was successfully converted into sinus rhythm. On the following day the patient suffered a wake-up stroke with a sudden right-sided motor weakness and dysarthria. A gadolinium-enhanced MRI confirmed multiple acute cerebellar infarctions in the territory supplied from the posterior inferior cerebellar artery, the cortical branches of the basilar artery and of the posterior cerebral artery left. Vascular investigations showed an acute occlusion of the P1 segment of the left posterior cerebral artery. No other intracranial arterial occlusions that could suggest an in situ atherothrombotic mechanism or an artery to artery embolism were documented. Because of the multiple infarctions in the posterior circulation and because of the clear association between the neurological deficit and the cardioversion a thromboembolic stroke following amiodarone was postulated. M-mode echocardiography revealed an enlarged left atrium, suggesting long-standing AF. Anticoagulation was started 4 days later. The patient showed a complete recovery and was discharged.

**Conclusion:** Thromboembolic events following electric cardioversion are a well described complication. However, thromboembolism by pharmacological cardioversion of AF may be underestimated and therefore the importance of anticoagulation prior to pharmacological cardioversion may not be underestimated.

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**High-intensity interval training as treatment strategy for heart failure patients with preserved ejection fraction: a protocol proposal for a prospective single-blind randomized controlled trial**

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**Background:** Chronic heart failure (HF) is a common symptom complex characterized by shortness of breath, fatigue, fluid retention and severe exercise intolerance. HF with preserved ejection fraction (HFpEF) occurs in about 50% of all HF patients. Remodeling and fibrosis stimulated by inflammation appear to be main factors for the progression of HFpEF. Furthermore, iron deficiency (ID) has been recognized to be a common comorbidity in HFpEF. The lack of prognostic treatment options in HFpEF urgently calls for new therapeutic approaches. While beneficial effects of exercise training and iron substitution have been demonstrated in HF with reduced ejection fraction, they have not yet been evaluated in HFpEF. Therefore, the aim of this study to be discussed is to investigate the effect of exercise training in HFpEF patients with optimally adjusted iron values. Exercise tolerance measured as peak oxygen uptake (VO2peak) will be the primary outcome.

**Method:** The proposed study will be a prospective single-blind randomized controlled trial in a primary care setting including 98 patients with stable HFpEF. Patients will undergo 3 study visits including measurements of disease-specific biomarkers, cardiac and arterial vessel structure and function, exercise tolerance, habitual physical activity, body composition and quality of life (QoL). After the first visit, patients with ID will undergo iron substitution until sufficient iron levels are reached (over max. 12 weeks), in order to ensure comparable baseline conditions for the training intervention. The study measurements will be repeated after 12 weeks in both, initially iron deficient and non-iron deficient patients. Patients will then be randomized to the intervention or control group, stratified by initial iron-deficiency status. The intervention group (n = 49) will attend a supervised 12-week high-intensity interval training on a bicycle ergometer. The control group (n = 49) will be advised to continue usual care. After 12 weeks, the study measurements will be repeated in all patients to monitor the effects of the intervention. At 6 months, 1, 2, and 3 years after the last study visit, telephone interviews will be performed to assess medical outcomes (e.g. hospitalizations, cardiac events, death) and QoL.

**Outlook:** This study is expected to add important knowledge about the potential utility of a novel treatment strategy in HFpEF patients, which may help to improve both, QoL and functional status.
Anaphylactic shock to bilastine

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Introduction: Antihistamines are drugs that antagonize the activity of histamine receptors. H1-Antihistamines are first-line treatment for chronic urticaria and are used to treat allergic reactions. Anaphylactic reactions to antihistamines are very unusual.

Methods: We describe the case of a 53-year-old woman with history of chronic urticaria experiencing urticaria, angioedema and syncope to multiple H1-antihistamines (hydroxyzine, cetirizine and fexofenadine). In order to proof tolerance with an alternative H1-antihistamine a double-blind provocation test with bilastine versus placebo was performed.

Results: After a cumulative dose of 37 mg bilastine (90 minutes), the patient developed generalized urticaria. Prednisolone 100 mg per os was given immediately. After 360 minutes, the patient felt dizziness with drop of blood pressure (84/54 mm Hg) and tachycardia (107/min). The patient recovered after intramuscular injection of 0.3 mg adrenaline. One hour after the reaction, blood sample showed an elevated tryptase (36.7 µg/l) which normalized several days later, consistent with a mast cell-activation in IgE-mediated reaction. Finally, the urticaria was treated with monthly injection of 300 mg omalizumab with good tolerance without recurrence of urticaria (follow-up 5 months).

Discussion: Hypersensitivity reactions to H1-antihistamines are very rare and only twelve cases have been reported in literature. Above all, cetirizine has been implicated in these reactions. The exact mechanisms are speculative, but the piperazidine ring has been implicated in some cases of cetirizine hypersensitivity. However, this hypothesis remains controversial as prochlorperazine, an antiemetic drug containing a piperazidine ring, was well tolerated in another case after cetirizine anaphylaxis. Other groups suspected a hypersensitivity to side chains of cetirizine. Interestingly, an intolerance reaction to cetirizine has also been reported.

Conclusion: This is the first report of an anaphylactic reaction to bilastine. Patients may react to one single or multiple H1-antihistamines, which is challenging in the treatment of chronic urticaria. Prediction of crossreactivity is difficult because the epitope has not been identified. Careful assessment of the risk/benefit ratio is necessary to avoid potentially harmful provocation tests. Omalizumab should be considered as first choice treatment in patients with chronic urticaria and H1-antihistamines hypersensitivity.

Painless swelling of the forefoot and recurrent subcutaneous abscesses of the lower leg – two distinct presentations illustrating the spectrum of eumycetoma in a non-endemic country

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Introduction: Eumycetoma is a neglected tropical disease that is characterized by the triad of painless swelling, sinus formation and purulent discharge. This chronic disease causes significant disability if diagnosed late.

Methodology: We report two cases of eumycetoma presenting to our hospital, one early presentation with a painful swelling of the left forefoot in a 41-year-old man from the Indian subcontinent (Patient 1) and one late presentation with recurrent subcutaneous abscesses of the left leg extending into the ankle joint in a 21-year-old Eritrean migrant (Patient 2).

Results: Patient 1 had emigrated from India to Switzerland in 1996, and his last visit to the Indian subcontinent (Pakistan) was five years ago. He presented with a soft tissue mass on his left forefoot, which has been steadily growing over three months. Owing to the initial suspicion of a soft tissue tumor, the patient underwent complete surgical resection. Histopathology revealed fragments of black grains and a granulomatous necrotizing inflammatory reaction surrounding fungal hyphae (fig. 1). Identification of Madurella mycetomatis as the causative organisms was established by panfungal polymerase chain reaction (PCR). The patient was treated with itraconazole for six months with regular therapeutic drug monitoring without evidence of relapse 30 months after treatment cessation. Patient 2 had emigrated from Eritrea about four months before presentation to our hospital with progressive pain and swelling of his left ankle. On examination, a painful fluctuation was noted below his medial ankle consistent with a subcutaneous abscess (fig. 2), which was drained and sent for culture.
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Fever after treatment with rituximab and bendamustine – don’t forget the ticks!
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Department Medizin, Kantonsspital Winterthur, Winterthur, Switzerland
Case report: A 79 year-old patient suffering from follicular lymphoma stage IV was referred to our clinic for further evaluation of daily fever >38 °C, fatigue, arthralgias, imbalance and weight loss. A recent relapse of lymphoma had been treated with rituximab and bendamustine. Clinical examination showed cachexia and slightly enlarged and indurated cervical, suprascapular (left) and axillary (right) lymph nodes. Laboratory analyses demonstrated anemia (Hemoglobin 9.2 g/dL; normal range: 14.4–17.5 g/dL), elevated C-reactive protein (CRP 86 mg/L; <5 mg/L) and ferritin (1600 mg/L; 22–275 mg/L) but normal lactate dehydrogenase (165 U/L; <220 U/L). Blood cultures and serologies for an infectious etiology (Parvovirus B19, Brucella, Coxella) were negative. PET-CT showed increased FDG-uptake in bone marrow and lymph nodes and needle biopsy of the latter was compatible with recurrent lymphoma. However, broad spectrum bacterial PCR (16s rRNA) from blood and lymph node was positive for Candidatus Neoehrlichia mikurensis establishing the diagnosis of neoehrlichiosis. Within a day after initiation of antibiotic therapy with doxycyclin fever ceased and the patient recovered quickly. He did not recall a tick bite.
Discussion: Candidatus Neoehrlichia mikurensis is a tick-transmitted, nonculturale intracellular bacterium recently identified to cause prolonged fever in immunocompromised patients particularly after rituximab. Additional symptoms include malaise, weight loss, myalgias, arthralgias as well as vascular and thromboembolic events. Up to 8% of Swiss ticks are infected with C. N. mikurensis. Nevertheless, neoehrlichiosis remains a rarely identified disease suggesting only mild and transient symptoms in immunocompetent hosts. However, neoehrlichiosis should be actively searched for using molecular diagnostics in immunocompromised patients. Fever and other unexplained inflammation since exposure is easily possible in Switzerland and treatment with doxycyclin is simple and highly effective.

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Pulse corticosteroids-induced bradycardia
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Introduction: High dose intravenous (pulse) corticosteroid therapy is used to treat a vast array of diseases. Pulse corticosteroids-induced bradycardia is rare and has been seldom reported. Methods: We describe the case of a patient with neutrophilic dermatosis who developed bradycardia after pulse methylprednisolone. We used the Naranjo adverse drug reaction probability scale to determine the likelihood of a causal relationship between bradycardia and steroid administration. Results: A 38 year-old woman was admitted to our unit for myalgia and fever. Patient’s medical, family, allergy and travel history was insignificant. She was taking no drugs or medications and denied contact with ill persons. A part from fever (38.8 °C), parameters (blood pressure, heart rate [HR], saturation) were normal. Physical examination revealed tenderness over the right deltoid and lumbar area, painful cervical lymphadenopathy and tender vesico-pustular lesions over the face, neck, arms, thighs and back; bilateral arthropathy was also present. Besides leucocytosis and an elevated CRP (233.5 mg/l), blood tests (kidney and liver function, common viral serologies and a complete immunological panel) were normal. ECG and chest X-ray were unremarkable. Biopsy of one skin lesion showed dermal neutrophilic infiltrate without vasculitis. We considered a diagnosis of acute neutrophilic dermatosis. Pulse methylprednisolone therapy (1 g/ day for 3 days) was introduced. Improvement was dramatic with rapid disappearance of pain and fever, resolution of skin lesions and normalization of inflammatory parameters. 48 hours after the first pulse of methylprednisolone, the patient presented asymptomatic bradycardia (HR: 40 BPM) with an HR of 32-38 BPM in the following days. ECG showed normal sinus rhythm without AV conduction abnormalities. We opted for watchful waiting. The patient was switched to oral prednisone (1 mg/kg per day) on day 4. 72 hours after the last pulse HR was normalised (>60 BPM). The patient was finally discharged at day 10. At 1-month follow-up the patient, still on oral steroids, is fine and HR is normal.
Conclusion: In the absence of other drugs or medical conditions that could affect HR, and with a Naranjo scale of 7 (probable relation), we believe that patient’s bradycardia should be ascribed to pulse methylprednisolone. We suggest that HR should be routinely evaluated in patients receiving pulse corticosteroids and particularly in those with cardiac risk factors.
A rare cause of severe systemic inflammation and bilateral femoral head osteonecrosis

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Introduction: Femoral head osteonecrosis is a rare disease occurring nct infrequently bilateral. Superinfections are rare and can be associated with risk factors for bacteremia (central lines, urinary tract infection, etc.).

Case report: A 63-year-old female patient with severe pain from bilateral femoral head osteonecrosis was admitted for bilateral hip joint replacement. Blood analyses are shown here:

<table>
<thead>
<tr>
<th>Table: Blood analysis</th>
<th>Result</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>66 g/l</td>
<td>120–160 g/l</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>13.5 G/l</td>
<td>4–10 G/l</td>
</tr>
<tr>
<td>Platelets</td>
<td>604 G/l</td>
<td>150–300 G/l</td>
</tr>
<tr>
<td>Albumin</td>
<td>18.9 g/l</td>
<td>34–48 g/l</td>
</tr>
<tr>
<td>C-reactive Protein</td>
<td>228 mg/l</td>
<td>&lt;8 mg/l</td>
</tr>
</tbody>
</table>

Three months earlier the patient was hospitalized in another clinic because of a urosepsis with Escherichia coli. At that time, chronic hip pain exacerbated and advanced bilateral femoral head osteonecrosis was diagnosed radiologically. Two weeks after discharge the patient had fever, felt weak and increased inflammatory markers (CRP 168 mg/l) and a low hemoglobin of 66 g/l (which was 89 g/l at discharge) were measured. An upper and lower endoscopy, CT scan and a bone marrow aspirate were performed without further diagnostic clues. Finally, an 18F-FDG PET/CT Scan showed FDG-uptake in both hips what was considered as a consequence of femoral head osteonecrosis.

![Figure 1: PET-CT Scan.](image)

The implantation of a total hip prosthesis was performed first on the right side. As preoperatively planned the femoral head was taken for histology and microbiological examinations. Postoperative antimicrobial treatment with intravenous amoxicillin/clavulanate was started. Histology showed destruction of the femoral head and osteonecrosis. A pansensible E. coli was grown. Ten days later, a Girdlestone situation was created on the left side. E. coli osteomyelitis could also be diagnosed there. Amoxicillin/clavulanate was changed to ceftriaxone and after 4 weeks to ciprofloxacin per os. A rapid clinical improvement and a slow decrease of the inflammatory markers occurred. After 12 weeks, antimicrobial treatment was stopped and after an interval of 2 weeks and normal CRP, the implantation of the left hip joint was done. One year later, the patient was free of pain and had a good functional result.

Conclusion: In patients with femoral head osteonecrosis and elevated inflammation markers, superinfection should be considered. It is very important to initiate a histological and microbiological examination of the femoral head. FDG uptake is unspecific and cannot differentiate between neoplasia and inflammation caused by necrosis or infection. Only few cases of documented bilateral superinfection of bilateral femoral head osteonecrosis were found in the literature.
Involvement of the adaptive immune system in metamizole-induced agranulocytosis

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Introduction: Metamizole is an analgesic and antipyretic drug that represents an alternative when NSAID and acetaminophen are contraindicated. Nevertheless treatment with metamizole can lead to life-threatening agranulocytosis in rare cases. To date mechanisms underlying metamizole-induced agranulocytosis (MIA) remain unknown. A few cases of patients re-exposed to metamizole reacted with rapid onset and more severe symptoms are known. This suggests that the adaptive immune system could be a key player in the pathogenesis of MIA.

Methods: A clinical cohort has been created including MIA patients, metamizole tolerant patients and unexposed healthy donors. PBMC of these three groups are being cultured with metamizole and its metabolites in vitro. Cellular activation is measured by analysis of CD69 upregulation and proliferation with flow cytometry. Generation of metamizole-reacting T cells lines is performed as well.

Results: The reactivity of T cells from MIA patients towards metamizole or its metabolites has been investigated using capacity of T cells to proliferate, to secrete cytokines (TNF-α) and to be cytotoxic (CD107a) after antigen encounter. So far a T cell response against metamizole could not be obviously shown. Indeed the proliferation seen in MIA patient was only moderate and did not reach statistical significance when compared with control groups. Furthermore, TCL generation was not easily achieved and TCL reactivity could not be kept in vitro over a long period. T cell response in MIA patients cannot be excluded either at this point.

Conclusion: These non-significant results may be due to several reasons: a low detection threshold, an inadequate stimulation, a still unknown metabolism or a maladjusted protocol to the drug used.

Comparison of new and old definitions for diagnosis of sepsis in non-ICU patients

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Background: Definition of Sepsis used to be based on SIRS criteria. However, these criteria turned out to be too permissive and diagnosis of sepsis did not have impact in prognosis or treatment. The new definition (Sepsis 3.0) is based on organ dysfunction and should more reliably select patients with critical infectious situations.

Methods: Inclusion of febrile patients, in whom an infectious disease consult was performed. ICU-patients were excluded. Sepsis diagnosis was made with both old and new definition. For the old definition, at least two of four SIRS criteria had to be present. For the new definition, quick SOFA score was done. If this was positive, sepsis was confirmed with an at least two point increase in SOFA Score.

Results: 176 patients were included. 29 patients had no sepsis in both definitions. While according to the old definition, 144 patients were diagnosed to have a sepsis, this was present in only 70 patients according to Sepsis 3.0. 67 patients were found to be septic in both the old and the new definition. Only three patients were “upgraded”, having no sepsis according to the SIRS definition but fulfilled the criteria of Sepsis 3.0.

Conclusion: In Non-ICU patients, only about half of the patients with Sepsis according to the old definition fulfill criteria of Sepsis 3.0. These could have implication for case-weights in the DRG-System.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Old Definition</th>
<th>New (Sepsis 3.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sepsis</td>
<td>144</td>
<td>67</td>
</tr>
<tr>
<td>no Sepsis</td>
<td>123</td>
<td>77</td>
</tr>
<tr>
<td>total</td>
<td>267</td>
<td>144</td>
</tr>
</tbody>
</table>

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Treatment of Helicobacter pylori unmasking Whipple’s disease

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Case: A 54-year old man presented with a 10 year long history of twice weekly intermittent fever, arthralgia, soft tissue swelling and systemic inflammation. Numerous medical evaluations at different institutions including innumerable tests for malignant, infectious or autoimmune diseases, including PET/CT scans and bone marrow biopsy yielded no conclusive results. Histology of a duodenal biopsy had shown no evidence for Tropheryma whippelii (TW) in 2009. The only short period the patient reported lack of symptoms was following a treatment with amoxicillin, metronidazol and pantoprazol for a helicobacter pylori (HP) infection. Triggered by the history of response of the symptoms to antibiotics during HP eradication therapy, a new search for Whipple’s Disease (WD) was initiated. Again no histological signs for TW were found in a duodenal mucosal biopsy. However, PCR for TW was positive in duodenal mucosa and in stool. Treatment with cotrimoxazol had to be changed to ceftriaxone due to a severe DRESS syndrome (drug reaction with eosinophilia and systemic symptoms), followed by doxycycline and hydroxychloroquine for an ongoing 2 months. The medical condition improved dramatically within days of starting ceftriaxone treatment: Systemic inflammation and symptoms disappeared and physical performance improved rapidly. The patient has been free of any symptoms since August 2016.

Discussion: Whipple’s Disease is a rare, systemic infection caused by the intracellular bacterium Tropheryma whippelii (TW). Clinical presentation may vary greatly and can mimic multiple clinical conditions. All organs can be affected. In classical gastrointestinal WD, the clinical condition and PAS-positive foamy macrophages in the lamina propria of duodenal mucosa lead to the diagnosis. In extraintestinal disease, the histological or PCR finding of TW in specimens are proof of infection. TW can be a commensal of the upper GI-tract, therefore a PCR result in both duodenal mucosa and stool leaves a 10% likelihood of false positivity. The diagnosis of a TW-associated condition must then be assumed by the clinical response to antibiotic therapy. In our patient, careful history taking led to a clinical suspicion, the response of a year-long clinical illness to antibiotics on two occasions makes us confident to classify our patient as having probable, albeit not completely proven TW associated systemic infection.
Written interprofessional communication in the follow-up of homebound patients

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Introduction: In the follow-up of homebound, polymorbid patients, health professionals in Geneva often use a point-of-care notebook to share information with each other (“carnet de liaison”). The aim of the study was to analyse how and for what health professionals used such notebooks and to explore their perceptions regarding the strengths and weaknesses of such written notes for interprofessional collaboration.

Methods: We conducted a mixed-method study among health professionals caring for homebound patients in the canton of Geneva, Switzerland. A sample of notebooks of homebound elderly patients in Geneva was first analysed descriptively. Then 6 focus groups interviews were conducted with different groups of health professionals (doctors, nurses and nursing aides). Focus groups were transcribed verbatim and analysed thematically.

Results: The analysis of 11 notebooks revealed that most of the time, the intended recipient of written information was unspecified; content focused mainly on somatic health and medication; explicit interprofessional communication was rare and patients never wrote down any information. There were no explicit care plan goals.

Thirty-one health professionals participated to the focus groups. Several themes emerged. Participants felt that the notebook embodied the primary care network and was a milestone in the follow-up of homebound polymorbid patient. However, in the absence of a shared electronic health record, most of them complained about having to write the information down at least twice. The fact that the notebook was accessible to anyone and was considered the patient’s property influenced how and what professionals wrote in the notebook. Lack of patient contributions to the notebook was a source of concern.

Conclusions: Our results show that fulfillment of notebook’s primary function (i.e. share information and communicate among health professionals) is suboptimal. In order to enhance patient-centered, written interprofessional communication, more attention should be paid to defining and implementing care plan goals. 

Regional variation in primary care in Switzerland?

Work Force Study 2015

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Introduction: The issue of shortage of General Practitioners (GPs) is an important matter of debate. With the Work-Force-Study 2015 the current work situation of GP was assessed. The aim of this study was to evaluate whether in primary care regional variation exist in terms of working hours, workload, and job satisfaction in Switzerland.

Methods: In 2015 a 7-page survey assessing the work conditions was sent to 3354 Swiss GPs. In total, 1299 surveys (response rate of 36.6%) were available for analysis. The questionnaire was available in German (n = 964), French (n = 273) and Italian (n = 62). The study population consisted of 26% female GPs and the average age was 55 years. The data was analysed for potential differences between cities, agglomeration, and countryside. For the classifications of these categories a definition of the Federal Statistical Office was applied. Additionally the data was investigated for potential differences between the three linguistic regions in Switzerland.

Results: GPs on the countryside have more patient contact per week compared to their colleagues in the cities (36.7 hours vs. 33.3 hours, p = 0.002). Rural doctors provide essentially (p < 0.001) more emergency services (38.1 days per year) than in the city (10.1 days per year). Country doctors are as satisfied with their workload (p = 0.35) and work situation in general (p = 0.415) as their colleagues in the other regions. The proportion of GPs who perceive a lack of GPs lies between 55.7% and 65.3% without reference to rurality (p = 0.053). In the German-speaking part, 11 GPs have weekly contact with their patients during 33.8 hours whereas in Romandy they have 35.6 hours and in the German-speaking part GPs have weekly contact with their patients during 33.8 hours whereas in Romandy they have 35.6 hours and in the German-speaking part GPs have weekly contact with their patients during 33.8 hours whereas in Romandy they have 35.6 hours and in

Conclusion: Despite higher workload on the countryside, the job satisfaction does not essentially differ between city and countryside. In the city as well as in GPs in areas short of GPs is considered a serious issue. We found significant differences between the linguistic regions in Switzerland that should be considered when implementing political measures.

Use of new oral anticoagulants in an academic primary care medicine facility: where are we now?

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Direct oral anticoagulants (NOAC) have become the first alternative to vitamin K antagonists (VKA) showing a reduced hemorrhagic risk, short half-life, lack of food interaction, need for monitoring and minimal drug interactions. The only drawback is the limited availability of an antidote. Few studies have looked at the adoption of these drugs by primary care physicians.

Objectives: To evaluate the proportion of patients currently receiving VKA eligible for NOAC and to facilitate interns uptake of the new recommendations.

Method: The study was conducted within the Division of Primary Care Medicine. All patients receiving VKA and followed-up between April 2015 and May 2016 were included. Based on the HUG recommendations on NOAC, we designed a study file exploring: sociodemographic and medical characteristics for any form of follow-up, number of venous and capillary INR checks, proportion of therapeutic values, therapeutic adherence, and the presence or absence of contraindications to NOAC. After a pilot test, interns were asked to analyze a set of electronic medical records (EMR).

Results: Each intern spent 2 hours conducting in-depth analysis of 5-7 EMR. Fifty-seven patients on VKA were identified (men: 71.9%; mean age: 63.6, standard deviation: 14.6 years). Indicators for anticoagulation were under treatment or prevention of thromboembolic events (n = 13, 23%), prevention of stroke by non-valvular atrial fibrillation (AF) (n = 19, 32.7%), prevention of stroke by valvular AF or mechanical valve (n = 17, 30.7%), others (n = 8, 13.6%). In the 35 (61.4%) patients eligible for NOAC therapy, the average duration of VKA treatment was 5.4 (SD: 4.7) years. The previous year’s mean number of venous and capillary INR measurements was 9.4 (SD: 10.6) and 9.7 (SD 9.5). The percentage of patients with INR within the therapeutic range in more than 50% of tests was 38.2%. Therapeutic adherence was evaluated as good in 50%. Only 21.2% had medical contraindications and 8.8% pharmacological contraindications. After considering all factors, 22 (63%) patients could benefit from a change in oral anticoagulation in favor of NOAC. However, only 11% had been switched to NOAC during the one-year study period.

Conclusion: A minority of patients had safe and effective anticoagulant therapy. Nearly two-thirds on VKA could theoretically be switched to NOAC while the actual rate of change was low. Next step will imply measuring the impact of training on the guidelines adoption.

Syrian crisis: an innovative sanitary response in the canton of Vaud

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Introduction: The Swiss government started a resettlement program, in collaboration with the United Nation High Commission on Refugees (UNHCR) to facilitate the arrival of particularly vulnerable refugees from Syria. As those refugee families don’t follow the usual procedure for asylum seekers, a dedicated healthcare program is needed. Around 1800 persons are expected to arrive in Switzerland between 2015 and 2017 from the resettlement program. The objectives of the present project are: 1) To provide the necessary healthcare for this particularly vulnerable population in the canton of Vaud. 2) To gather information about this population, in terms of medical conditions, but also from a more holistic view of the families, as we know they are selected on vulnerability criteria. This can be used as a feedback to the health authorities about the specific needs of this population.

Method: An interdisciplinary family consultation was set up for those families, staffed with a pediatrician, a general practitioner, an interpreter, as well as a nurse practitioner. At the 1st consultation, a health assessment is provided to the family at the same time.
Vaccinations are proposed and screening for tuberculosis is planned for children systematically. Patients can then be oriented toward different medical specialties as needed. A second consultation is planned two months later for a clinical follow-up, to pursue the vaccination plan, and to discuss the results if tests were performed. A shared meeting with the medical team concludes the assessment. After this 2nd consultation, a follow-up with a private general practitioner and/or pediatrician is organized.

Results: Between July and December 2016, 60 persons have been seen for a first medical evaluation, including 32 adults and 28 children. The adults had on average complaints concerning 3.1 chapters of the ICPC-2 classification (classification of symptoms and medical conditions for primary care), and children 1.3. With the use of a validated vulnerability scale published by Bodenmann & al. 2 adults were identified with 4 axes of vulnerability and 3 with 3 axes. One child was identified with 3 axes.

Conclusion: The interprofessional model of a consultation for Syrian migrant families is feasible. It could be implemented in other cantons receiving Syrian refugees and could be extended to different refugee populations. Medical information about this population can be useful to the health authorities.

Monitoring of patients with chronic diseases in primary care using electronic medical record

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Purpose: Non-communicable diseases account for about 80% of health costs in Switzerland. Long term care for patients with chronic diseases poses a huge challenge. Deficits exist regarding monitoring and structured follow up. Our goal was to develop an evidence based and practical tool to help monitor patients with chronic diseases by means of an electronic health record (EHR).

Methodology: Five highly prevalent chronic diseases were chosen to develop the monitoring tool: Diabetes mellitus type 2, arterial hypertension, asthma, osteoarthritis and chronic heart failure. A best practice review among international guidelines was performed searching for indicators how to monitor each disease. In order to find further relevant indicators, this search was complemented by a systematic review of primary literature on the subject “monitoring”. The resulting two data sets were then combined and evaluated by selected experts of each specialty by means of a Delphi procedure (fig. 1).

Results: This multi-step procedure resulted in a condensed set of indicators, divided into sublayers to maximise ergonomics. A cockpit serves as an overview of fixed goals and set procedures to facilitate disease management. An additional tab contains information on non-disease specific indicators, as for example allergies and vital signs (fig. 2).

Conclusion: To our knowledge this study represents the first scientifically founded recommendation for the standardised long term monitoring of chronically ill patients in general practice. The ergonomic layout of the monitoring tool enhances user friendliness and facilitates chronic care by means of an EHR. In the near future, the Delphi procedure will be extended to an international level aiming at a European consensus paper on monitoring of chronic diseases by means of EHR. IHAMZ: Institut für Hausarztmedizin Zürich (Institute of Primary Care, University of Zurich)

Involvement of a group of simulated patients in a patient advisory group to conduct iterative cycles of evaluation and adaptation of communication material to the public. Results from a pilot project

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Introduction: Guidelines recommend a participatory approach with target populations when developing decision aids and communication materials (CM). While focus groups enable patients to comment on CM, they are often conducted with final versions of CM, limiting opportunities for significant changes. Iterative cycles of evaluation and adaptation allow users to shape CM at early stages of development and to verify whether changes improve the CM. We aimed to test the feasibility and yield of involving a group of simulated patients in a patient advisory group to improve CM developed within a statewide colorectal cancer (CRC) screening program.

Methods: We invited simulated patients aged 50–69 years involved in the teaching of medical students from the University of Lausanne to participate in a patient advisory group. Exclusion criteria were personal history of CRC. We planned 2h meetings every 3 months and used a cyclic approach: we submitted the CM beforehand, collected the comments during group discussions, identified specific adaptations to be made, adapted the CM, and re-submitted the modified CM to the group for further adaptations. Participants received a CHF 50.– voucher per meeting for their participation.

Results: Out of the 20 eligible simulated patients invited, 5 (25%) accepted the invitation. They came to 4 meetings every 3 months over a 12-month period. Their comments helped to identify discrepancies between the intended and perceived tone of messages in CM, test the proposed solutions and readapt based on repeated evaluation. In particular, they commented on the overall presentation, the vocabulary, formulations, and the character of the message. In addition, they suggested developing new CM for people with special needs. All participants said they would recommend others to participate in these groups and approved the process of implicating patients in the development of CM.

Conclusion: The participative approach of having CM be reviewed by a patient advisory group improved the CM and helped identify critical elements and avoid discrepancies in the CM. The cyclic approach was useful to clarify our understanding of the comments of the participants. This pilot project highlighted the willingness of participants to be implicated in the process of evaluation of medical CM. The method should now be rigorously tested in particular with populations with special needs.
4-year-long-term follow-up in diabetes patients after implementation of the Chronic Care Model in primary care

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Introduction: Implementing the Chronic Care Model (CCM) via involvement of specially trained practice nurses improves cardiovascular risk profile as well as perception of care among type 2 diabetes patients in small primary care practices (PCP) on the short term. Little is known on the long term effects of this intervention.

Methods: Cross-sectional survey among the participants of the cluster randomized controlled CARAT trial (30 PCPs, 303 diabetes patients) three years after its completion.

Outcomes: proportion of patients still treated according to CCM, possible reasons for discontinuation, glycosylated hemoglobin (HbA1c), blood pressure (BP), LDL-cholesterol, and accordance to CCM (assessed by PACIC (Patient Assessment of Chronic Illness Care)).

Results: 40.9% of practices (40.7% of patients) continued using the CCM. PCPs originally randomized to the intervention arm were significantly more likely to still using the CCM (p < 0.001). Main reasons for discontinuation were organizational (40.9%) and financial aspects (18.1%) and the general practitioner refusing to hand over treatment responsibility (18.1%). Development of HbA1c, BP, LDL-cholesterol and PACIC showed some significant positive effects in favor of practices originally randomized to the intervention group and practices continuing to treat patients according to the CCM.

Conclusions: Diabetes care according to the CCM including the involvement of practice nurses is a reasonable tool to improve care also in the long-term. CCM-training of the whole team is essential to overcome organizational challenges. Continuous team education, technical decision support, as well as recognition of the importance of these new structures by health care policy might improve the long term clinical effect of the team approach.

TRIAL REGISTRATION: The study protocol was published in Cardiovascular Diabetology in 2010, registration number: ISRCTN05947538.

Vulnerable patients in an academic community health centre in Geneva: health needs, services utilization and impact of nurses front-line consultation

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Introduction: The community health centre (CAMSCO) of the Geneva University Hospital (HUG) is a unique academic structure in Switzerland, serving as a walk-in clinic for patients with socioeconomic vulnerability and as a port of entry into the public healthcare system. Nurses conduct first-line comprehensive assessment and do triage and orientation. We aimed at characterizing patients health needs, health services utilization and the impact of front-line nurses consultation.

Methods: We included all patients consulting in August 2016 and extracted data from their health records.

Results: The 483 patients were mostly female (60.9%), aged 40.1 (SD: 11.9) years old. Only 1.5% were insured in Switzerland and 8.1% were homeless. They originated from Europe (17.4%), Asia (23.2%), Latin America (39.5%) and Africa (19.9%). It was the first contact ever with HUG in 26.7%, whereas 47.3% had consulted CAMSCO in the previous year. The mean number of HUG consultation in the previous year was 2.8 (SD: 5.4). Patients entailed 533 consultations and had an average of 1.5 (SD: 0.7, range: 1-6) health complains. Women chief complains were sexual or reproductive (38.5%) and osteoarticular (9.1%) whereas men had mainly dental (14.6%) and skin (11.4%) complains. Mental health problems were frequent secondary complains. Access to prescription medicines was the main reason for consulting in 10.5% of the whole cohort. Seventeen (3.1%) consultations were triaged urgent and required referral to the emergency room and 22.6% necessitated a complementary consultation by the intern on site. Nurses could manage 21.5% cases alone. Main referral destinations were division of primary care medicine (22.6%), gynecology and obstetrics (16.6%) and dentists (8.5%). On a 5-point Likert scale assessing subjective case complexity, average score was 2.2 (SD: 1) points. On average, consultations lasted 21 (SD: 14) minutes.

Conclusion: CAMSCO acts as an advanced primary care health post in the community with a high patients turnover. Its activity highlights hidden healthcare needs of very diverse populations in urban context in Switzerland. Front-line nurses solve a consequent share of cases and patients showed overall limited health services utilization. Yet, given the variety of health problems severity and nature, effective referral processes with secondary structures is required. Access to dental healthcare and to medicines represents major challenges in this vulnerable group of population.
Case report: A 52-year old woman with marked persistent eosinophilia, cough and fever episodes every two to three weeks was admitted to our hospital for further evaluation. The chest x-ray showed an enlarged heart. Blood tests showed a severely elevated blood eosinophilia of 75% (absolute 11 G/l) (fig. 2). Abdominal ultrasound, gastroscopy and colonoscopy showed no organ manifestation. Results for HIV, parasites and a rheumatological screening were all negative. The transthoracic echocardiography and CT scan of chest (fig. 1) showed a large pericardial effusion. After puncture (700 ml) just three days later the pericardial effusion filled up again. The cytological examination showed no malignant cells but also lots of eosinophils, as did the investigations of the lung (broncho-alveolar lavage and biopsy). A bone marrow puncture showed a slight hypercellular blood forming bone marrow with overcome of eosinophils as can be seen in an early phase of an eosinophilic leukaemia or an idiopathic hypereosinophilic syndrome. The genetic results showed no positive results for associated myeloproliferative neoplasms. The idiopathic hypereosinophilic syndrome is an exclusion diagnosis and we assume in our case, because we found no other reason, that’s the most likely diagnosis. Because of the large pericardial effusion and marked persistent eosinophilia and pulmonary involvement we started with an immunosuppressive medication (prednisolone). Just ten days after the eosinophilic blood count normalized (fig. 2) and under the therapy echocardiographically no pericardial effusion was seen anymore.

Conclusion: Marked persistent eosinophilia is a diagnostic dilemma and identifying the cause is a challenging problem. A systematical approach can help to detect organ involvement and thus prevent of ongoing severe organ damage.

Figure 1: Large pericardial effusion in CT scan.  
Figure 2: Count of Eosinophils in peripheral blood.

Methods: Data concerning patients admitted in two medical rehabilitation services were extracted from the information system of the Geneva University Hospitals. Only patients discharged towards rehabilitation services were extracted from the information system of these validated scales are, actually, related with early readmissions. Since 2014 rehabilitation structures in Switzerland are requested to collect both comorbidty measured by the Cumulative Illness Rating Scale (CIRS) that assesses on a 4 level scale the severity of the diseases affecting 14 organic systems; and functional impairment measured by Functional Independence Measure (FIM scale) for the building of a national tariff structure. We took this opportunity to examine whether these validated scales are, actually, related with early readmissions.

Methods: We measured Mst1 levels in patients’ plasma in order to elucidate their correlation with the overall and disease free survival (OS, DFS). ELISA was used as an efficient and effective method to quantify Mst1-concentration in the serum of breast cancer patients. Blood samples were prospectively collected for 12 months at the Department of Breast Surgery, Yangpu Hospital. 98 women were included and completed the follow up of 98 months. Blood samples were taken prior to any surgical or antitumor treatment. Distribution of tumor grades and receptor status were representative. The majority of the patients presented with carcinoma of a ductal type with luminal subtype, grade 2.

Results: Average Mst1-level was 1.8 µg/mL and was used to discriminate Mst1-positive vs. Mst1-negative breast cancers. Patients with positive expression of Mst1 had a significantly better overall and disease free survival (P <0.0001) (fig. 1A, B). Univariate Cox analysis indicated that Mst1 positivity had a significant difference in overall survival in breast cancer patients (P = 0.010). In multivariate Cox analysis, Mst1 positivity maintained significance as an independent prognostic factor in breast cancer (P = 0.002).
their own home were included. Any new hospital admission occurring within 30 days in any of the structures of the Geneva University Hospitals after discharge was considered as an event. If patients were hospitalized several times during the observation period, only the first stay was considered. Survival analysis methods were used for describing readmission dynamics and assessing which variables were associated with the failure events.

Results: During the years 2014 and 2015, 3374 patients were included in the analysis. Among them 424 (11.2%) were readmitted within 30 days, of which half of them being readmitted within 13 days. The risk of readmission was at its peak 9 days after discharge of the index stay, decreasing steadily after.

Table: Variables associated with early readmissions.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per additional year)</td>
<td>0.99</td>
<td>0.98–1.01</td>
</tr>
<tr>
<td>Sex (M vs. W)</td>
<td>1.08</td>
<td>0.76–1.54</td>
</tr>
<tr>
<td>CIRS scale at admission of index stay (per additional point)</td>
<td>1.03</td>
<td>1.01–1.06</td>
</tr>
<tr>
<td>FIM scale evolution during index stay (per additional point)</td>
<td>0.99</td>
<td>0.99–1.01</td>
</tr>
</tbody>
</table>

Comorbidity was the only variable significantly associated with an increased risk of early readmission.

Discussion: The dynamics of early readmissions in medical rehabilitation was not different from the one observed in general internal medicine. In this study, we did not make a distinction between planned and unplanned readmissions. However, people returning home after medical rehabilitation are rarely planned for additional investigations or procedures. Comorbidity was the only dimension associated with early readmissions. The distinction between avoidable and unavoidable readmissions should be further investigated as the former may be related with quality of care.

Interprofessional training in “Breaking bad news” with simulated patients: participants’ satisfaction

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Background: Breaking bad news is a stressful situation for patients, their family and also caregivers. This difficult task needs many skills such as communication and interprofessionalism. These two skills are increasingly taught in Swiss University. However, only a few practical courses exist for physicians and nurses during postgraduate and practice years. A program has been tested for five years at Lausanne University Hospital. It gives caregivers the opportunity to practice breaking bad news in pair, namely physician and nurse, with simulated patients. We aimed to assess the satisfaction of the participants.

Methods: From 2011 to 2016, 35 practical courses were given to 3–11 participants each. Physicians (including students in practical years) and nurses participated after achieving a 1.5 hour theoretical course. Each four hours practical course contains two to three 15 minutes long scenarios, with simulated patients. These are replayed up to twice and feedback is given. All participants received a questionnaire with 14 items and the possibility to add comments. Three items of applicability/transferability, personal achievement and tailored/personalised teaching were evaluated. We regrouped the free comments into four main themes.

Results: Of 257 participants, 136 were nurses (52.9%), 112 physicians (43.6%) and 9 were from other fields such as psychologists (3.5%) (fig. 1). 142 assessments (55%) were obtained, anonymised and analysed. Of the three items evaluated all were highly accepted (fig. 2). The evaluations’ qualitative analysis permitted the extraction of the following main four themes: 1/ the course could be longer and might be offered periodically as continuous training (refresh courses); 2/ the high quality/fidelity of the simulated patients; 3/ the particularly adapted scenarios (timeframe and contents) which were transferable to the participants day-to-day reality and 4/ the development of interprofessionalism as a strong new skill.

Conclusions: Interprofessional training in “breaking bad news” with simulated patients gives high satisfaction to pairs of physicians and nurses. However, few have the opportunity to attend, depending on the number of sessions. Larger resources could improve attendance rates. Further research is needed to measure the efficacy of this training on participants’ skills improvement and patient’s satisfaction.

Hypercalcemia – an uncommon summation of causes

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Introduction: Hypervitaminosis D and milk alkali Syndrome both are rare causes of hypercalcemia. We present a case with severe hypercalcemia due to these two causes in combination.

Case report: A 52 year old mental coach presented with a right-sided paroxysmal headache since 3 days, global muscle weakness, great thirst and polyuria. He denied taking any medication. Blood tests showed severe hypercalcemia with suppressed parathyroid hormone, very high 25-OH and elevated 1,25-OH-vitamin D3 levels and acute kidney injury. Computed tomography of the chest and abdominal sonography were unremarkable, free light chains in serum were normal. No evidence was found for a parathyroid-independent extrarenal calcitriol production like a granulomatous disease or malignancy. Intravenous saline hydration was started. After two days we added Torsamid 5 mg/d for 5 days. Because of the slow regression of calcium we applied intravenous Pamidronate (Aredia) 60 mg once. Interrogated again the patient specified the substances he took with a view to purification and encouraging health. He took every day four capsules of WLS Vitamin D3 containing 50.000 units of vitamin D3 for at least two weeks. For the same duration he consumed every day four capsules of WLS Vitamin D3 containing 50.000 units of vitamin D3 for at least two weeks. For the same duration he consumed more than 3 months later 25-OH vitamin D3 level was still above 418 nmol/l.

Conclusion: Hypercalcemia with consecutive kidney injury due to vitamin D intoxication is rare because very high doses are necessary. Consumption of large doses of vitamin D (50,000 IU/d) for 8 weeks in
young men did not change their calcium levels significantly. Therefore, we assume that the ingestion of Basenpulver and milk products (resulting in a milk alkali syndrome) enhanced the hypercalcemia. It is alarming that over the counter vitamin products which are supposed to benefit health are sold with no recommendation of exact daily or maximum dosage and no warning for the manifestation symptoms. Patients do not consider vitamins or food supplements as medication. Therefore they often do not specify them when asked and do not fear side effects. Thus, it is very important to ask patients specifically for vitamins or food supplements.

**Drug rechallenging and an unlucky acute generalized exanthematous pustulosis manifestation**

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Drugs sides effects especially antibiotics side effects are often misdiagnosed and classified as allergy. Drug allergy is reported in 20–40% of patients in the USA but close to 95% is not a real allergy. The most recent guidelines stress about reintroduction of antibiotics in patients with possible but not confirmed past drug reaction. Penicillin allergy histories are more likely to be rechallenged with the same or similar medications in the future, especially if Penicillin is the preferred therapy. Antibiotic re-introduction challenging is crucial even if adverse events may happen. Acute Generalized Exanthematous Pustulosis (AGEP) is a rare severe T-cell mediated drug reaction with an incidence of 1–5 per million/year. AGEP is characterized by acute formation of sterile pustules on erythematous background, fever and neutrophilia. We reported a case of a 68 years old male patient hospitalized for a dermohypodermitis with a reported unspecific cutaneous rash after Amoxicillin administration in 1980. Amoxicillin+clavulanic acid was the preferred antibiotic to treat the recent infection. Forty-eight hours after first dose administration, the patient quickly developed a diffuse erythema with several follicular pustules suspected for AGEP with diagnostic score at 8 (EuroSCAR) (Image 1 and 2). Causative drug was immediately removed and antibiotic change was provided. None of systemic complications of AGEP had been observed. Cutaneous test had been done 6 weeks later and confirmed Amoxicillin allergy. Our unlucky experience must not discourage antibiotics rechallenging. Penicillin allergy encompass different hypersensitivity reactions. Past history with antibiotics should be interpreted carefully in order to give opportunity to rechallenge patients with antibiotics.

**Protocol of the Swiss Longitudinal Cohort Study (SWICOS) in rural Switzerland**

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**Introduction**

Increased longevity and consequent major changes in demographics and population lifestyles necessitate new approaches to reduce the burden of age-related disease (including CVD) and maintain an optimal quality of life. This study aims to examine and longitudinally follow health status and disease risk factors in a Swiss rural cohort, evaluating all health related research and practice disciplines to assure development of new implementable and successful preventive strategies for healthy aging.

**Methods**

Small villages of rural regions in Switzerland with low migration rates have been selected for this longitudinal prospective study. All residents (age ≥6 years, no upper age limit) are eligible. Target enrolment number per village is 300. Examinations and measurements encompass medical history, anthropometry, cardiac and vascular health, pulmonary function, physical performance, nutritional, mental and emotional status, biochemical and molecular analyses. Follow-up examinations (identical to baseline) will be performed after 5 and 10 years, and in 10-year intervals thereafter.

**Results**

In the first participating village, more than 300 participants have been enrolled so far. Enrollment will start in a second participating village in 2017.

**Conclusions**

This study will allow to: (1) identify ‘hidden’ (asymptomatic and/or unrecognized) health problems which enhance risk for chronic diseases; (2) identify barriers to accessing health care and adapting health behaviours; (3) evaluate efficacy of present preventive strategies and recommendations; (4) evaluate knowledge and attitude towards ongoing health programs and public health recommendations; (5) monitor change and progress towards the national health objectives; (6) formulate new preventive strategies and recommendations based on the findings and knowledge base of the last 10 years; (7) formulate models for successful prevention of chronic diseases and for healthy aging.

**Summer swimming in the lake of Zurich suddenly turning into shortness of breath and hemoptysis**

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**Case report**

A 66 year old male presented with acute onset of shortness of breath NYHA IV, coughing and hemoptysis. Spending a summer afternoon together with his wife and children while the lake of Zurich, the symptoms began after having swum about 200 meters. Ambient and water temperatures were around 20.0 °C. He had no relevant past medical or allergic history. He denied submersion injury or aspiration. His intake of cigarette was 90% with normal blood pressure. A respiratory examination showed bilateral crackles. Laboratory findings included a normal arterial blood gas analysis and electrolytes, a pro-NT-BNP within normal limits and a slightly elevated troponin 1 of 84 ng/l (<57 ng/l). Resting ECG did not show any signs of acute ischemia and echocardiography showed normal ejection fraction with normal wall motility. A thoracic computed tomography scan showed bilateral ground glass opacities in the peripheral lungs. We initiated treatment with furosemide intravenously. Symptoms of pulmonary edema resolved within 24 hours. We diagnosed swimming induced pulmonary edema (SIPE) because of typical clinical manifestation and complete remission of symptoms after very short duration. Slightly elevated troponin was interpreted secondary to possible elevated pulmonary arterial resistance during SIPE with normal ECG and returned to baseline within two days.

**Discussion**

The etiology of acute pulmonary edema is interpreted as fluid movement into the alveoli secondary to alteration in one or more of Starling’s forces. The exact mechanisms of SIPE, however, remain unclear. It has been hypothesized that immersion elevates cardiac output for a given oxygen consumption and increases preload and thus leads to capillary leakage.

**Conclusion**

In the setting of acute onset of dyspnea and coughing after swimming exercise and without notable co-morbidities, SIPE is an important differential diagnosis. Risk factors for developing SIPE have been identified as exposure to cold water, arterial hypertension, overhydrating, female gender and previous episodes of SIPE. SIPE is frequently a self-limiting condition, prognosis is good with supportive treatment only.

**Effectiveness of lipid-lowering therapy in a hematopoietic stem cell transplant cohort**

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**Introduction**

Hyperlipidemia is frequently observed in patients after hematopoietic stem cell transplantation (HSCT), but is often undertreated. With a growing appreciation of the elevated incidence
of cardiovascular complications in these patients, the use and effectiveness of lipid-lowering therapy is of great interest.

**Methods:** A retrospective, single center cohort study with a total of 1196 patients (>16 years) who underwent a first autologous or allogeneic HSCT at the University Hospital Basel from 1973 to 2013 and survived >100 days after was performed. Patients were grouped according to the type of their first HSCT (autologous or allogeneic) and follow up was censored if a subsequent HSCT of the other type was performed. The examination of the effectiveness of the therapy, total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and triglyceride (TG) values before and a minimum of 30 days after start of treatment were analyzed. The frequencies of prescriptions of different drugs were further examined.

**Results:** A total of 223 patients (18.7%) received any kind of lipid lowering therapy at any time point during the follow-up time, 33 of which (14.8%) were already treated at baseline. 53 patients (23.8%) underwent at least one autologous, 170 (76.2%) at least one allogeneic HSCT (11 and 16 of them more than one, respectively).

Figure 1: Lipid values before and after therapy.

Table: Drug Prescriptions.

**Conclusion:** Lipid-lowering therapy leads to a significant reduction of TC, LDL-C and TG levels irrespective of the type of transplantation. Therapy was started significantly later among patients who received an allogenic transplantation.

POSTERTOUR 3: MÉDECINE SPECIALISÉE IV / FACHMEDIZIN IV

**P413**

The relation of bloodpressure and target organ damage in the Swiss Hypertension cohort study

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**Introduction:** Arterial hypertension is widely spread. Previous studies have shown an association between elevated blood pressure and target organ damage (TOD). The aim was to analyze differences between TOD groups regarding systolic and diastolic office blood pressure (SObP, DObP). Further, patients who developed symptomatic TOD during study period were compared with patients not developing TOD focusing on blood parameters at baseline (BL).

**Methods:** The Swiss Hypertension Cohort Study was a prospective observational study recruiting patients in primary care between 2006 and 2013. Patients eligible had to be ≥18 years old. TOD was defined as myocardial infarction, coronary artery disease, revascularization, stroke/TIA, heart failure, arterial obstructive disease, stenosis of the carotid arteries, a glomerular filtration rate ≤30 ml/min and retinopathy. Asymptomatic TOD was defined as left ventricular hypertrophy in the ECG or echocardiographic, chronic kidney disease with GFR 30–60 ml/min, microalbuminuria (30–300 mg/24h), an elevated fasting blood glucose level (>6.9 mmol/l) or postprandial blood glucose >11 mmol/l or HbA1c>7% or carotid stenosis.

**Results:** The mean age of the cohort at BL (n = 1004) was 64 years (SD = 13.22), 55.6% were male. At baseline 49% (n = 489) had no TOD, 30% (n = 300) had asymptomatic TOD and 21% (n = 214) had symptomatic TOD. During study period, 32 patients developed a new symptomatic TOD. We found that DObP significantly differed across hypertensive TOD groups at various time points indicating lower DObP with increasing TOD (see fig. 1).

Figure 1: DObP over follow up and TOD categories.

This effect was less pronounced in SObP where lower SObP was only observed in the group of symptomatic TOD at BL (see fig. 2). Further, patients who developed a symptomatic TOD during study period had lower HDL cholesterol (median = 1.2 vs 1.36 mmol/l, p =
Characteristics and outcome of migrant patients without a stable resident status starting hemodialysis in a Swiss university hospital center

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Background: Migrants without permanent resident status is a vulnerable population in regards of medical care. They frequently present with chronic medical conditions, including Chronic Kidney Disease (CKD). In this work, we analyzed the characteristics and the outcome of migrant patients starting chronic hemodialysis in our center.

Methods: Migrant patients without a stable resident status in Switzerland were retrospectively identified among patients who started hemodialysis between 2000 and 2014 in the hemodialysis center of the University Hospital of Geneva. Demographic and medical data were recorded by reviewing their medical records.

Results: Among 594 patients starting hemodialysis, we identified 29 migrant patients (4.9%, 133 patients per year) of whom 15 came from Africa, 2 from South America, and the 12 others from Eurasia. Eighteen were asylum seekers, 3 had a tourist visa, and 8 were undocumented. Compared to the local Swiss resident, migrant patients were significantly younger (mean age 44 ± 52 years), more of female gender (55% vs. 45%) and had less cardiovascular comorbidities. Two thirds of the patients had vascular and diabetic causes for End Stage Renal Disease and 34% were smokers. Seven patients were already hemodialyzed before arriving in Switzerland. Seventeen obtained a permanent resident status, 5 are still waiting for regularization, and 4 left Switzerland and were lost to follow-up. Among the 22 patients who stayed in Switzerland, 2 died while on hemodialysis, 11 were transplanted of whom one died accidentally after being transplanted and 9 were still on hemodialysis. Mean time from first dialysis in our country to transplantation was 268 ± 126 weeks.

Conclusions: In our center, nearly 2 migrant patients per year start hemodialysis without a permanent resident status in Switzerland. They are significantly younger and more often women, and had less cardiovascular comorbidities than our permanent Swiss resident patients. Sixty-six percent obtained a permanent resident status and 38% received a renal transplant.

Anti-GBM antibody (Goodpasture’s) disease

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Introduction: Anti-glomerular basement membrane (GBM) antibody disease is rare, with an estimated incidence of 0.5 to 0.9 cases per million per year in Caucasian populations. The disease is caused by autoimmunity to the NC1 domain of the α-3-chain of type IV collagen and leads to rapidly progressive (crenscient) glomerulonephritis and pulmonary haemorrhage. The prognosis of untreated anti-GBM antibody disease is extremely poor.

Case report: A 55-year-old male smoker was admitted with pulmonary haemorrhage since 6 weeks. X-ray showed diffuse pulmonary infiltrates, CT scan demonstrated multiple nodules as well as ground glass opacities, and the performed bronchoscopy verified alveolar haemorrhage. Renal workup showed a moderate insufficiency and glomerular haematuria. Together with demonstration of anti-GBM-antibodies the diagnosis of anti-GBM antibody (Goodpasture’s) disease was made. The patient was transferred to a tertiary care hospital. The patient was treated with steroids, cyclophosphamide, and plasma exchange. Pulmonary haemorrhage improved rapidly and glomerular filtration rate (GFR) returned to normal. Due to thrombocytopenia kidney biopsy was refused.

Discussion: Pulmonary haemorrhage and rapidly progressive (crenscient) glomerulonephritis are clinical hallmarks of anti-GBM disease. Anti-GBM antibodies are almost present and the antibodies level correlates with the severity of nephritis. Although X-ray and CT-scan can demonstrate pulmonary infiltrates, an increased uptake of inhaled carbon monoxide (D,CO) is the most sensitive indicator of recent pulmonary haemorrhage. Patients with lung pulmonary haemorrhage are often current smokers. Kidney biopsy,
Limited knowledge about limitations of a laboratory parameter: physicians and HbA1c

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Background: Since discovery of HbA1c in the late 60ies and its implementation into clinical practice in the 70ies and 80ies of the last century, this parameter has become a hallmark of diabetes care. However, this test has limitations, and we conducted a questionnaire with key questions about laboratory test.

Methods: A survey using a questionnaire with five open questions was conducted: 1. HbA1c shows mean glucose values of what time period? 2. What exactly is measured by the test? 3. What is a normal value for HbA1c (diabetes)? 4. What circumstances may lead to false low HbA1c values? 5. What circumstances may lead to false elevated HbA1c values?

Results: S3 physicians participated (28 residents, 4 students and 20 senior physicians) conducted in a department of internal medicine in hospitals of Switzerland. For question one, two and three, correct answers where given in 85, 85 and 55 % respectively. However, for question four and five concerning limitations of the parameters, correct answers were given in 11 and 19 % respectively. In exception of question 1 (HbA1c shows mean glucose values of what time period?), no differences between junior and senior physicians were present.

Conclusion: Our survey shows a considerable lack of knowledge about limitations of a widely used laboratory test. This might reflect our general inadequate high confidence in laboratory tests.

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Denosumab disguises the true cause of severe and sustained hypophosphatemia in a patient with advanced prostate cancer

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Introduction: Concurrent hypophosphatemia and hypocalemia are well known adverse events in treatment with denosumab, which is widely used in metastatic bone disease. Fibroblast growth factor 23 (FGF23) mediated tumor induced osteomalacia (TIO) is a rare paraneoplastic syndrome, leading to severe hypophosphatemia. Here, we present a patient with advanced prostate cancer, who developed hypocalemia and severe, sustained hypophosphatemia after initiation of denosumab therapy, primarily masking the cause of phosphate (Ph) wasting, which in particular was due to FGF23 induced TIO.

Case report: A 79-year old man with bone and lymph node metastases from castration-resistant prostate cancer (mCRPC) presented with severe hypophosphatemia (0.2 mmol/L, normal range 0.8–1.5 mmol/L) and hypocalemia (1.5 mmol/L, normal range 2.2–2.6 mmol/L). Treatment with abiraterone/prednisone and denosumab had been initiated three weeks earlier. Renal function was normal, parathyroid hormone (PTh) levels were elevated and levels of 25-OH vitamin D3 were normal with oral calcium (Ca) and vitamin D3 supplementation. Inadequately high renal Ph excretion without additional urinary electrolyte wasting was detected (Ph excretion fraction 24%). Treatment with high parenteral doses of Ca, Ph, oral 25-OH and 1,25-(OH)2 vitamin D3 normalized serum Ca- and PTH levels within one month. However, severe hypophosphatemia due to urinary Ph loss persisted despite high doses of Ph supplementation (8.5 g/d). Additional workup excluded renal phosphate wasting. Analysis of FGF23 (4 times above upper limit of normal). Ph and calcitriol supplementation was continued until the patient died from progressive prostate cancer 13 months later.

Conclusion: Denosumab induced hypophosphatemia was initially suspected in this patient with mCRPC. FGF23 induced hypophosphatemia is an uncommon but potentially life-threatening paraneoplastic syndrome most commonly found in mesenchymal tumors. Tumor induced osteomalacia in mCRPC is rare but may be underdiagnosed and should be considered in severe and sustained hypophosphatemia. Although clinical studies are lacking, several lines of evidence suggest that TIO may be associated with aggressive mCRPC behavior. FGF23 excess and severe hypophosphatemia may both contribute to a poor prognosis in affected patients. FGF23 receptor inhibitor treatment is under preclinical/clinical development and may be an approach to control TIO and the underlying malignant disease in the future.
GLP-1 Analogs for the treatment of postprandial hyperinsulinemic hypoglycemia after gastrectomy – a novel therapeutic option?

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Introduction: Severe postprandial hypoglycemia is a well-known if rare phenomenon in patients after gastrectomy for any indication. Since bariatric surgery is the most effective available treatment to achieve sustained weight loss in obese patients the number of procedures is increasing and more patients suffer from adverse effects including postprandial hypoglycemia. Pathogenesis is not fully understood; presently treatment is based on dietary advice and a variety of compounds. In 2013 Abrahamsson published case reports of patients suffering from significant postprandial hypoglycemia treated with iraglutide, a GLP-1 agonist. We present two cases responding to once-weekly GLP-1 agonists exenatide slow release and dulaglutide.

Methods and results: Case 1: A 51-year-old patient suffers from gastrointestinal stroma tumor (GIST) first diagnosed 12 years ago. In two steps she underwent gastrectomy and esophagojejunostomy. The GIST is controlled with Imatinib. For the past 9 years she suffered from daily hypoglycemic events including several instances of unconsciousness and seizures. Treatment with dulaglutide led to cessation of symptoms. We used continuous glucose measurement (CGMS, images 1 and 2) before and after the intervention to demonstrate the effect of the drug. Case 2: A 42-year-old, man with obesity stage III (BMI 41.6 kg/m²) had Roux-en-Y gastric bypass surgery six years earlier. Ever since he suffered from multiple neuroglycopenic episodes including several times hypoglycemia induced seizures. Dietary education and a trial with hydrochlorothiazide did not improve his situation. We started him on exenatide slow release. There was no further event while on the drug. CGMS to document hypoglycemia off the drug could not be written, the patient died 12 weeks later. We discontinued the treatment for this purpose.

Discussion: Bariatric interventions lead to increasing numbers of patients with the uncommon but potentially debilitating complication of severe postprandial hypoglycemia. Excessive incretin answer to glucose stimuli is thought to be partially responsible. Treatment with GLP-1 is therefore counterintuitive. Published case reports and our own limited experience seem to indicate that there is a place for GLP-agonists in this situation. Further studies will be necessary to elucidate the mode of action and to determine the validity of the approach in clinical practice.

Prolactinoma, an often missed cause of hypogonadism in man

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Introduction: Prolactinomas are the most frequent type of pituitary adenomas. Hyperprolactinaemia in man induces central hypogonadism, but decreased libido as initial symptom is often dismissed and diagnosis delayed until symptoms as headache, visual impairment or hypopituitarysm appear. The occurrence of sudden headache, diplopia, visual field defects, nausea and vomiting should suggest pituitary apoplexy as a result of an unrecognized pituitary adenomas.

Case report: A 43-year-old male suffering from recurring vomiting, nausea and diplopia when looking upwards since several days presented in our emergency service. He referred testosteron deficiency since 2006 treated with Nebido (Testosterone) every 4 weeks. In the physical examination he had ptosis, incomplete oculomotor palsy on the right, bitemporal hemianopsy and slight edematous swelling of the skin. Laboratory testing revealed severe hypoosmolar hyponatremia (119 mmol/l) due to hypocortisolism (<40 nmol/L; 101–536 nmol/l), central hypothyroidism (fT4 <5.2 pmol/L; 9.0–19.1 pmol/L) and hyperprolactinemia (4807 mU/L; 45–230 mU/L). MRI showed subacut bleeding in a cystic intra- and suprasellar pituitary adenoma (2.3×1.9×1.4 cm) with infiltration of the cavernous sinus, elevation of the chiasm and optic nerve and affection of the oculomotor nerve on the right consistent with hemorrhagic apoplexy of a macroadenoma. We initiated substitution with Hydrocortison and Levonothyroxin and started dopaminagonist therapy with Cabergolin. Furthermore, sellary pressure was released by transphenoidal surgery. Sodium concentration increased rapidly, Prolactin dropped and four weeks later, ptosis and incomplete oculomotor palsy completely resolved. Testosterone withdrawal failed, therefore it was reintroduced by transdermal application.

Conclusion: Particulary in men with unexplained gonadal dysfunction, prolactin should be measured. In patients suffering from sudden headache, vomiting and diplopia pituitary apoplexy should be considered. In case of a hypooosmolar hyponatremia, which simulates SIADH (syndrome of inappropriate antiureisis) cortisol determination should be carried out.
Patients with diabetes and chronic kidney disease: an interdisciplinary program to support medication adherence (PANDIA IRIS STUDY)

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Introduction: Despite effective treatments, 30% of diabetic patients (type 2) develop kidney disease over time. A diabetes-kidney interdisciplinary program was set up by the Lausanne University Hospital (CHUV) and the PMU (Pollicinale Médicale Universitaire). A novel medication adherence program is part of this approach. The purpose of the study is to assess the impact of the medication adherence program on the long term medication adherence and clinical outcomes of patients with diabetes and chronic kidney disease.

Design: One-center, prospective, randomized study (6- vs. 12-month intervention).

Intervention: usual medical consultations (every 2–3 months) will be preceded by a 20-minutes interview with a pharmacist. The interview is semi-structured with a motivational feedback based on the adherence data. Adherence will be measured using electronic pillbox (gold standard). A report of the interview will be sent to the physician(s) and the nurse(s). Group A (n = 35) will benefit from this program during 12 months and group B (n = 35) during 6 months. At the end of the intervention, the interviews will be interrupted but the medication adherence will continue to be monitored electronically (tot. = 24 months).

Inclusion criteria: Patients of either gender aged ≥18 years; type 2 diabetes; chronic kidney disease (estimated MDRD-eGFR ≤60 ml/min/1.73 m2 or albumin/creatinin >30 mg/mmol); complete exams performed within the previous 6 months.

Outcomes: Electronic medication adherence (longitudinal data) during 24 months; ADVANCE score (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) and UKPDS score (United Kingdom Prospective Diabetes Study) at baseline, 6 months and 12 months post-intervention; patients' satisfaction.

Results: The inclusions started in April 2016. Currently, 13 patients are included in the program; 10 refused to participate. The reasons for refusal are: the use of the pillbox, perceived as too complicated (n = 5); too many appointments (n = 2); complex social and economic situation & difficult to change pharmacy (n = 1); not interested unless paid (n = 1); no time (n = 1); refuses any study (n = 1).

Conclusion: Pilot phase shows that the study is feasible. Pharmacists, physicians and nurses involved in the program are showing interest and are pro-active in the inclusion process. The abstract was presented at the Forum Managed Care (Bern, 15.06.2016).

Vascular amyloid deposition and necrotizing myopathy – an uncommon clinical presentation in immunoglobulin light chain amyloidosis

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Introduction: Typical clinical manifestations of Immunoglobulin light chain (AL) amyloidosis include nephrotic-range proteinuria, restrictive cardiomyopathy and hepatomegaly. We present a rare manifestation with vascular amyloid deposition and necrotizing myopathy and suggest a link between these histopathological alterations.

Case report: A 72-year-old man is admitted to the department of general internal medicine with an eight months history of proximal muscle weakness, progressive dysphagia, and weight loss of 10 kg in absence of night sweat or fever. Monoclonal gammopathy of undetermined significance was diagnosed 15 years ago; follow-ups were stopped after 4 years. On physical examination macroGLOSSIA and proximal tetraparesis (M4) are noted. Laboratory evaluation reveals elevated liver enzymes, creatinine, creatine kinase (CK), and a nephrotic-range proteinuria. An M-gradient IgG lambda is demonstrated by electrophoresis/immunofixation (21 g/l), together with elevated free light chains (FLC) lambda (512 mg/l) and normal FLC kappa (17 mg/l). Ratio 0.30. Bone marrow biopsy demonstrates 20–30% infiltration with clonal plasma cells. Cardiac magnetic resonance imaging (MRI) reveals global left ventricular late gadolinium enhancement. Brain natriuretic peptide and highly sensitive troponin I are moderately elevated (481 ng/l and 91 ng/l (ref. <30 ng/l)). Electroneuromyography of the deltoid muscle and MRI of the thighs are suggestive of myopathy. Endoscopic swallowing evaluation reveals severe oropharyngeal dysphagia. All remaining CRAB-criteria are negative. No amyloid is detectable in the periumbilical subcutaneous fat. A vastus medialis muscle biopsy confirms vascular AL amyloidosis and necrotizing myopathy. Other common causes for necrotizing myopathy such as anti-SRP syndrome, preceding infectious disease or statins are absent. A nerve biopsy shows no amyloidosis. Weekly dose-reduced bortezomib, cyclophosphamide, and low dose dexamethasone are started to prevent further organ damage.

Conclusion: We hypothesize that in analogy to nervous system and kidney, vascular amyloid deposition might facilitate myopathy through blood supply impairment. Two negative biopsies highlight the focal nature of the disease. A negative biopsy must never exclude amyloidosis. Amyloidosis should be suspected in patients with a monoclonal plasma cell disorder presenting with proximal muscle weakness, macroGLOSSIA, dysphagia, and elevated CK.
Small molecule screen for inhibitors of adipogenesis as a strategy to accelerate hematopoietic recovery

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Background: Worldwide, more than 50,000 Hematopoietic Stem Cell Transplantations (HSCT) are performed annually, although the mortality rate still is close to 50% after allogeneic transplantation. Forty percent of these fatalities relate to the patients being severely immune compromised during the post-ablation period, before the graft has fully reconstituted the hematopoietic system. Reducing the time of engraftment is therefore critical to increasing the chance of survival in these patients. Preventing bone marrow (BM) adipocyte formation in the post-transplant period has been demonstrated to accelerate hematopoietic stem (HSC) engraftment and subsequent hematopoietic recovery in mice.

Methods: In order to uncover novel modifiers of BM adipocyte differentiation, we performed a high-throughput label-free in vitro screening on the human mesenchymal stromal cell (MSC) line, OP9. This cell line was demonstrated to be a both a useful model to efficiently differentiate into adipocytes as well as to support hematopoiesis in vitro. Using Digital Holographic Microscopy (DHM), we screened the bestsuitable library of FDA-approved drugs, the Swiss Chemical and the Natural Product collections for inhibitors of adipocytic differentiation based on real-time lipid accumulation. We have validated this novel method with existing adipogenesis quantification tests using simultaneously quantifying cell confluency and toxicity thanks to an in-house developed Cell Profiler plugin. Hits have been validated via dose-response curves and counterscreens including hematotoxic assays and functional in vitro and in vivo assays.

Results: From the initial panel of more than 4000 compounds, around 1% were rendered as validated hits that inhibited OP9 adipocytic differentiation. These compounds were also non-toxic to the stroma, did not affect cell number and had a strong potency (EC50 < 1 μM). From these compounds, 15 were permissive for primary murine hematopoietic stem and progenitor cell (HSPC) expansion and are currently being tested in primary HSPC/MSC co-cultures and in murine HSC transplantation. Of note, MarrowQuant and whole mount confocal microscopy techniques have been developed to measure in vivo BM adipogenesis in this context.

Conclusion: All current clinical approaches to enhance hematopoiesis target the HSC itself. Here we propose targeting BM adipogenesis as an alternative pharmacological strategy to improve hematopoietic recovery beyond current G-CSF standard.

Paraneoplastic dermatomyositis revealing non-Hodgkin lymphoma

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Introduction: Dermatomyositis is an inflammatory disorder of unknown origin. Twenty to thirty percent of cases of this disease is associated with a cancer. The most involved organs are the ovary, the breast, the digestive tract and the nasopharynx. The association to hematologic malignancies is rare. We report the case of a dermatomyositis revealing non-Hodgkin lymphoma.

Case report: A 55-year-old woman without pathologic history presented a typical dermatomyositis diagnosed with the presence of eyelid heliotrope erythema, Gottron's papules in the right hand, perungueal erythema and muscular weakness in the pelvic and scapular belt. The muscular dysfunction was confirmed by electromyography and biopsy. On the first examination, no evidence of malignancy was seen. Ototrinolaryngeal examination, CT scan, colonoscopy, fibroscopy and mammography were normal. A treatment by corticosteroids was started relayed by methotrexate due to severity of the dermatomyositis. Secondary, the patient received intravenous immune globulines because of corticoid resistance. The outcome was favorable. Six months later, appeared a febrile pancytopenia. The CT scan showed disseminated hepatic nodules associated with intraperitoneal effusion leading to an exploratory laparotomy. The hepatic biopsy revealed a large B cell lymphoma CD20+ on immunohistochemistry. The patient presented a septic shock two days after laparotomy leading to death.

Conclusion: The diagnosis of dermatomyositis must lead to systematic and repeated screening for an associated cancer or hematologic malignancy to initiate an adapted chemotherapy.

Modern first-line treatment of metastatic germ-cell cancer

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Introduction: The treatment of metastatic germ-cell cancer (GCC) is based on the prognostic classification of the international group IGCCCG that was published in 1997 based on treatments delivered between 1975 and 1990. Many diagnostic and therapeutic advances have occurred since then.

Method: We recently reviewed charts of 1163 patients with GCC who were treated at the University Hospital Zurich between 1991 and 2016 for whom electronic files were available. Overall 204 patients who received cisplatin plus etoposide based first-line chemotherapy were identified and analyzed.

Results: Median follow-up time was 4.7 years (range 0.3 to 22.4 years). Patients belonged to the good risk (n = 127), intermediate risk (n = 39) or poor risk (n = 38) groups according to the IGCCCG classification. The progression-free survival (PFS) probability was 71% and the overall survival (OS) probability was 88% at 5 years for the entire patient cohort. PFS at 5 years differed in the three prognostic groups according to the IGCCCG score: 83% (good risk), 69% (intermediate risk) and 30% (poor risk), p < 0.001. However, OS at 5 years was not different among good risk and intermediate risk patients (94% vs 91%, p = 0.62), but differed to poor risk patients (65%, p < 0.001). OS, but not PFS seems better than predicted by the published IGCCCG score, particularly in the intermediate and poor risk groups, which may be explained by better salvage treatment.

Conclusions: The overall survival of patients with GCC has improved. An update of the IGCCCG score that is currently used for prognostic classification is urgently needed.

Chronic diarrhea at advanced age – a rare case of chronic myelomonocytic leukaemia manifested as colitis

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Introduction: Chronic myelomonocytic leukemia (CMML) is a rare malign disorder in stem cells which can be diagnosed by a monocytesis in peripheral blood and by dysplasia in bone marrow overlapped with myeloproliferative neoplasms. Most patients are in the seventies and show extramedullary manifestations in lymphoreticular organs, but also in brain, testes and ovaries. In only 5.7–13% is the gastrointestinal tract involved [1]. The here described patient presents a more even rare case of CMML which started as chronic diarrhea and ended up in being a leukemic colitis.

Case report: A 83 year old male was presented with a 1-month-history of chronic diarrhea, no fever but an abnormal weight loss of 14 kg. With stool and blood cultures infections could be excluded as root causes for diarreha. The colonoscopy (fig. 1) showed an ulcerous colitis with inflamed tissue; medical treatment with NSAIDs as potential explanation could be excluded and CT scan did not show any signs for ischemia.

Figure 1: Sigmoid colon, inflammation and ulceration.

A first therapy approach with steroids and mesalazin against inflammatory bowel disease brought no improvement. A full blood exam stated leukocytosis, monocytesis, thrombocytopenia and anemia which lead to a bone-marrow puncture. All signs were pointing to CMML and genetic analyses were performed to complete the diagnosis along the WHO definition. However, the patient didn't show any typical CMML-symptoms. Progressive symptoms with hemorrhagic
Digital clubbing, painful joint swelling and periostitis in a patient with lung cancer – a paraneoplastic syndrome known as hypertrophic pulmonary osteoarthropathy or Pierre Marie Bamberger syndrome. A case report

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Introduction: Hypertrophic pulmonary osteoarthropathy (HPO), also known as the Pierre Marie Bamberger syndrome, is defined by painful swollen joints, digital clubbing and periostitis. It is a paraneoplastic syndrome with an incidence ranging from 0.64 to 17% in patients with lung cancer. But it can also be associated with extrapulmonary malignancies and various other diseases. The primary form of hypertrophic pulmonary osteoarthropathy is less common. We present the case of a lung cancer patient with disabling pain of the right lower leg caused by a soft tissue metastasis and a HPO.

Case description: A 58-year-old woman with an adenocarcinoma of the lung, AJCC stage IV, presented with enduring pain in the right lower leg for two months. The therapeutic regimen had just been switched to Nivolumab because of tumor progression on first-line treatment. The patient was referred for a local radiation which brought relief. The most efficacious therapeutic option for HPO is the treatment of the underlying malignancy. But in this case, due to tumor progression, the patient was referred for a local radiation which brought relief. The most efficacious therapeutic option for HPO is the treatment of the underlying malignancy. But in this case, due to tumor progression, the patient was referred for a local radiation which brought relief. The most efficacious therapeutic option for HPO is the treatment of the underlying malignancy. But in this case, due to tumor progression, the patient was referred for a local radiation which brought relief. The most efficacious therapeutic option for HPO is the treatment of the underlying malignancy. But in this case, due to tumor progression, the patient was referred for a local radiation which brought relief. The most efficacious therapeutic option for HPO is the treatment of the underlying malignancy. But in this case, due to tumor progression, the patient was referred for a local radiation which brought relief. The most efficacious therapeutic option for HPO is the treatment of the underlying malignancy. But in this case, due to tumor progression, the patient was referred for a local radiation which brought relief. The most efficacious therapeutic option for HPO is the treatment of the underlying malignancy. But in this case, due to tumor progression, the patient was referred for a local radiation which brought relief. The most efficacious therapeutic option for HPO is the treatment of the underlying malignancy. But in this case, due to tumor progression, the patient was referred for a local radiation which brought relief.

Results: CMML is a rare form of leukemia and manifests usually with symptoms like fatigue, weight loss, fever and night sweats. Chronic diarrhea as primary manifestation is untypical and very rarely described in literature [2]. Nevertheless, leukemic infiltration should be considered as part of differential diagnosis, when all other common causes have been ruled out.

Conclusion: Complex cases with atypical symptoms demand a close collaboration of medical disciplines to identify non obvious causes for seldom diseases.


Sclerosing mesenteritis – a rare disease mimicking malignancy

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In March 2016, a 74-year-old woman presented herself at our emergency department with coughing, abdominal pain, emesis and bloody diarrhea for several days. She reported weight loss of 20kg during the last 6 months. Her body mass index was 12.2 kg/m². She complained of recurring abdominal pain and diarrhea for a longer time. However, several gastrointestinal endoscopic examinations did not explain her complaints. The patient has been treated for a large cell lung cancer several years ago and was since then in complete remission. Furthermore, she had a history of alcohol- and benzodiazepine abuse and she continued smoking. She was known to have an alcoholic liver cirrhosis with a stage Child A. At admission, the patient was in a reduced general condition, hypotensive, the oxygen saturation was not measurable and her mental status was seriously altered. A CT-scan of the lung and abdomen was performed, showing bilateral infiltrates suggestive for pneumonia and massive non-specific intraabdominal calcifications. A bronchoscopy demonstrated a purulent bronchitis and S. aureus was isolated. Appropriate antibiotic therapy was initiated and infection parameters decreased, but the general condition remained poor. Unexpectedly, the patient died after 13 days. At autopsy a purulent pneumonia was found and interpreted as the most probable cause of death. In addition, the mesenterium showed extensive calcifications, fibrosis and chronic inflammation. After exclusion of a neoplasia and a lgG4-associated disease as well as in correlation with the clinical patient history a Sclerosing Mesenteritis was diagnosed. Sclerosing Mesenteritis is an idiopathic primary inflammatory and fibrotic process that affects the mesentery. Its etiology remains unclear, although several mechanisms have been suggested such as previous abdominal surgery or trauma, autoimmune, paraneoplastic syndrome, ischemic injury, and infection. Furthermore, there seems to be a strong association with nicotine abuse. Patients affected often present with anorexia, nausea, diarrhea, weight loss and fever. A standard therapy is not established, mostly prednisone is used, but experience is limited.

Conclusion: Sclerosing Mesenteritis may mimic malignancy or infection. It should be considered in the differential diagnosis of abdominal tumors.
The intimate relationship between Foley catheters, urinary incontinence, and death after a new-onset stroke

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Introduction: Urinary incontinence (UI) increases mortality after new-onset stroke. However, this association might be confounded by frequent indwelling urinary catheters (IUC) in this population. The aim of the present study was to explore the relationship between IUC, UI and death in the post-stroke period. We also explore the best time to assess UI (at the time of maximal neurological deficit, or one week after the stroke) to predict one-year mortality.

Methods: We included all patients with a first-onset stroke recorded between 1995 and 2011 in the prospective South London Stroke Register. The patients were followed for one year. The unadjusted impact of UI and IUC on time to death was analysed using Kaplan-Meier survival analysis and unweighted two-sided logrank test to compare groups. A multivariate Cox model was used to adjust for age, Glasgow coma scale, pre-stroke and post-stroke Barthel indices, sex, impaired swallow test, motor deficit, diabetes, and inclusion year. The predictive values of UI assessed at maximal deficit or seven days after stroke were compared using receiver-operating curves.

Results: 4477 patients were followed for one year after their first stroke. UI and IUC were present in 43.9% and 31.2% of patients. UI and IUC were both associated with one-year mortality in unadjusted (HR 6.84; 95% CI: 5.97–8.38 and HR 5.30; 95% CI: 4.70–5.98) and adjusted analysis (aHR 1.78; 95% CI: 1.46–2.19 and aHR 1.84; 95% CI: 1.54–2.19). Stroke patients with UI and IUC had twice the mortality rate compared to patients with only UI (HR 10.24; 95% CI: 8.72–12.03 vs. HR 4.70; 95% CI: 3.88–5.70, p < 0.001). UI assessed after one week performed slightly better for predicting one year mortality than UI assessed at maximal neurologic deficit. Limitations of this study include the lack of a standardized definition of UI and the lack of information regarding the indication for urinary catheterization.

Conclusion: IUC in the post-stroke period is associated with death, especially among UI patients.

Spontaneous intracranial hypotension

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Introduction: We describe a case of spontaneous intracranial hypotension with a fluctuating disease course over several weeks. Definitive diagnosis could only be made with repeated magnetic resonance imaging (MRI).

Case report: A 25-year-old woman presented with acute headache that had begun after strenuous exercising but without notable trauma. She reported the pain to vanish in a horizontal position and to reoccur within seconds when being upright. She also reported repeated vomiting. Neurological examination and cranial computed tomography (CT) were normal. Brain MRI showed no clear signs of intracranial hypotension which was suspected due to the orthostatic nature of the headache (fig. 1). MRI of the cervical spine showed T1 isointensity in the epidural space from C2-C4 which was interpreted as an epidural hematoma. The patient was referred to the neurosurgical department at the University Hospital in Zurich. Repeated spinal MRI showed no focal cerebrospinal fluid leak (CSF). The patient improved spontaneously and was discharged with the presumptive diagnosis of spontaneous intracranial hypotension. Three days later she presented with severe headache, neck stiffness and right sided peripheral facial palsy. Repeated brain MRI showed diffuse pachymeningeal contrast enhancement as a typical sign of intracranial hypotension (fig. 2). CT myelography showed a CSF leak at L5/S1. Application of an epidural blood patch resulted in prompt resolution of the headache and the facial palsy.

Discussion and conclusion: Spontaneous intracranial hypotension refers to the occurrence of a CSF leak leading to CSF hypovolemia and hypotension without a preceding causative event. Orthostatic headache is the prototypical manifestation. Diagnosis is made by MRI [1]. The acronym SEEPS (for Subdural fluid collections, Enhancement of the pachymeninges, Engagement of the venous structures, Pituitary enlargement, and Sagging of the brain) recalls the typical findings [2]. It is frequently misdiagnosed because the neurological examination is usually normal. Our case is notable because initial brain MRI was negative. It stresses the importance of the history of present illness as the most important diagnostic tool. Confronting a specific and persisting symptom clinicians must refrain from excluding a diagnosis prematurely and consider repeated testing.


Complementary and alternative medicine use by forced migrants living in the canton of Vaud: a pilot survey

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Introduction: Complementary and alternative medicine (CAM) is used by about a third of the population in different countries. In Switzerland nearly half of the population used CAM at least once during their life, and the most frequently types of CAM used were homeopathy, osteopathy and acupuncture. Among migrants, studies in the US and in Asia showed the same prevalence of CAM use as the native population of a country. However the type of CAM used varied according to ethnicity. Some studies showed an association between self-perceived discrimination and CAM use. The objective of this pilot study was to search for the prevalence and type of CAM used by forced migrants in the canton of Vaud and to evaluate their self-perceived discrimination.

Methods: A cross-sectional study with questionnaires was performed among a convenience sample of forced migrants in the canton of Vaud in December 2015 using face-to-face interviews, in French, English, Arabic and Tigrinya languages.

Results: In this first study in Switzerland about CAM use and self-perceived discrimination among forced migrants, a total of 61 of them participated in the study. The mean age of the sample was 27.8 (IQR: 18–48) and 78.7% were male. Eritrea (55.7%), Kosovo (4.9%) and Afghanistan (4.9%) were the most often encountered nationalities. The majority (91.7%) declared they trust their physician about their healthcare advices. Lifetime prevalence of CAM use was 45.9%. A third (31%) of the CAM used was herbal medicine. CAM use during the last twelve months was reported by 27.9% of them. Herbal medicine use was much more with self-use (70%) than with the recommendation of a health professional. Among forced migrants who were using CAM, 54.2% informed their physician about their use.
Self-perceived discrimination was reported by 36.7% of forced migrants, with 70% of them reporting discrimination because of their national origins. CAM users reported significantly more discrimination than non-users (44.4% versus 30.3%, p = 0.027).

**Conclusion:** Forced migrants used complementary and alternative medicine for a high number of chronic conditions estimated to 52% and 35% with and without discrimination, respectively.

**Results:** Prevalence of two or more chronic conditions, and three or more chronic conditions, was estimated and stratified by gender and age group. We also examined which group of chronic conditions participated most to this multimorbidity.

Prevalence of multimorbidity in Swiss family practices: a cross-sectional study within the Swiss Sentinel Surveillance System (Sentinella)

**Introduction:** Hypothenar-Hammer-Syndrome (HHS) is a rare disease, primarily affecting young men, presenting with painful, cold, and pale digit IV and V. Repetitive, blunt trauma to Guyon's canal leads to thrombus formation, subsequent occlusion of hand arteries and ischemic necrosis. Local anatomy of the ulnar artery (superficial palmar arc) makes it susceptible to injury. Angiography is the diagnostic gold standard. Management of choice is intra-arterial lysis; operative approach is rarely required.

**Case report:** A 30-year-old male presented in our ER with sharp pain, pallor, numbness and temperature loss in left fingers IV and V, which began 5 hours prior, after using his hand as a hammer whilst tiling floors. Patient's medical and family history was unremarkable, especially no Raynaud's-, cardiac, rheumatic, vascular or coagulation disorders were known. He regularly consumed alcohol, tobacco and cannabis. Clinical examination showed skin marbling, hypothermia and dysesthesia of the hypothenar, digits IV and V, with prolonged capillary refill and pathological Allen-test. Segmental pulse oscillography showed a pathological flow volume diagram of digits III–V. Primary Raynaud's seemed unlikely due to isolated occurrence in digits IV and V and secondary Raynaud's entities e.g. acroangiosclerosis, diabetes or lupus. Normal differential blood count spoke against myeloproliferative neoplasia. Cardiac arterial emboli, cryoglobulinemia, thoracic-outlet-syndrome, CREST and paradoxical embolism were ruled out. CT-angiography revealed distal thrombotic occlusion with no aneurysm of the ulnar artery at the pisiform bone, and no stenosis further proximally. HHS was diagnosed. We commenced pulse-spray arterial lysis and systemic anticoagulation with i.v. heparin. Control angiography at 24h showed regular perfusion of the ulnar interdigital arteries, with persistent partial thrombosis of the distal ulnar artery up to the superficial palmar arc. Anticoagulation was converted to phenprocoumon and combined with an antiplatelet agent (aspirin). Clinical and radiological examination at week 12 revealed normal results.

**Summary:** HHS is an important differential diagnosis in patients presenting with unspesific Raynaud's-signs, ischimic pain and hypothermia of the ulnar palm and fingers. Significant delay of diagnosis and therapy is associated with high morbidity. It thus remains imperative to draw physicians' attention to the disease's presentation and treatment options.

Prevalence of multimorbidity in Swiss family practices: a cross-sectional study within the Swiss Sentinel Surveillance System (Sentinella)

**Introduction:** Multimorbidity, commonly defined as two or three or more chronic conditions within one person, is a growing challenge in view of the aging of the population. Management of multimorbidity is frequently the responsibility of the family practitioner, increasing the complexity of health care. Estimation of its prevalence differs significantly between studies according to different methodologies and definitions of multimorbidity. We estimated prevalence of multimorbidity in a national and representative sample of patients from family medicine practices using the Sentinelia network.

**Methods:** We used data from 2904 patients of all ages, attending 118 family practitioners from the Sentinelia network from September to November 2015. Recorded data included date of birth, gender and a list of 75 chronic conditions derived from International Classification for Primary Care version 2 (ICPC-2). Prevalence of multimorbidity, defined first as two or more chronic conditions, and secondly as three or more chronic conditions, was estimated and stratified by gender and age group. We also examined which group of chronic conditions participated most to this multimorbidity.

**Results:** Prevalence of two or more chronic conditions, and three or more chronic conditions, was estimated and stratified by gender and age group. We also examined which group of chronic conditions participated most to this multimorbidity.
Methods and results: We assessed claims of a non-accident insurance plan of a major Swiss health insurance company (Helsana group) for surgery rates of APM, arthroscopic debridement and lavage in patients over the age of 40, comparing years 2012 and 2015. Claims were analyzed for prevalence of osteoarthritis, associated interventions and insurance status. Surgery rates for Switzerland were calculated using weighted projections. In all, 648,708 and 647,808 patients were examined in 2012 and 2015 respectively. The incidence of APM, debridement and lavage was 2,520 in 2012 and 2,282 in 2015 in non-traumatic patients aged over 40, consisting mostly of APM (95.6%). Osteoarthritis was diagnosed in 24.6% of inpatients. In all of Switzerland, APM was performed an estimated 9,958 and 10,203 times in middle-aged (40–64) and 5,854 and 4,815 times in elderly (≥65), non-traumatic patients in 2012 and 2015, respectively. This translates into a surgery rate of 209 per 100 person-years for all ages. Supplementary private hospital insurance and chronic diseases were associated with a higher risk for surgery. High deductible class and use of pain medication were associated with a reduced risk for surgery.

Interpretation: APM is widely-used in non-traumatic patients in Switzerland, although it provides no significant benefit according to current evidence. Surgery rates did not change in non-traumatic middle-aged patients between 2012 and 2015. Accordingly, the potential of inappropriate use of APM in non-traumatic patients in Switzerland is high and current practice needs to be changed.

Performances of a brief assessment tool for the early diagnosis of geriatric syndromes in family medicine

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Introduction: Although early detection of geriatric syndromes has been shown to limit functional decline, it is rarely implemented in family medicine because of lack of training and lack of time for a full geriatric assessment. The AGE project (active geriatric evaluation) aimed at developing and validating a brief assessment tool (BAT) for family physicians (FP) to detect geriatric syndromes. This study aimed to estimate diagnostic performance of the BAT compared to a comprehensive geriatric assessment.

Methods: Prospective diagnostic study conducted in one university primary care clinic and three private practices, canton of Vaud, Switzerland. Eligible patients were aged at least 70 years old, routinely followed in one of the recruitment sites, able to provide informed consent and without previous geriatric assessment, FPs performed the BAT, followed by a comprehensive (2 hours) geriatric evaluation performed within the next two months. Both the BAT and the full geriatric assessment targeted the following eight syndromes: cognitive impairment, mood disorder, urinary incontinence, visual impairment, hearing loss, undernutrition, osteoporosis, gait and balance impairment.

Results: Out of 85 patients, 53 (62.4%) were included at the university clinic and 32 (37.7%) in private practices. Mean age was 78 years (SD 17.7), 52% were males, and 67% were with their GP for >5 years.

Conclusions: The BAT performed well to screen elderly patients for geriatric syndromes when compared to a full geriatric assessment, and was feasible in routine practice.

We assessed patient experience at baseline (before the first renovation) and after 2 months (follow-up 1, FUP1) in a previous study and extended FUP for this study to 14 months (FUP2) after the first and 3 months (FUP3) after a second renovation. Each time, we invited a consecutive sample of 180 patients presenting for a routine consultation to participate anonymously in a paper survey. Patients graded patient experience in 4 domains on a 6-point Likert-scale: appearance of the office; qualities of medical assistants and GPs; and general satisfaction. We compared crude mean scores of each domain from baseline until FUP3. In a multivariate regression model, we adjusted for patient’s age, gender and for how long patients had been with their GP.

Results: The response rate for all consecutive samples of patients was 84–94%. At baseline, patients aged 60.9 (17.7) years, 52% females, and 67% were with their GP for >5 years.

We could reproduce this bias in a second renovation strengthening evidence for causality. This implies, to restrict measurement of patient experience to at least one year after interior renovation in primary care and therefore avoid biased estimates when measuring patient experience.
The life threatening side of otitis media – a case report of pneumococcal meningitis
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Introduction: Acute otitis media (AOM) is a common infection, mainly affecting children, typically presenting with unilateral otalgia and decreased hearing. Otoscopic examination is the diagnostic standard. Streptococcus pneumonia is the most frequent bacterial cause. Complications such as mastoiditis, facial paralysis, labyrinthitis and meningitis develop in less than 0.5% cases in adults. Therapy of choice is amoxicillin.

Case report: A 55-year-old female was referred to our ER after having been found in her home with an altered, confused mental status. Recently, she had been complaining of ear pain. At admission, she was restless, septic, with a GCS of 6, requiring intubation. Orientating cranial CT showed opacification of the left mastoid air cells, as well as intracranial air entrapment and cerebral edema. During the CT, the patient suffered a seizure, which was successfully terminated with midazolam. With a high clinical suspicion of otophenic bacterial meningitis, empirical antibiotic therapy with tazobactam was commenced. In left ear otoscopy otitis media was diagnosed. Lumbar puncture revealed a high intracranial pressure (>50 mm Hg), liquor was positive for pneumococcal antigen. The antigen was also detected in the urine, confirming the diagnosis of pneumococcal meningitis. Antibiotic therapy was converted to empirically ceftarion and vancomycin, then ceftriaxone only (as per antibioticogram). A surgical exploration of the mastoid was performed, revealing purulent secretion. A tympanostomy tube was temporarily inserted. In the control CT scan signs of high intracranial pressure were persistent. Neurovascular ultrasound showed an increased blood flow in the medial cerebral artery, which we interpreted as indirect signs of vasospasms. A therapy with nimodipine was installed. Within 12 days a vast clinical improvement was observed. The patient suffered no neurologic deficits, was spatially and temporally orientated and independently mobile so that discharge to a neurorehabilitation was feasible.

Summary: Despite AOM being generalised as a trivial infection, delay in diagnosis and therapy can be lethal. Pneumococcal meningitis is a rare, life threatening complication, occurring in only 4% of invasive pneumococcal infections, with a case-fatality rate of up to 25%.

Interprofessional collaboration between physicians and community pharmacists – where are barriers and facilitators?
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Introduction: Today, one profession can no longer hold all knowledge and skills that is needed for safe and quality care. Although the Federal Office of Public Health published in 2013 concrete examples of interprofessional collaboration, many mistake it for interdisciplinary work. Because different professionals can hardly work together if they do not learn together, Swiss research programs will be launched in 2017 for projects in interprofessional teaching in medicine curriculum. Simultaneously, a political proposal (so called Postulat Humbel) requested in 2012 to demonstrate which new role community pharmacies could play to guarantee access to high quality care. In this context, we aimed at searching literature for barriers and facilitators to physician-pharmacist collaboration in primary care.

Methods: A pragmatic literature search was performed in PubMed and google scholar on Jan 1 2017 with variations of the terms: interprofession* OR collaborati* AND physician* AND pharmac* AND “primary care” AND “primary barrier” and the restriction “-education”. We present the key messages of the 156 retrieved articles which may be pertinent for Switzerland.

Results: Individual, contextual and exchange factors influence interprofessional relationship. Some issues seem predisposed such as medication review, medication dose adjustment, repeat dispensing, therapeutic substitution and medication adherence. Management of patients with abuse potential could be expanded. Physician-pharmacist collaboration in primary care is highly facilitated by reciprocal trust in capabilities and knowing each other, co-location or geographical proximity, and regular face-to-face contact. Beside lack of motivation and willingness, lack of time and remuneration are often cited as barriers to the implementation of interprofessional collaboration. Technical difficulties may hinder information sharing, and confidentiality remains a topic of concern. The current main barrier seems the poor acceptance of the new pharmacists’ role and their provision of additional services. Adding diagnosis to prescriptions could represent a first step in shared decision making. Prescribing by pharmacists represents a clear hurdle.

Conclusion: The literature contains many articles on physician-pharmacist collaboration, but implementation is still in its early stages. However, the Swiss Federal Council is evaluating how community pharmacists could play a more important role in primary care in future.

Concordance in the perception of complaints between general practitioners and their multimorbide patients: a cross-sectional study in Swiss primary care
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Background: Multiple chronic health conditions (multimorbidity) is inevitably leading to multiple treatment procedures, unless health conditions are prioritized along patients’ needs and preferences. Thus, for improving healthcare, it is crucial for GPs to know what condition the patient is suffering most. The aim of our study was to investigate to what degree GPs’ perceive the subjectively most important complaint (MIC) of their multimorbide patients, and therefore to assess the GP-patient concordance in regard to MIC’s.

Methods: Cross-sectional analysis based on a cluster-RCT among 46 GPs and 334 multimorbide patients (≥60 years taking ≥5 drugs for at least 6 months) in Northern Switzerland recruited between March 2015 and July 2016. Intervention group GPs (n = 20) were asked to list the four MIC of the patient, and patients (n = 128) were asked to list their MIC. MIC’s were classified using the ICPC-2 coding system on chapter and component level. We defined as concordance if the ICPC-2 code of patient’s MIC was identical with one of the MIC codes on GP’s list.

We classified concordance into full, moderate and low, depending on the patient’s MIC code ranked first, second or third/fourth on GP’s list. We defined as discordance if the patient’s MIC code was not listed on GP’s list. Complaints frequencies were measured in the whole study sample (n = 334). Statistics included descriptive measures using the statistical software R, version 3.2.

Results: Mean age of patients was 76.9 (SD 8.1) years, 38% male, taking 73 (SD 2.6) drugs on long-term. The most frequent complaints were pain, weakness / tiredness, shortness of breath and dizziness (fig. 1). Patient-GP concordance of the MIC was given in 101/128

Figure 1
(78.9%) on the ICPC-2 chapter level, while 86/128 (67.2%) were full, 8/128 (6.3%) moderate and 7/128 (5.5%) low concordance. If the MIC’s were classified on ICPC-2 component levels, concordance was given in 83/128 (64.8%), whereby 72/128 (56.3%) were full, 6/128 (4.7%) moderate and 5/128 (3.9%) low concordance (fig. 2). In 27/128 (21.1%) there was discordance (chapter level).

Conclusion: A majority of GPs perceives the MIC of the multimorbid patient correctly, but there is room for improvement: 21% of family physicians do not list the MIC of the patient at all in a four-part list. Thus, directly addressing patient’s complaint as part of the encounter might help for better coping with multimorbidity and improving the quality of care for multimorbid patients.

Diversity in the clinic: analysis of transcultural consultations requested by primary care physicians
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Introduction: Because of current geopolitical contexts and migratory fluxes, primary care physicians (PCP) encounter an increasing amount of culturally diverse patients in their practice. This cultural diversity impacts the consultation and requires additional expertise. At the Geneva University Hospitals, a transcultural consultation is available for all health care professionals, providing cultural evaluation of referred patients, and issuing clinical recommendations. The aim of this research was to understand the type of clinical difficulties encountered by PCP caring for culturally diverse patients and their relevance for cultural competence training of PCP.

Methods: We conducted a retrospective analysis of all transcultural consultations requested by PCP between 2006 and 2015. We included situations for which a cultural evaluation was completed and excluded those for which only telephone advice was given. We analyzed consultation request intake forms and consultation reports issued to the PCP. We analyzed patient and provider characteristics, motives of consultation requests, issues identified by the cultural evaluation and recommendations made to PCP.

Results: 32 consultations were included in the analysis. The main reasons for consultation were clarification of patient’s socio-cultural context and exploration of patient’s explanatory model of illness. The main issues identified by the cultural evaluation were the high level of socioeconomic vulnerability interfering with health care management, divergent explanatory models between patient and PCP, necessity to refer to mental health care, and linguistic barriers to optimal communication. Recommendations included integration of additional professionals and modifications of clinical management.

Conclusion: PCP confronted with culturally diverse patient population need additional knowledge and skills. Useful competencies include understanding the impact of socio-economic vulnerability on illness self-management, tools to explore patient models of illness and the impact of culture on the expression of distress.

Autoimmune limbic encephalitis with anti-LGI1 antibodies, a treatable cause of behavior and memory disorder: a case report
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Introduction: A 79 year-old healthy man was hospitalized with progressive memory impairment, confusion and abnormal perioral movements. Brain magnetic resonance imaging (MRI) revealed left amygdalo-hippocampal swelling with contrast enhancement. Electroencephalography (EEG) revealed paroxystic electrical activity without clinical correlate. Antiepileptic treatment did not alter the symptoms. A repeated MRI showed a second similar lesion located in the right hippocampus. Cerebrospinal fluid (CSF) was clear with one leucocyte pro microliter and normal proteinorachia. Antibodies with anti-LGI1 specificity were positive in the blood and CSF. A diagnosis of autoimmune limbic encephalitis with anti-LGI1 antibodies was made, and treatment consisting of high dose methylprednisolone bolus followed by 0.6 mg/kg of prednisone orally and 2 g/kg of immunoglobulins intravenously was administered, with dramatic improvement of symptoms. A thorough investigation for the presence of neoplasia was negative.

Methods: We searched PubMed® for relevant articles using the keywords “limbic encephalitis”, “LGI1 antibody”, and “faciobrachial dystonic seizure”.

Results: Limbic encephalitis is a subacute disease, with progressive memory impairment and confusion, with or without faciobrachial dyskinesia. Men in the 7th decade are mostly affected. The EEG is pathological in more than 50% of patients. MRI shows hypopactic hypersignal in T2 or T2 FLAIR. The diagnosis is confirmed by isolation of anti-VGKC antibodies above 400 pmoL, with anti-LGI1 specificity, in the CSF and serum. A neoplasia is associated in 10 to 20% of cases. Administration of corticosteroids for 4 to 6 months, along with immunoglobulins or plasmapheresis, leads to rapid clinical improvement. Relapses are rare and generally respond to Rituximab administration. Atrophy or sclerosis of the hippocampus can occur in case of delayed treatment.

Conclusion: Autoimmune limbic encephalitis with anti Lgi1 antibodies should be evoked in patients with subacute memory and behavioral troubles, in particular when associated with faciobrachial dyskinesia. Though the etiology is rarely paraneoplastic, assessment for the presence of cancer is warranted. Timely treatment with corticosteroids and immunoglobulins leads generally to remission of the symptoms. For these reasons, awareness of its semiology and early diagnosis are important in order to start specific treatment as soon as possible.

Securing an adequate follow-up in patients with discrepancies between the preliminary and final radiology report in the emergency department
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Introduction: In the setting of an emergency department (ED), preliminary radiological findings are often reported via telephone. The final report can be different, especially after being reviewed by a senior radiologist. If those additional findings aren't adequately communicated, they are prone to be lost to follow-up with possibly detrimental results e.g. in the case of suspect pulmonary lesions. In larger departments, validating hundreds of reports per day can be strenuous, therefore an automated process is desirable.

Methods: Diagnoses and radiology reports are usually recorded in an unstructured manner. We used natural language processing (NLP) and...
Abdominal pain and very high alkaline phosphate level – is there a coherence? 
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Introduction: Little is known about a coherence of intestinal angioedema, very high alkaline phosphate level, asymptomatic factor V Leiden Mutation. 

Case report: A 22 years old professional endurance sportswoman was presenting several time with sudden abdominal pain, nausea and vomitus over a period of almost 2 years. An asymptomatic factor V Leiden Mutation was known and the only daily taken drug was an oral desogestrel. In the physical examination we founded an epigastrical pain on pressure without peritonism. The blood results showed a very high level of alkaline phosphatase (3500 UI/l) with normal inflammation parameters and gamma-GT. In a computer-tomography we documented edematous thickened ileum terminals and colon ascendens. A stenosis of the terminal ileum, with a normal mucosa was found in the colonoscopy. In a MRI which was performed a day after, the stenosis and the edematous tissue was disappeared. Therefore an intestinal angioedema was proven. We did not find any infection (EBV, CMV, Leishmania, Yersinia or salmonella). The C1-Esterase and tryptase levels were normal. We stopped Desogestrel and the patient was asymptomatic and two months later alkaline phosphatase was 135 UI/l. 

Discussion: The clinical signs can be explained with an intestinal angioedema. High levels of alkaline phosphatase are known as transient benign hyperphosphatasemia in children but not in adults and especially not in coherence with angioedema. As we know there is no coherence known with angioedema, transient benign hyperphosphatasemia factor V-Leiden Mutation and desogestrel. We consider that there is a coherence and the patient therefore was without any symptoms after stopping the intake of daily desogestrel. 

Conclusion: This case shows that a very high alkaline phosphatase without signs of a liver disease or osteomalacia also in adults should be considered as transient benign hyperphosphatasemia. Also there might be coherence with intestinal angioedema, factor V-Leiden Mutation and desogestrel. Further research is needed. 

Sleep disturbance related to nocturnal leg cramps in Geneva: a prospective observational study with a feasibility perspective 
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Introduction: Cramps are involuntary painful muscle contractions. They affect almost one in two people over 60 in primary care. In declarative retrospective study, cramps were shown to cause severe pain and sleep disturbance. Studies are needed to assess therapeutic options, but before considering a randomized controlled trial, we wanted to confirm a burden related to cramps in a primary care setting as well as the feasibility of such a study. 

Objective: The objective of this study was to prospectively explore the cramps’ frequency, duration, severity and related sleep disturbance. 

Methods: We planned to enroll 600 patients in 30 practices, between March 2014 and September 2015. Questionnaires and daily log were distributed to patient to prospectively obtain information about demographics, cramp frequency, severity, sleep disturbance, and treatment. A research assistant realized 3 telephone interview during the the study. 

Results: We included only 102 people in 14 practices, among them, 86 (86%), reported cramps during the 2 weeks of the study. Overall cramp frequency was 2.26/week, overall duration was 5 minutes. Overall severity was 4.17 on analog numerical scale from 0 to 10, overall sleep disturbance was quoted 5.28 on analog numerical scale from 0 to 10. Overall Pittsburgh sleep quality index was 7, while 28 patients reported a score >8 and 46 reported a score >5. 

Conclusions: These results confirmed the severe pain and sleep disturbance already showed in previous studies but questioned the feasibility of a randomized controlled trial in our setting. 

Access to electronic records of general practitioners and specialists in rural central Switzerland for spatial analyses 
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Background: For many countries, the geographic distribution of general practitioners (GPs) and specialists remains insufficiently unequal despite the notable increases in overall supply. How physicians are distributed and how their patient populations differ in healthcare utilization dependent on geographical and demographic factors are aspects requiring great consideration during healthcare planning. Therefore, we asked, is there a maldistribution of physicians in Central
Switzerland and if so, does it influence healthcare accessibility in rural areas?

Methods: Data was provided from the Physicians Association's and MedKey, a patient data trust center. Physicians were asked prior to analysis for access to their patient's electronic health records. They were given 3 options to choose from, (1) full access to anonymized electronic records for all research going further, (2) only allow access to records for this research project, and (3) no access to records. For this analysis responses one and two were treated as a yes and option three as no. Using the Eurostat's degree of urbanization, physicians were designated into regions (urban, suburban, rural) dependent on population density. The physicians' locations will be geocoded, at the street level, and paired with their patient population, at the zip code level. Analyses will be performed to estimate travel time and distance between physicians and their patients, and to examine the associations between physician's distributions by the degree of urbanization and patient characteristics.

Results: From the data provided, 938 letters for consent to utilize electronic records were sent to practicing physicians working in Central Switzerland. 183/342 (54%) urban physicians responded, 141 (41%) of them give access to the records. 236/433 (55%) suburban physicians responded, 173 (40%) of them give access. 95/163 (58%) rural physicians replied, 87 (53%) of them give access. Of the respondents 345 (67%) were GPs and 169 (33%) were specialists. Yes responses by Cantons, 222 were from Lucerne, 65 Zug, 52 Schwyz, 24 Nidwalden, 18 Obwaiden, and 17 from Uri.

Conclusions: From the gathered data, a spatial analysis will investigate the distribution, provision and utilization of primary care and specialty care in Central Switzerland. Generalizability will be limited due to varying response, however, rural physicians were more willing to give access to their data than urban or suburban physicians.

Which factors influence the use of Electronic Health Record (EHR) during the first ten minutes of the clinical encounter?

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Introduction: The Electronic Health Record (EHR) is used in about 12–55% of clinical encounters, especially at the beginning. Several factors related to physician, patient, consultation or spatial characteristics may influence the use of the EHR. However no studies have specifically assessed the relative importance of each of these factors for EHR use during clinical encounters. The aim of the study was to identify the physician, patient and consultation characteristics that influenced EHR use by primary care physicians during the first ten minutes of the consultation.

Methods: A cross-sectional study was conducted at the Division of Primary Care at the Geneva University Hospitals. Seventeen residents at the end of their training as general internists provided 6–8 self-videotaped clinical encounters. Use of the EHR was defined by use of the keyboard and/or screen during the first 10 minutes of the clinical encounter. The influence on EHR use of patients' characteristics (sex and age and language spoken), physicians' characteristics (sex, age, self-perceptions regarding EHR use) and consultation characteristics (new-follow-up, content of consultation, language used) were evaluated using multivariate analyses.

Results: A total of 142 videotaped consultations were included. Both addressing biomedical content (p = .0178) and having little clinical experience (p = .0213) increased the use of the EHR. There was also weak evidence that being a male MD (p = .1010) or conducting a new consultation rather than a follow-up (p = .0967) could also increase the amount of EHR use. There was no evidence that physicians' self-perceptions regarding the use of computer, or patients' characteristics influenced their EHR use.

Conclusion: The results suggest that only a few elements regarding the physicians or the consultation characteristics were associated with EHR use during consultations. Because lack of clinical experience seemed linked to increased use of the EHR, training on how to use the EHR in a patient-centered manner should take place early in medical training in order to minimize the negative impact of EHR use on the physician-patient relationship.
When your dog suddenly barks silently

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Case description: A 59-year-old patient was admitted due to acute onset of dizziness, vomiting and bilateral hearing loss. A week earlier, his illness started with influenza-like symptoms, followed by severe nausea, profound emesis, progressive dizziness, vertigo and unstable gait. Almost complete bilateral hearing loss occurred the day before admission. The patient lived alone with numerous small animals (goats, cats, dogs), he consumed alcohol excessively. On examination, he had a temperature of 38.2 °C, looked ill with signs of severe vestibulo-cochlear failure (unsteady gait with drift to left, Weber and Rinne-testing was not heard, bilateral positive head impulse test and spontaneous left-beating nystagmus) but no neck stiffness. Blood tests showed leucocytosis of 20.7 G/L with marked left shift, thrombocytopenia of 43 G/L, and C-reactive protein of 85 mg/l. Cerebrospinal fluid (CSF) analysis revealed a polynuclear pleocytosis of 493/µl, with a lactate of 3.3 mmol/l (N <2.0). Treatment with ceftriaxone, amoxicillin and acicllovir was started. A cerebral MRI disclosed multiple small subacute supratentorial ischemic lesions. The echocardiography demonstrated an apical akinisia as sequela of a myocardial infarction and a thrombus within the apex. Coronary angiography was normal without coronary stenosis. Cultures of blood and CSF were negative. However, broad-spectrum PCR of the CSF was positive for Capnocytophaga canimorsus. The patient was treated with i.v. Ceftriaxone for 10 d, recovered slowly of his neurologic deficits over 6 months but at the end needed a cochlear implant for persisting deafness.

Discussion: Capnocytophaga canimorsus, a slow growing gram negative rod, is part of the commensal oral flora of dogs and cats. It can cause severe septice infection, especially in immunocompromised patients (i.e. asplenia, liver cirrhosis, excessive alcohol consumption). C. canimorsus infection activates the blood coagulation cascade; thromboembolic myocardial infarction has been described in patients with C. canimorsus and normal coronary arteries. Meningitis due to C. canimorsus goes along with a high risk of sensorineural hearing loss. Our patient with typical risk factors of dog and cat exposure, combined with excessive alcohol consumption, suffered from two classical complications of systemic C. canimorsus infection, notably meningitis with bilateral hearing loss and thromboembolic cardiac involvement despite normal coronary arteries.

Ivermectin-associated arthralgias. Blame it on the mite?

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Introduction: Ivermectin is used to treat a variety of parasitoses. Post-treatment side effects, or Mazzotti reaction (i.e. fever, headache, chills, arthralgia, rash, eosinophilia, anorexia) may occur due to antigen release from dying parasites. Common in onchocerciasis, Mazzotti reaction in scabies has been described only once in a patient presenting with crusted form. (Ito T., 2013).

Results: Two days after the second dose, the patient developed serious polyarthralgias requiring hospitalisation. Pain relief was obtained with paracetamol and opioids. Patient's past medical, family, allergy and travel history was insignificant. Parameters were normal. Physical examination revealed painful and tender elbow, wrists, knees and ankles. Itchy erythematous, papular and vesicular lesions on the trunk, buttocks, thighs and wrists were present. Besides an elevated CRP, blood tests comprising common viral serologies and a complete immunological panel were normal. Dermoscopy allowed identification of Sarcoptes scabiei and a diagnosis of scabies was made. Because of incomplete response to previous treatment, an additional cycle of ivermectin (2 doses 10 days apart) was prescribed. Arthralgias briefly worsened with the first of these 2 doses. The patient was discharged at day 7. At 1-month follow-up skin lesions had totally regressed and arthralgias disappeared.

Conclusion: In the absence of other drugs or medical conditions that could explain patient’s symptoms, arthralgias were ascribed to a post-ivermectin Mazzotti-like reaction. Although hardly reported in scabies, it is likely that such reaction developed because of high parasite load from long mistreated scabies. Clinicians should be aware of this potential complication particularly when treating crusted or long-standing scabies.

A rare form of granulocytic meningitis

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Introduction: Granulocytic meningitis is a rare form of central nervous system (CNS) inflammation of various infectious, autoimmune and other causes. Exclusion of opportunistic infections, especially in patients with autoimmune diseases treated with immunosuppressive agents, can be a challenge. Brain biopsy is often needed for definite diagnosis.

Case report: A 60-year-old woman was referred for evaluation of weight loss (10 kg in 3y), increasing confusion and anemia. A seronegative, anerocusive rheumatoid arthritis (RA) had been diagnosed a year earlier and was being treated with leflunomide. The occurrence of memory loss and dysarthria had been ascribed to an atypical cerebral hemorrhage due to amyloid angiopathy a few months earlier. The patient's cognitive functions deteriorated rapidly and she started having fluctuating motoric neurologic deficits. The cerebrospinal fluid (CSF) was slightly xanthochromic, showed a lymphocytic pleocytosis (37 Ly /39 cells/µl) and an elevated protein (1087 mg/l). The MRI (fig. 1) revealed leptomeningeal thickening with contrast enhancement as well as progredient subarachnoidal and parenchymatous micro-hemorrhages. Biopsies of meninges and brain confirmed the diagnosis of a granulomatous inflammation and amyloid angiopathy (fig. 2).

Search for infectious causes by culture and PCR was negative. Therapy with leflunomide was stopped, intravenous pulse corticosteroid therapy was given for 5 days followed by oral prednisolone tapered over several months. Additionally, two doses of 1000 mg each of Rituximab were applied. Over 6 months, the ESR fell to 493/µl, with a lactate of 3.3 mmol/l (N <2.0). Treatment with ceftriaxone, amoxicillin and aciclovir was started. A cerebral MRI disclosed multiple small subacute supratentorial ischemic lesions. The patient was treated with i.v. Ceftriaxone for 10 d, recovered slowly of his neurologic deficits over 6 months but at the end needed a cochlear implant for persisting deafness.

Discussion: Capnocytophaga canimorsus is a slow growing gram negative rod, is part of the commensal oral flora of dogs and cats. It can cause severe septice infection, especially in immunocompromised patients (i.e. asplenia, liver cirrhosis, excessive alcohol consumption). C. canimorsus infection activates the blood coagulation cascade; thromboembolic myocardial infarction has been described in patients with C. canimorsus and normal coronary arteries. Meningitis due to C. canimorsus goes along with a high risk of sensorineural hearing loss. Our patient with typical risk factors of dog and cat exposure, combined with excessive alcohol consumption, suffered from two classical complications of systemic C. canimorsus infection, notably meningitis with bilateral hearing loss and thromboembolic cardiac involvement despite normal coronary arteries.
changes, changes of consciousness, focal neurologic signs and seizures, headache, weakness and weight loss. Since RLM can develop regardless of systemic disease activity, it should be considered in any patient with RA and unexplained neurologic symptoms. Brain and meningeal biopsy are needed for diagnosis, allowing also to exclude opportunistic infections. Therapy consists of corticosteroids followed by immunosuppressive agents. Recent case reports show that the historically poor prognosis of RLM can thus be improved.

Adult-onset Still’s disease

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Introduction: Adult-onset Still’s disease (AOSD) is a rare systemic inflammatory disease that occurs in less than 1 in every 100,000 people per year. Its classic symptoms consist of a triad of high spiking fever, joint-pain and a salmon-colored bumpy rash. It is a diagnosis of exclusion and symptoms may be unspecific and lead to a challenging search for a diagnosis.

Case: A 51-year-old male patient was admitted to our unit due to fever of unknown origin since three months, following a cold with a sore throat. He reported having episodes of exceptionally high fever spikes, predominantly at night. Patient history showed that he had been suffering from joint pain in his distal and proximal phalanges in both hands for over 1.5 years and his right hip for approximately 4 years. Joint pain was manageable with the use of mefenamic acid. He had not travelled outside of Switzerland or Austria for the past 9 years and worked in the recycling industry, as well as the fire department and denied contact with toxic substances. On admission blood work-up showed signs of inflammation, procalcitonin was negative, increased GOT, GPT, GGT, AP and markedly increased ferritin. Compared to a blood sample 4 months ago, we saw a substantial decrease in renal function, mixed proteinuria and an elevated erythrocyte sedimentation rate. Abdominal ultrasound and CT-scan only showed splenomegaly. Infectious diseases, hematological malignancies and immunological disorders were ruled out. AOSD was diagnosed with Yamaguchi’s diagnostic criteria, of which the patient fulfilled three major (fever spikes, joint pain, leukocytosis) and four minor criteria (sore throat, elevated liver enzymes, negative tests for rheumatoid factor and antinuclear antibody, splenomegaly). Kidney biopsy showed acute interstitial nephritis, most likely drug-related (mefenamic acid) and no signs of vasculitis. The patient was started on 1000 mg methylprednisolone i.v. daily for three days and subsequently 50 mg prednisolone orally per day. Symptoms improved shortly after therapy was started.

Conclusion: AOSD is a rare disorder that should be considered in patients with fever of unknown origin. The distinctive salmon-colored bumpy rash might be a give-away symptom, but as seen in this case, is not obligatory. Infectious, hematological and immunological causes need to be ruled out beforehand and the diagnosis can be made with Yamaguchi’s criteria, which are 96.2% sensitive and 92.1% specific for AOSD.

Figure 1: Renal histology 1.

Figure 2: Renal histology 2.

Atypical presentation of pneumocystis pneumonia in a tofacitinib treated patient with rheumatoid arthritis

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Introduction: Pneumocystis pneumonia (PCP) is a potentially life-threatening opportunistic infection in immunocompromised individuals. HIV-negative PCP patients, particularly those with inflammatory rheumatologic diseases, rapidly develop fulminate pneumonia with severe respiratory failure. As a diagnostic pitfall, in the early stages of PCP in these patients, respiratory symptoms are nonspecific and nonsevere. We report the case of a patient with rheumatoid arthritis (RA) treated with tofacitinib, who developed severe PCP with atypical clinical presentation.

Case report: A 78-year old male patient with RA treated with tofacitinib, an oral JAK inhibitor (a non-biologic targeted synthetic DMARD), methotrexate (MTX) and low dose corticosteroids (Prednisolone 5 mg daily) was admitted with arthralgia, nausea and confusion. Laboratory findings revealed hypercalcemia 3.12 mmol/l albumin-corrected with normal PTH and elevated 1,25-dihydroxyvitamin D3 (162 ng/l). Therapy of hypercalcemia was initiated at admission with intravenous sodium chloride solution (0.9%), for further investigation of hypercalcemia we performed a CT scan, that showed bilateral interstitial pneumonic infiltrates.

We started an antibiotic therapy with ceftriaxone and clarithromycin. The patient developed respiratory failure with need for non-invasive ventilation/ high flow oxygen therapy on ICU. Bronchoalveolar lavage revealed a positive pneumocystis jiroveci PCR and adequate therapy with trimethoprim/sulfamethoxazole (TMP/SMX) and prednisone was initiated. After seven days intensive care, the patient was referred to the normal ward. Treatment with TMP/SMX had to be stopped because of severe hyponatremia and acute status of confusion. As second line therapy we initiated cldamycin and primaquine. Four days later we stopped the therapy due to thrombozytopenia. The patient recovered respiratorilly after 17 days of antibiotic therapy. Hypercalcemia resolved under adequate therapy of PCP and was – after exclusion of other possible causes – probably fungal associated.

Conclusion: PCP should be considered in RA patients on Tofacitinib treatment. The diagnosis can be challenging because of atypical clinical presentation. Hypercalcemia in conjunction with a pulmonary infection should raise the clinical suspicion of PCP. Considering the potentially fatal courses of PCP and with the rise of new biological and non-biological DMARDS it is important to carefully consider the need for PCP prophylaxis.

Figure 1: CT scan: bilateral pneumonic infiltrates.

A rare reason for genito-oral ulcerations

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Introduction: Behcet disease (BD) is an inflammatory multisystem disease of unknown origin. The clinical presentation is heterogeneous, leading to delayed diagnosis. However, the main characteristic sign is a bilateral aphthosis. The prevalence is high in countries along the silk road (from Japan over the middle east to the Mediterranean countries), BD is rare in western Europe. However, an increase of case reports in our geographic region during the last years indicates the importance of knowing and recognizing the clinical symptoms of BD. Because of the lack of universally accepted diagnostic criteria, the mainstay of diagnosis is the clinical presentation and the exclusion of differential diagnosis.

Case description: We describe the case of a 20 years old male Swiss. He presented with oral and genital aphthosis. Because of oral...
Pain, intake of food and fluids was limited and the patient dehydrated. Two weeks before, the patient had already consulted several other physicians and was prescribed several symptomatic treatments without improvement of symptoms. The former medical history was unremarkable. Infectious causes and Crohn’s disease were excluded by serologies and endoscopic and histologic investigations. Therefore, the suspicion of a first episode of BD was raised. After starting a therapy with prednisone and colchicine, the patient recovered quickly. After hospitalization, the patient was seen in the rheumatological outpatient clinic. To underpin the diagnosis, HLA B51 was tested to be positive.

Conclusion: Our case is a classical example that the diagnosis of BD is difficult and needs a high clinical suspicion. The diagnosis of BD is hard to prove and can often only be confirmed only at the long run after excluding many other possible diagnosis. Our patient was of western European origin, an ethnicity that typically is rarely affected by BD. Our case report shows, that BD may occur as well in patients of western European origin. BD in our western population is probably more frequently then assumed. Therefore thinking of BD is those symptoms is not an orphan diagnosis.

Amoebic liver abscess in a man with liver hemangioma

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Entamoeba histolytica is a protozoan parasite that colonizes the large intestine of humans causing amoebiasis. It remains a significant cause of morbidity and mortality in developing countries and is responsible for up to 100,000 deaths worldwide each year. The clinical outcome of an E. histolytica exposure varies greatly and can present as diarrhea, dysentery or invasive amoebiasis. Amoebic liver abscess is the most common manifestation of extra-intestinal amoebiasis. We report the case of a man known for hemangioma, with superimposed amebic liver abscess. A 51-year-old male patient with a history of 3 weeks abdominal discomfort with epigastric heaviness, abdominal bloating, weight lost and the last 2 days fever up to 39 °C. He spent one week in India 4 months before. Clinical examinations show normal blood pressure (108/66 mm Hg), low-grade fever (37.3 °C) while the abdominal exam is insignificant. Laboratory tests show increased C-reactive protein (221 mg/l) and leukocytosis (15,0 G/l) without eosinophilia. Liver and pancreatic enzyme levels are normal. Urinary, stool and blood cultures are negatives. Antibody tests for Campylobacter Versinia and Salmonella are negative. Abdominal ultrasound shows several hemangioma (V, VI and VII segments) and a new lesion at hepatic dome entering in differential diagnosis between abscess and hemangioma. An abdominal MRI confirms the presence of several hemangioma and shows an abscess of 4.5 cm in diameter, hard to drain, because of the diaphragmatic proximity (fig. 1). Two different antibody tests (ELISA at 1.43, IFAT at 320) confirm the diagnosis of amoebiasis. Under the treatment of 14 days of Metronidazole, followed by a week of paromomycine the patient fully recovers. A control MRI 6 months later shows a complete regression of the liver abscess, confirming ALA (fig. 2). Ameobic liver abscess (ALA) is an uncommon but potentially life-threatening complication of infection with the protozoan parasite E. histolytica. Complications involve rupture of the abscess causing spreading into the peritoneum, pleural space or pericardium. Recognition of variable presentation of ALA is vital, considering the curable nature of this disease and potentially fatal outcome of untreated abscess. In our patient, the presence of liver hemangioma was tricky, potentially leading to erroneous diagnosis. Travel history represents a key moment in the diagnostic process.
gram positive rod capable of replication at a broad range of temperatures insensitive to refrigerated food (at 4 °C). It can be found on fruits, vegetables, meet, fish and cheese and may cause febrile foodborne enteritis. Immunodeficiency, pregnancy, alcoholism and advanced age are risk factors for invasive listeriosis like. The present case showed a meningo-encephalitis, only postmortem. The clinical presentation is often different to pneumococcal or meningococcal meningitis with a more gradual onset, less nuchal rigidity and more prominent movement disorders. Invasive Lm-infection is an important but rare disease with an incidence of 0.5–1 case/100’000 inhabitants and year (50–100 cases / year in Switzerland). Lm is inherently resistant to cephalosporins. Therefore, amoxicillin should be added to the empiric treatment regimen of suspected bacterial meningitis in patients with risk factors.

### GASTGEGESSELLSCHAFT SGH / SOCIÉTÉ CONVIÉE SSH

#### POSTER PRESENTATIONS

**Impact of T-cell depletion on outcome of patients undergoing allogeneic hematopoietic cell transplantation (HSCT) for myelodysplastic syndrome (MDS)**

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**Background:**

T-cell depletion (TDEP) is an increasingly used strategy for allogeneic hematopoietic cell transplantation (HSCT) in the elderly, to reduce the risk of acute and chronic graft-versus-host disease (GvHD). Here, we compared 3-years overall survival (OS), progression free survival (PFS), GvHD-free-relapse-free survival (GRFS), relapse incidence (RI) and transplantation-related mortality (TRM) between TDEP patients and non TDEP ones allografted for MDS. We also evaluated the impact of TDEP on acute and chronic GvHD.

**Methods:**

Retrospective study included 100 patients aged at least 65 years old and hospitalized for initiation of anticoagulation, was performed in an Internal Medicine Department between 2000 and 2015.

**Results:**

- Among the 100 patients, 25% were female, median age of 75.7 ± 6.9 years.
- The indication for anticoagulation treatment required great caution in the elderly because of their frequent polypharmacy and polypharmacy. The aim of our study was to investigate the particularities of the use of anticoagulants in the elderly.

**Methods:**

Retrospective study included 100 patients aged at least 65 years old and hospitalized for initiation of anticoagulation, was performed in an Internal Medicine Department between 2000 and 2015.

**Results:**

- There were 55 women and 45 men (sex ratio: 0.81), with a mean age of 75.7 ± 6.9 years.
- The indications for anticoagulant treatment were venous thromboembolism (VTE) (92%) and atrial fibrillation (AF) (8%).
- The VTE were divided into deep venous thromboembolism (DVT) of the inferior members (85%), superficial venous thromboembolism (SVT) (9%) and pulmonary embolism (PE) (6%).
- Eight patients had simultaneously two reasons for anticoagulation. Low molecular weight heparin (LMWH) was prescribed in 90% of patients and unfractionated heparin (UFH) in 20% of patients. The indication of UFH in our patients was a renal failure (creatinine clearance <30 ml/min).
- Overdose with heparin without bleeding was observed in 4 patients (30.7%) exclusively on heparin sodium. Heparin-induced thrombocytopenia was observed under LMWH in 2 patients (2.5%) and UFH in 4 patients (20%).
- The average length of overlap Sintrom®-heparin was 10.83 days ± 5.8.
- The average duration of treatment with Sintrom® was 17.22 days ± 7.9.
- The dose of Sintrom® initiation was 1 mg in 85% of patients and 2 mg in 15%.
- INR <2 was observed in 15% of patients. INR in the target area was obtained in 47% of patients with a mean dose of 2.33 mg of Sintrom®.
- An overdose under Sintrom® was noted in 38% of patients:
- average INR at 4.7. Seven patients had bleeding events. An overdose was noted in 4 among them.
- Fever, infection, inflammatory syndrome, hypoalbunemia, hypoproteinemia and malnutrition were associated with a greater risk of overdose in our patients.

**Conclusion:**

The use of anticoagulants in the elderly requires a comprehensive assessment including comorbidities, geriatric settings and social environment.
4.6 years (range: 0–15). There was no significant difference between TDEP and non-TDEP for patient characteristics. OS, PFS were estimated using the Kaplan-Meier method. Cumulative incidence estimates of TRM and GvHD were calculated with RI defined as competitive events by the Fine and Gray method.

Results: 3-year OS for all patients was 42 ± 14%, PFS 40 ± 14%, GRFS 26 ± 12%, RI 37 ± 15% and TRM 25 ± 12%, 3-years OS for TDEP patients and for non TDEP ones was not different (48 ± 18% and 34 ± 21% respectively, p-value 0.317) (Graph). Similarly, there was no difference between TDEP and non TDEP patients for 3-years PFS (48 ± 18% and 28 ± 20%, p-value 0.321), 3-years GRFS (32 ± 17 vs 19 ± 17, p-value 0.111) (Graph), 3-years RI (36 ± 18% and 37 ± 20%, p-value 0.622) and 3-years TRM (26 ± 16% and 23 ± 18%, p-value 0.933). Finally, TRM had no significant impact on 3-years grade 2-4 aGvHD when compared to the non TRM (26 ± 18% and 31 ± 16%, p-value 0.656). It had not either on 3-years cGvHD (26 ± 18% and 28 ± 34%, p-value 0.637).

Conclusions: Our study shows that TDEP is feasible on patients undergoing HSCT for MDS and does not make the outcomes worse compared to non TDEP (OS, PFS, RI and TRM). Unexpectedly, TDEP does not significantly reduce the incidence of acute or chronic GvHD. However, the number of patients is small and the period span is long. These finding should be confirmed prospectively in larger cohort.

Figure 2

Pretransplant lung function and performance status as mortality predictors after allogeneic hematopoetic stem cell transplantation: a single-center cohort study
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Introduction: Allogeneic hematopoietic stem cell transplantation (HSCT) remains associated with a high morbidity and mortality in spite of advances in HSCT management. Specifically, pulmonary complications account for a substantial proportion of deaths within the first 100 days after HSCT. Given the inconsistent association of pretransplant lung function parameters on mortality after HSCT and the significant changes in HSCT care over the last decades, the aim of our study was to estimate the effect of pulmonary function and comorbid conditions on mortality in patients undergoing HSCT.

Material and methods: We retrieved relevant clinical data of all consecutive patients at the Hematology division of the Basel University Hospital with a transplant for hematological disorders between 2008 and 2015. We examined the lung function at baseline and 3, 6 and 12 months after HSCT – including the 1-second forced expiratory volume (FEV1 % of predicted), FEV1/VCmax and diffusing capacity for carbon monoxide (DLco). Additionally, we assessed pretransplant conditions such as age, sex, Karnofsky Performance Status (KPS), donor type, and various risk scores in HSCT (HCT-CI, European Society for Blood and Marrow Transplantation [EBMT], revised Pretransplant Assessment of Mortality Score [PAM]). Using uni- and multivariate survival analysis, we evaluated potential patient- and transplant-related risk factors for all-cause mortality by including the following candidate variables: FEV1, KPS, age, conditioning intensity and donor type.

Results: Within the study period, 24 patients (42%) had predominantly acute leukemia (64%) or lymphoproliferative disorders (28%) underwent myeloablative (n = 330) and non-myeloablative (n = 99) HSCT at a median age of 54 years (interquartile range [IQR] 43–61 years). The analysis of the HCT-CI, KPS, EBMT and PAM score revealed median values of 2 (IQR 0–3), 90% (IQR 90–100%), 4 (IQR 3–5) and 15 (IQR 11–20), respectively. In univariate and multivariate analyses with a median follow-up of 12 months (IQR 3–36), a FEV1 of 50–79% vs. particular lower FEV1 of <50% and an impaired KPS <50% was significantly associated with a higher risk for all-cause death – independent of age, conditioning regimes and donor type

Conclusions: Taken into account the changes in practices, supportive care and management of comorbidities, in our cohort, a reduced pretransplant lung function and impaired performance status remain independent predictors of mortality in HSCT.

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Haploidentical hematopoetic bone marrow transplantation with consecutive living kidney transplantation from the same donor in a sickle cell disease patient with end-stage renal failure
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Introduction: Homozygous Sickle cell disease (SCD) patients suffering from end-stage renal disease (ESRD) show a variable outcome after kidney transplantation. We present a case of a 27-year old patient with severe SCD and ESRD who underwent haploidentical bone marrow transplantation (BMT) with consecutive living kidney transplantation (LKT).

Methods: The patient suffered from multiple complications of SCD including stroke with secondary hemorrhage, symptomatic epilepsy, ESRD and uncontrolled hypertension. The rationale for BMT was uncontrollable iron overload. A reduced intensity conditioning regimen was used with (fludarabine, cyclophosphamide and 2Gy of TBI, dose-adjusted to ESRD). Graft-versus-host disease (GvHD) prophylaxis consisted of post-transplant high-dose cyclophosphamide, cyclosporine A (CyA) and mycophenolate mofetil (MMF). The donor was her 56-year old mother with HbS trait, the stem cell source was bone marrow, the cell dose 4.74x108 nucleated cells/kg. During conditioning daily hemodialysis was performed to keep drug levels stable. Neutrophil engraftment occurred on day +28, chimerism at day +19 was 98%, Hbs increased from 1.3% pre-HSCT to 40.0% 6 months after HSCT. Hemoglobin values increased from 70 g/L pre-HSCT to 110 g/L post-HSCT and reticulocytes from 16 G/L to 124 G/L.

Erythropoietin levels increased from 2.3 IU/L pre-HSCT to 178 IU/L and 37 ± 13% respectively, p-value 0.317) (Graph). Similarly, there was no significant impact on 3-years GRFS 26 ± 12%, RI 37 ± 13% and TRM 25 ± 12%.

Figure 2

6 months after HSCT. During the follow-up, the patient did not show any sign of acute GvHD or vaso-occlusive crisis, hemolysis or sickling. Relevant complications were disease-related (therapy resistant hypertension and epileptic seizure due to former brain damage). On day +151 a LKT from the same donor was performed. The initial immunosuppressive treatment with MMF was continued. CyA was switched to tacrolimus and steroids were added for 3 months. The post-transplant period was uneventful. Currently, 12 months after haploidentical BMT and 6 months after LKT there are no signs of GvHD, the blood chimerism is 100%, the kidney allograft function is very good (SFGR 73 ml/min/1.73 m²) and immunosupression is withdrawn. Iron overload is being corrected by regular phlebotomies. The patient no longer requires antihypertensive medication and there is evidence of vascular remodeling.

Conclusions: This is the first report of a successful haploidentical BMT followed by kidney transplantation from the same donor in a patient with SCD.
Efficacy of granulocyte colony stimulating factor in combination with erythropoiesis stimulating agents in the treatment of anemia in patients with lower-risk myelodysplastic syndromes: a systematic review

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Introduction: The myelodysplastic syndromes (MDS) are a group of heterogeneous hematopoietic stem cell disorders characterized by dysplasia and peripheral cytopenias with a propensity to evolve towards acute myeloid leukemia (AML). The treatment of patients with lower-risk MDS (IPSS: low or intermediate-1) includes the application of hematopoietic growth factors like erythropoietic stimulating agents (ESA) eventually in combination with granulocyte colony stimulating factor (G-CSF). However, the evidence on the additional effect of G-CSF on erythropoiesis remains unclear.

Methods: In this single-center retrospective analysis, we evaluated our strategy using a single dose of 35 mg/m² vinorelbine and filgrastim as a rescue procedure to remobilize PBSC of AML patients in first complete remission (CR1) following primary mobilization failure after two cycles of induction chemotherapy. We aimed to determine the survival rates of AML patients successfully remobilized with vinorelbine compared to conventionally mobilized patients.

Results: Between 05/2005 and 01/2015, 69/85 (81%) AML patients in CR1 underwent subsequent collection of PBSC after two cycles of induction treatment whereas 16/85 (19%) patients had primary mobilization failure. With 37.5% (6/16 patients), the rate of mobilization failure was highest in NPM1mut-FLT3wt patients as compared to the other genomic subgroups. In 9 of the 16 (56%) patients with primary mobilization failure, subsequent treatment with vinorelbine and filgrastim mobilized sufficient PBSC to enable these patients to proceed to ASCt consolidation whereas the seven patients with failure after vinorelbine mobilization ultimately underwent conventional chemotherapy consolidation. Finally, we observed that progression free and overall survival rates were not different between primary and secondary mobilizers nor were hematologic recovery or transplant-related mortality.

Conclusion: Our data suggest that vinorelbine remobilization is an effective rescue option for AML patients in first remission with primary PBSC mobilization failure, thereby enabling such patients to proceed to subsequent ASCt consolidation.
relapse after ASCT1 between 2002 and 2015. We assessed the survival rates of myeloma patients consolidated with ASCT in second remission (ASCT2), and we compared them to myeloma patients receiving prolonged reinduction treatment without ASCT2.

Results: The cohort comprised 108 myeloma patients relapsing after melphalan-based high-dose chemotherapy (HDCT) with ASCT1. The second remission was consolidated in 68 patients with ASCT2, whereas 40 patients were treated without ASCT2. ASCT2 was more likely to be performed in myeloma patients with longer remission duration after ASCT1 (29.7 vs. 20.7 months) and with better response after ASCT1 (CR1 achieved in 66% versus 28%), whereas other parameters did not differ. There was no treatment-related mortality associated with ASCT2. ASCT2 was associated with longer progression-free survival as compared to a strategy omitting ASCT2 (PFS2: 30.2 months versus 13.4 months; P = .019). Despite a longer median follow-up of patients with ASCT2 (39.6 months versus 16.3 months; P = .012), fewer patients (57%; 39/68 patients) relapsed so far after ASCT2 compared to patients (70%; 28/40 patients) relapsing after second-line treatment without ASCT2 (P = .045). Overall survival (OS) was better for patients with ASCT2, with the median value not yet reached, compared with 25.9 months in patients without ASCT2 (P < .0001). We observed fewer patients (25%; 17 patients) dying of myeloma progression in the group with ASCT2 compared with 58% (23 patients) in the cohort without ASCT2 (P = .001).

Conclusion: Our results suggest that consolidating a second remission with melphalan-based HDCT with ASCT2 is associated with better survival rates in myeloma patients relapsing after first-line treatment including HDCT and ASCT1.

Trends of incidence and mortality of chronic myeloid leukemia in Switzerland between 1995–2013

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Background: Chronic myeloid leukemia (CML) is a clonal haematopoietic stem cell disorder characterized and diagnosed by the presence of the oncogenic BCR-ABL fusion gene. CML is treated with specific tyrosine kinase inhibitors (TKIs), a standard therapy since the early 2000. This targeted treatment option has completely changed the treatment including HDCT and ASCT1.

Methods: A retrospective observational analysis (age, incidence rate, mortality rate) was performed on data from pts with CML (ICD-O-3 code) reported to the Cantonal Cancer Registries between 1995 and 2013. This represents an median annual case number of 1'843 new CML cases in the Swiss population and aggregated by the National Institute for Epidemiology and 2013 and mid-year Population Estimates and the Cause of Death Statistics from all persons in Switzerland. Three time periods were defined, 1995–2003, 2004–2006 (matnib era) and 2007–2013 (first and second generation TKI era).

Results: 1'122 new CML cases were registered, corresponding to an extrapolated number of 1'843 new CML cases in the Swiss population during 1995-2013. This represents an median annual case number of 55 males (range 36 to 87) and 42 females (range 27–56) in entire Switzerland. Age-adjusted incidence rates of males were around 40–70% higher compared to females, however, remained stable for males and females during the observation period. Age-adjusted mortality rates decreased in males and females over the three time periods by 50–80% (fig. 1).

Conclusions: The results are the first population-based epidemiological data analysis from CML patients in Switzerland. We found a stable incidence of CML over the years observed and importantly, a significant decrease in the mortality rates reflecting the high efficacy of TKI treatment. Further survival analyses are planned to examine this decline in more detail. Moreover, longitudinal data on treatment, side-effects and outcomes is warranted.

Revisiting G-CSF support for hemato logic recovery after autologous transplantation in AML patients

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Introduction: In acute myeloid leukemia (AML), the use of granulocyte colony-stimulating factor (G-CSF) to support hemopoietic recovery in induction and consolidation treatment reduces the number of febrile episodes as well as the duration of neutropenia and of hospitalization. Despite these facts, it is not routinely used partly because of concerns of G-CSF possibly promoting the growth of residual leukemic cells. However, a number of prospective studies in AML patients have failed to demonstrate negative effects on survival rates when G-CSF is used to enhance hematologic recovery. In contrast, studies in AML patients undergoing autologous stem cell transplantation (ASCT) have not been reported so far. Therefore, it is largely unknown whether administration of myeloid growth factors after ASCT is safe in AML patients.

Methods: At our center, it was our policy to administer G-CSF after ASCT in all AML patients. In June 2015, however, increasing economic pressure prompted us to omit G-CSF after ASCT thereby saving the costs of G-CSF. In this retrospective study, we assessed the effects of changing our strategy from applying G-CSF for hematologic recovery after ASCT (in 103 AML patients) to omitting G-CSF (12 patients).

Results: We found that administering G-CSF shortened the median duration until neutrophil recovery was > 5.0 G/L and > 1.0 G/L after ASCT by four days (P = .0001) and five days, respectively(P = .0020), whereas no differences were observed for platelet recovery and transfusion needs. At least one febrile episode during neutropenia after ASCT occurred in patients with (87.7%) and without (100%) G-CSF support (P = .1932), but patients with G-CSF tended to have fewer bacteremias (38.3% versus 66.6%; P = .0654). The median duration of hospitalization was two days longer in patients without G-CSF support (25 days versus 23 days; P = .0603). According to the current version of the diagnosis-diagnosis-related index of the Swiss in-patient reimbursement system, the shorter hospitalization of +G-CSF patients resulted in decreased total costs per patient of 3305 CHF (48 Mio U of G-CSF) and 3367 CHF (30 Mio U). No differences were observed in disease free (P = .0938) and overall survival (P = .7999) rates between +G-CSF versus -G-CSF patients.

Conclusions: Our data suggest that G-CSF support after ASCT is safe and associated with shorter time until neutrophil recovery, fewer bacteremia episodes, shorter hospitalization, and lower costs.

Impact of different T-cell depletion techniques on the incidence of infectious complications after allogeneic hematopoietic stem cell transplantation

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Introduction: T-cell depletion (TCD), obtained by either anti-thymocyte globulin (ATG) administration or depletions, is a strategy for Graft-versus-Host Disease (GVHD) prevention after allogeneic hematopoietic stem cell transplantation (HSCT) [1–4]. The prolonged lymphopenia can result in increased incidence of disease relapse1 and infections.

Patients and methods: We retrospectively evaluated the incidence of infectious complications in 236 consecutive patients who underwent allogeneic HSCT at our center from September 2010 to December

Figure 1

![Figure 1](https://example.com/figure1.png)
Introduction: Myelodysplastic syndromes (MDS) are heterogeneous clonal hematopoietic disorders affecting the hematopoietic stem cells, leading to ineffective hematopoiesis with a propensity to evolve towards acute myeloid leukemia. An increased prevalence of systemic inflammatory and autoimmune manifestations (SIAMs) has been described anecdotally in myeloid malignancies. Here we present an interim analysis of a study investigating the differences of disease- and patient-based factors as well as outcomes in MDS patients with/without SIAMs.

Methods: We performed a retrospective study of a patient cohort at our institution with newly diagnosed MDS between 01.01.08 and 31.09.16. Medical records of MDS patients were reviewed. We included additional MDS patients from this national and potentially international collaborators (Düsseldorf MDS Registry).

Results: We didn't observe any significant difference in the 1-year cumulative incidence of bacterial infections in patients receiving TCD by ATG (45% (95%CI 35%–54.5%)) vs pTCD (58.8% (95%CI 31.2–78.5%)) or both [55% (95%CI 41.4–66.7%)] compared with patients receiving No TCD (52.5% (95%CI 38.9–64.5%)). Similarly, the 1-year cumulative incidence of viral infections or reactivations was comparable in patients receiving No-TCD grafts [80.3% (95%CI 66.8–88.8%)] compared with patients receiving TCD grafts [ATG: 82.9% (95%CI 72.9–88.6%); pTCD: 76.5% (95%CI 45.7–91.2%); ATG+pTCD: 81.7% (95%CI 68.9–89.6%)].

Conclusion: The results indicate that the cumulative incidence of infections are similar in patients receiving TCD grafts compared to those receiving No-TCD graft, suggesting a favorable toxicity profile of different TCD strategy in respect of infections. These results should be confirmed by similar analysis in large scale, prospective clinical trials.

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Systemic inflammatory and autoimmune manifestations in the Bernese Myelodysplastic syndromes cohort and their influence on outcomes

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Introduction: Paraproteinemia after allogeneic hematopoietic stem cell transplantation: a transient phenomenon of underexplored significance

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Introduction: The clinical and biological relevance of paraprotein that newly arises after allogeneic hematopoietic stem cell transplantation (allo-HSCT) in non-myeloma patients is unknown. In healthy subjects, the incidence of monoclonal gamopathy of undetermined significance (MGUS) ranges from 3–9% and significantly increases with age. In these individuals, the absolute risk of progression to plasma cell myeloma at 20 years is 5–38%, depending on the MGUS subtype. The aim of this study was to investigate the incidence, the course and the clinical relevance of paraproteins found after allo-HSCT.

Methods: We retrospectively analyzed a cohort of 403 non-myeloma patients (median age: 48y, range: 18–69y, 57% men, 43% women) who underwent allo-HSCT at the Division of Hematology of the University Hospital Zurich between January 2004 and December 2014. Patients with a MGUS before allo-HSCT were excluded from the study. The immunoglobulin subtype and the light chain restriction of paraproteins were determined by immunofixation. The immunoglobulin subtype and the light chain restriction of paraproteins were determined by immunofixation.

Results: The incidence of paraproteinemia after allo-HSCT (56/403 patients, 14%) was higher than the reported incidence of MGUS in age-matched healthy subjects and in contrast to MGUS did not correlate with age. The majority of patients carried an IgG paraprotein (80%), while IgM paraproteins were detected in 12.5% of patients. Rarely, two types of paraproteins were identified simultaneously. In most patients (44/56, 79%), the paraprotein appeared transiently
within the first year after allo-HSCT with a median duration of 5.8 months (range 2.5–43.9 months). Post-allo-HSCT para-proteinemias was significantly associated with chronic GVHD, but no association was found with other clinical and laboratory parameters. Importantly, development of plasma cell myeloma or lymphoma was not observed in patients with para-proteinemias arising after allo-HSCT.

Conclusions: Our study reveals a high incidence of transient para-proteinemias after allo-HSCT that unlike MGS are not related to age and follow the expected immunoglobulin subtype distribution. Patients with post-allo-HSCT para-proteinemias are at increased risk of developing plasma cell myeloma as observed for MGS inferring a distinct pathogenetic mechanism. Skewing of lymphocyte subpopulations and alterations in cytokine levels in chronic GVHD may explain the expansion of a specific plasma cell subset.

Hypothyroidism following allogeneic hematopoietic stem cell transplantation for acute myeloid leukaemia

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Introduction: Hypothyroidism may complicate of allogeneic hematopoietic stem cell transplantation (allo-HSCT); risk factors are analysed. Methods: We studied 229 patients with AML who underwent an allo-HSCT between 2003 and 2013 with different conditioning regimens (myeloablative, reduced-intensity, chemotherapy-based, total body irradiation-based). Thyroid stimulating hormone (TSH) and free thyroxin levels (FT4) were available in 104 patients before and after allo-HSCT. Results: Median age at transplantation (n = 104) was 47 years [IQR 40–59], 37 (35.6%) were female and overall mortality was 34.6% (n = 36). After a median follow-up period of 47 [IQR 25–84] months, overt hypothyroidism (basal TSH >4.49 mIU/l, FT4 <11.6 pmol/l) was observed in 4 patients (3.8%) and subclinical hypothyroidism (basal TSH >4.49 mIU/l, normal FT4) was observed in 20 patients (19.2%). Positive thyreoperoxidase (TPO) antibodies were found in 5 (4.8%) patients. A total of 13 patients (12.5%) were treated with thyroid hormone replacement. Acute graft versus host disease of any grade (aGvHD) occurred in 55 (52.9%) and chronic GvHD of any stage (cGvHD) in 74 (71.2%) of the patients. The risk of developing hypothyroidism was higher in patients with repeated allo-HSCTs (cGvHD) in 74 (71.2%) of the patients. The risk of developing hypothyroidism was inversely proportional to age (p = 0.043). No correlation was found with GvHD, HLA-mismatch and gender.

Conclusions: After allo-HSCT a significant number of patients experience thyroid dysfunction including subclinical and overt hypothyroidism. Long-term and continuous follow-up for thyroid function after HSCT is important to provide timely and appropriate treatment.
Thalassemia intermedia with a rare mutation and unusual management: a case report
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We present the case of a 32 year old man from Sicily with β-thalassemia (Th). His parents and sister had a β-Th trait. At the age of 2 he showed hemoglobin (Hb) of 9 g/dL with HbA1 94.9% and HbA2 5.1%. Th trait was diagnosed. At 4 he got EBV-infection with symptomatic anemia (Hb 6.4 g/dL) and received first red blood cell concentrates (RBCc). HbA2 was 3.9% HbF 65% and diagnosis was changed to Th intermedia. Later his Hb remained at a level of 9 g/dL without transfusions. At 5 transfusions 2–3 RBCc every 3 weeks were started with concomitant chelation therapy to prevent from growth failure. His ferritin persisted below 1000 µg/l and clinically showed normal development without endocrine dysfunction, HIV or hepatitis, bone disease or pulmonary hypertension. Liver and heart MRI T2* / SQUID showed a severe iron accumulation in the liver but none in the heart. On 10/ 2014 he moved to Switzerland for work, hemotologic controls were started in our policlinic. The patient showed good clinical condition with jaundice and slightly enlarged spleen. The Hb was 9.7 g/dL. (2 days after RBCc), nucleated red blood cells (NRBC) 2/100 WBC, Platelets 120 G/l, Bilirubin 114 µmol/l, Ferritin 866 µg/l, HbA2 3.1% and HbF 22.2%. A molecular analysis showed two heterozygotic mutations in HBB: c.93-21G>A (IVS-1-110) and HBBc. -13C>T (87C>G). We rated the aggressive transfusion regime as unnecessary and proposed its gradual reduction.

Methods: We aimed to identify the right transfusion regime and the need of additional therapy for this patient. RBCc were administered when anemia symptoms occurred or NRBC rose. A therapy with hydroxyurea was started on 02/2015, likewise antiplatelet therapy.

Results: Transfusion of RBCc could be reduced to 3 RBCc every 6–7 weeks with even improving quality of life. Hb below 7 g/dL and/or rising NRBC triggered transfusion although the patient generally had no symptoms of anemia. Last ferritin values varied between 300 to 500 µg/l, chelation could be consequently reduced. The HbF rose to 43%. Conclusion: This compound heterozygocity of two known mutations is an unusual combination not previously reported in the literature. Both mutations found in mediterranean countries, usually lead to β-Th severe/intemedia. This patient was interpreted and managed during 25 years like a Th major. Therapy changes, prioritizing health status were well tolerated without clinical complications avoiding therefore unnecessary transfusions.

Donor specific antibodies in haploidentical allogeneic stem cell transplantation: a case report
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Introduction: Haploidentical stem cell transplantation (haplo-SCT) is increasingly performed if a HLA-matched donor is lacking. Data show an association of donor specific HLA-antibodies (DSA) with graft failure in this setting. DSA occur in up to 14% of recipients, and are oft a reason for rejecting the donor, but can be reduced with plasmapheresis and immunosuppression. Patients with myelodysplastic syndrome (MDS) oft develop alloantibodies because of transfusions and underlying immunologic dysregulation. We report on a patient with MDS and rapidly developing DSA, who successfully underwent haplo-SCT.

Case report: A 67 year-old man with transfusion dependent anaemia and severe thrombocytopenia was diagnosed with MDS RAEB I in August 2015. Azacytidin treatment had no effect on transfusion requirements. A decision for allo-SCT with BM as preferred stem cell source was met, only his two sons (SM*1982 and GM*1989) were identified as possible donors. In July 2016, an antibody screening revealed broad HLA-alloimmunisation and anti-c and -E alloantibodies, showing incompatibility to SM*1982 (DSA B*50:01, MFI 4600; anti-c-and E alloantibodies). RBC incompatibility but no DSA was also
The Swiss MDS Registry/Biobank: sharing first experiences of the pilot phase of a cooperative research platform for personalized medicine in haematology-oncology

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Introduction: Myelodysplastic syndromes (MDS) are malignant hematological disorders with an increasing incidence in the elderly. Sequential accumulation of genetic lesions in hematopoietic stem cells and clonal selection are responsible for initiation and progression to secondary acute myeloid leukemia (sAML). Motivated by increasing insights in the heterogeneity of these disorders, the emerging impact on healthcare resources, the limitation of available data and the utility of longitudinally collected data/samples for translational studies, we set out to implement a cooperative research platform.

Methods: The Swiss MDS Study Group was founded in 2015. It is the first collaborative research consortium of hematopoietic stem cell donation instead of BM. An antibody screening for HLA-antibodies 3 weeks before SCT revealed 49 new specificities and DSA also against GM*1989 (B55*01, MFI 12’000). Because of progressive disease, SCT was nevertheless carried on. DSA reduction was made with a single dose rituximab on day –12 and plasma exchange from day –3 until day –1. On day 0, the B55*01 DSA was negative (MFI 199), with anti-c and anti-E alloantibodies still present. A reduced intensity conditioning (fludarabine, cyclophosphamide, TBI 200 cGy), post-SCT high dose cyclophosphamide and meltycorine at a total of 5.50/31 prophylaxis were given. Neutrophils engrafted on day 17. At day 30, platelets were >50x10³/µl, the absolute reticulocyte count was >30x10³/µl and chimerism was 100% donor type. At day 180, he had hyporegenerative anaemia supported with erythropoietin and sustained engraftment of neutrophils and platelets. Alloantibodies against c, E and HLA-antigens were detected, but the B55*01 DSA was negative.

Discussion: In haplo-SCT, the presence of DSA can be challenging. A careful evaluation of donor-recipient compatibility, including HLA- and RBC-antibody assessment, is of great relevance, especially in HLA mismatched and haplo-SCT.

Figure 1: Platform for personalized medicine in MDS.

Figure 2: Swiss MDS Registry and Biobank platform.
Cytogenetic analysis was performed by conventional cytogenetics and PML-RARalpha (monocytic) that are characterized by established oncogenic drivers. Phosphoproteome characterization in myeloid cell lines.

Results: There were 4 men and 5 women (sex ratio: 0.8). The median age was 47.35 years with extremes of 27 to 81 years. Initial hemoglobin was 5.7 g/dl with extremes of 3.9 to 7.6 g/dl. The mean globular volume was 66.22 fl (59.5–72.5). Ferritin levels were less than 7 ng/ml in all patients. The indications for treatment with injectable iron were malabsorption in 4 cases (celiac disease: 1 case, malabsorption post-gastrectomy: 2 cases and esophageal atresia: 1 case). In the other five cases, injectable iron was administered in the presence of a history of oral intolerance and non-response to iron. One of these patients also had anxiety attacks during transfusions. The mean dose received of intravenous iron was 310 mg distributed over 4 infusions (2–7). The mean difference in hemoglobin after one week, after the second to third injectable iron cure, was 1.38 g/dl (0.45–2.8).

Ferritinemia was corrected in all cases. The injectable iron treatment in this series had good tolerance in 8 cases: no allergic manifestations, no tachycardia, and normal systolic and diastolic blood pressure before and after the infusion. Only one case of tachycardia, agitation, tremor, and chills was noted in the same patient with transfusion intolerance.

Conclusion: Treatment with injectable iron has proved its effectiveness in our series as well as in the literature in the treatment of iron deficiency. No serious adverse effects were noted and the cures were very well tolerated with a correction of the maternal reserves. It is, however, a series of small numbers.

Injectable iron: fast, effective and well tolerated

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Phenotypic assays using zebrafish models for elucidation of hematopoietic toxicity

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Phenotypic assays using zebrafish models for elucidation of hematopoietic toxicity

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Hematologic findings are one of the most common side effects encountered in preclinical safety testing of new drug candidates. The consequences of direct or indirect damage to blood cells and their precursors can be potentially life-threatening, and hence, hematotoxicity can lead to the termination of a promising drug candidate. Current hematotoxicity testing employs in vitro models with a cell viability read-out. However, this approach only allows a limited read-out and, for example, does not capture effects on later maturation stages of blood cell progenitors. Here, we propose the zebrafish as an alternative animal model that captures the full range of hematopoietic lineages and maturation stages in an in vivo setting. Therefore, we use different transgenic zebrafish lines that specifically mark subsets of different hematopoietic lineages, flow cytometry, high content live-imaging and automated drug administration and image analysis.

Integrative bioinformatic characterization of oncogenic pathways by phosphoproteomics in myeloid cell lines: developing a novel diagnostic pipeline for personalized treatment

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Phenotypic assays using zebrafish models for elucidation of hematopoietic toxicity

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Hematologic findings are one of the most common side effects encountered in preclinical safety testing of new drug candidates. The consequences of direct or indirect damage to blood cells and their precursors can be potentially life-threatening, and hence, hematotoxicity can lead to the termination of a promising drug candidate. Current hematotoxicity testing employs in vitro models with a cell viability read-out. However, this approach only allows a limited read-out and, for example, does not capture effects on later maturation stages of blood cell progenitors. Here, we propose the zebrafish as an alternative animal model that captures the full range of hematopoietic lineages and maturation stages in an in vivo setting. Therefore, we use different transgenic zebrafish lines that specifically mark subsets of different hematopoietic lineages, flow cytometry, high content live-imaging and automated drug administration and image analysis.
We have recently established an in vivo model that allows analysis of the potential impact of chemical compounds on the erythroid lineage (Lenard et al, 2016). Here, we use Phenylhydrazine to generate a haemolytic anaemia model and assay the effect of concurrent drug treatment on modulation of erythroid regenerative capacity. Now, we are applying this procedure to a large size compound library of FDA-approved chemicals and optimize the procedure for automated drug administration, data acquisition and analysis. We are now one step closer in introducing this novel multiplex in vivo model to predictive and mechanistic preclinical safety testing, which eventually will complement existing in vitro hematopoietic approaches.

Dissecting mechanisms of proliferative aging in hematopoietic stem cells

Dario Neri
Antonia Müller

Treatment of AML with immunotherapies

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Introduction: Immunotherapies such as Bispecific T-cell engaging (BiTEs) antibodies and Chimeric Antigen Receptor (CAR) T cells have had a major clinical impact in the treatment of B cell neoplasias in recent years. BiTE antibodies consist of two antibody fragments (scFv) linked together where one scFv always targets CD20. Binding of a BiTE to T cells and target cells results in the formation of an immunological synapse, T cell activation and killing of target cells. CAR T cells consist of a scFv linked to the signaling machinery of the T-cell receptor and can docks to the surface of target cells binding directly to their target cells. Acute Myeloid Leukemia is a clonal disorder of the hematopoietic stem/progenitor cells (HSPCs) and contains a subpopulation of leukemia-initiating cells (LiC) that can self-renew and give rise to a hierarchy of maturing blasts. While the proliferating mature blast pool is highly sensitive to chemotherapy, the quiescent LiCs are relatively resistant and can be a source of relapse. We postulate that the only way to lasting success in poor-risk disease is to radically eliminate LiCs and accept collateral damage to HSCs that, subsequently, can be replaced by transplantation. We aim to create a platform for the generation of immunotherapies directed against leukemia and HSC antigens, the first of which will be c-Kit (CD117).

Methods: To use mouse AML models as well as humanized models carrying human AML cell lines and primary human leukemia to evalute safety and efficacy of BiTE antibodies, CAR T-cells and monoclonal depleting antibodies. The capacity to eliminate LiCs as well as bystander effects on healthy hematopoiesis will be assessed.

Results: We have established mouse leukemia cell line engraftment in wild type mice C57BL/6 as well as a human AML cell line (Kasumi-1) in NSG immunodeficient mice. We used a human phage display library and recombinant soluble mouse cKit protein to identify a novel anti-mouse cKit scFv. This scFv was expressed as an IgG and BiTE antibody as well as expressed on murine CAR T cells. In vitro and in vivo experiments are underway to determine the leukemia cell killing potential of the IgG and BiTE antibodies as well as the CAR T cells.

Conclusion: Our goal is to use these immunotherapies to radically eliminate both AML-LiCs and HSCs by targeting non-tumor-selective HSC antigens and to subsequently deal with the life-threatening HSC depletion by allogeneic HSC transplantation.

A standardized quantification tool for bone marrow cellularity in histological sections

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The bone marrow (BM) is the seedbed of our blood, existing as hematopoietic/red or adipocytic/yellow marrow heterogeneously distributed with skeletal location, age, and physiological condition. Patients who undergo chemotherapy or suffer acute BM failure have a rapid adipocytic conversion of the marrow (red-to-yellow transition). After hematopoietic recovery such as upon hematopoietic stem cell transplantation (HSCT) following intensive chemotherapy, functional hematopoiesis is restored (yellow-to-red transition). Pathologist assessment of BM cellularity in H&E sections constitutes the Gold Standard to quantify hematopoietic function. BM failure or aplasia is usually defined as BM cellularity <10%. This range is not accessible to all laboratories, and multi-site standardization of BM cellularity quantification is often critical in the clinical and fundamental research setting. In our effort to systematically quantify BM components in histological sections in an unbiased manner, we developed and optimized a semi-automated image analysis tool for ImageJ, MarrowQuant. Area of hematopoietic cells, red blood cells, bone, and adipocytic ghosts are identified based on color and texture variation of H&E stained histological sections. We find that BM cellularity quantification correlates directly with scoring by four independent clinical pathologists from different countries, while quantification of bone and adipocytes compare with microCT volumetric measurement. The C57BL6 mouse has become the standard model of mammalian hematopoiesis. We have established a consistent map of cellularity in BM sections of homeostatic C57BL6 mice, and observe highly predictable red-to-yellow marrow transitions in the caudal tail and tibia. With age, regions of BM adipocytes increase inversely correlates with kinetics of hematopoietic recovery. BM adipocytes reach maximum expansion 17 days post-transplant and hematopoiesis recovers after 25 days consistent with the exit of severe neutropenia and recovery of pre-transplant blood counts. We have observed that MarrowQuant can offer greater discrimination than pathologist evaluation on extreme cellularity (eg. 0–20% and 80–100%), which could become useful in certain settings. Validation on human trephine biopsies is currently ongoing, opening avenues for its application in experimental or clinical contexts requiring standardized measurements of various BM components.
Correlation study between osteoporosis and hematopoiesis in the context of adjuvant chemotherapy for breast cancer

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Introduction: It was established that adipocytes in the bone marrow have an inhibitory activity on hematopoietic proliferation (Naveiras et al., Nature 2009). In osteoporosis, the osteoblastic/adipocytic differentiation equilibrium of the bone marrow stroma cells is altered, resulting in an adipocytic infiltration of the bone marrow. This work attempts to establish if there is a correlation between osteoporosis and hematopoiesis before and after an adjuvant chemotherapy in the context of breast cancer. Osteoporosis is used as an indirect marker of the bone marrow adipocytic activity.

Method: The clinical data of patients from the “breast cancer” cohort of the CHUV with a bone density exam (± 3 years from the diagnosis) were included in this project and classified according to their osteoporosis status. The evolution of the blood count was studied before and following the first cycle of adjuvant chemotherapy for breast cancer in correlation with the presence or absence of osteoporosis adjusted for age, toxicity of the chemotherapy and G-CSF treatment.

Results: Blood counts before chemotherapy: Our results, consistent with published data, indicate a negative association between t-score and neutrophil as well as thrombocyte counts prior to chemotherapy. Recovery after 1st cycle of chemotherapy: The evolution of the blood counts during the first cycle of chemotherapy was analyzed. The average day of leucocyte nadir is 9 ± 4.2 days. An increase of one point in TBS correlates with a decreased of 0.43 days on the time for leucocyte nadir with a p value of 0.0004. Our data thus suggests that the healthier the bone, the faster the decrease in total leucocyte after the onset of chemotherapy. Data points were insufficient to address the rate of recovery. From our analysis, the other significant response variable was infection with an odd ratio of 2.08 and a p value of 0.000989. The analysis suggests that a healthier bone is associated with a higher risk of infection. Probable selection and sampling bias will be discussed.

Conclusion: Our data confirmed the association between osteoporosis and lower blood count, already shown, in postmenopausal breast cancer patients, with a younger breast cancer cohort. The result of the blood count following chemotherapy suggests that the healthier the bone, the earlier the lowest blood count value. Further studies are needed to analyze the recovery after the lowest blood count and understand the dynamic behind it.
Evaluation of the hemostatic profile in mouse models of advanced chronic liver disease

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Introduction: Advanced chronic liver disease (ACLD), a condition including cirrhosis and fibrosis, is characterized by changes in the coagulation system that embrace both hypo- and hypercoagulability. In this rebalanced situation, hypercoagulability can contribute, like genetic predisposition or environmental factors, to fibrosis progression and cirrhosis complications. Common routine hemostasis tests fail to reflect bleeding and thrombotic tendencies in ACLD patients. Therefore, a better understanding of underlying mechanisms is mandatory for setting-up new assays and treatments. Here, we assessed the hemostatic changes in 2 different models of ACLD in mice.

Methods: 9–15 adult male mice received i.p. 200 mg/kg of thioacetamide (TAA) 3×/week for 12 weeks or 1 ml/kg carbon tetrachloride (CCL4) and phenobarbital (0.3 g/L in drinking water) twice per week for 11 weeks. At the end of the treatment mice were sacrificed; blood and organs were harvested for investigation.

Results: We observed a slight increase in body weight in both CCL4/Phenobarbital (28.0 ± 2.7 vs 24.5 ± 3.9, P <0.0001) and TAA (23.9 ± 3.6 vs 21.5 ± 3.9, P = 0.0025) treated mice compatible with ascites development while mortality rate was higher in the CCL4/Phenobarbital than in the TAA group (32% vs 13%). In control mice, liver histology revealed normal parenchymal architecture without fibrosis. In CCL4/Phenobarbital treated mice, livers displayed extensive fibrosis with both portal-to-portal and portal-to-central bridging. Albeit present, fibrosis in the TAA treated group was less extensive. Interestingly, occulsive centrallobular vein thrombosis was more prominent in the TAA than in the CCL4/Phenobarbital group, where we observed also partial periportal thrombosis. Coagulation investigation showed a slight decrease of fibrinogen in both CCL4/Phenobarbital and TAA groups compared to the controls (1.4 ± 0.1 vs 1.7 ± 0.1 g/L, P = 0.04 and 1.3 ± 0.1 vs 1.7 ± 0.1 g/L, P = 0.01) and prolonged prothrombin time in both CCL4/Phenobarbital and TAA groups compared to the controls (9.3 ± 0.1 vs 8.9 ± 0.03sec, P = 0.01 and 9.8 ± 0.2 vs 8.9 ± 0.03 sec, P = 0.007). Factor VIII was highly increased in the CCL4/Phenobarbital group compared to the controls (350.4 ± 17.3 vs 194.3 ± 34.8%, P = 0.002) but not in the TAA group (282.8 ± 32 vs 194.3 ± 34.8%, P = ns).

Conclusion: These data provide the first evaluation of hemostatic profile in mice with ACLD. Additional data are needed to further characterize the bleeding and thrombotic tendency linked to murine ACLD.

Comparison of two laboratory methods for thrombin generation in pregnancy with high risk for thrombosis

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Aims: Pregnancy and delivery are high-risk conditions for thrombotic complications. Women with heritable thrombophilia with or without thromboembolism in their medical history are at additional higher risk to develop thrombosis and are normally followed-up during pregnancy for evaluation of the prothrombotic state. Follow-up is done by clinical evaluation and sometimes it includes biological markers of activation of coagulation. A disproportional increase would theoretically predict high risk for thrombotic events but usefulness of these markers has not been validated in an evidence-based setting. Aims of this study were: a) to describe changes of biological markers of coagulation activation and thrombin generation in each trimester of pregnancy, b) to compare two different methods for assessment of thrombin generation, c) to check whether heparin prophylaxis in the third trimester affects thrombin generation.

Methods: Data on file of 102 consecutive pregnancies with hereditary thrombophilia or thrombosis were retrospectively analyzed. Pregnant women were routinely followed every 4–6 weeks for thrombotic complications during pregnancy. Any thrombotic event or pre-eclampsia or premature delivery were recorded. Thrombin-Antithrombin-Complex (TAT), D-Dimers (DD) and endogenous thrombin potential (ETP) by a functional chromogenic assay (CAT, calibrated automated thrombogram) were assayed routinely once in the middle of each trimester using standard methods.

Results: TAT (4.3 ± 2.9, 6.4 ± 5.2, 7.7 ± 4.3 microg/L) and DD (0.9 ± 1.5, 1.6 ± 2.1, 2.0 ± 2.3 microg/mL) were increased slightly but continuously and statistically significantly from each trimester to the other. Women receiving heparin prophylaxis showed the same pattern and did not differ from the whole cohort. CAT did not show any differences between trimesters. Women in third trimester with or without heparin prophylaxis did not differ with respect to DD (2.0 ± 2.6 vs. 2.0 ± 1.7 microg/mL), TAT (7.5 ± 2.9 vs. 8.2 ± 5.9 microg/L), CAT-ETP (1696 ± 962 vs. 1715±804 AU).

Conclusions: TAT and DD were elevated as pregnancy progressed, as expected. CAT-ETP in addition to TAT does not add any value of information. TAT and DD do not add any safe value of information with respect to the effect of heparin prophylaxis and they might not be needed as isolated observation tools.

Acute health problems due to recreational drug use in patients presenting to an urban emergency department in Switzerland

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Objective: We described the frequency and the acute medical problems due to recreational drug use in patients presenting to an emergency department in Switzerland during 11 months. The results were compared with data from previous years.

Methods: The retrospective study was conducted at the University Hospital of Basel, Switzerland, between October 2015 and August 2016 and within the Euro-DEN project. All cases presenting with symptoms/signs consistent with acute toxicity of recreational drug use were included. Isolated ethanol intoxications were excluded. Drug tests were performed using immunoassays and liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Results: During the study period there were 47769 emergency department attendances of which 211 were directly related to acute toxicity of substances used recreationally. The mean patient age was 32 years, 71% were male. Alcohol co-use was reported in 46% of the cases, use of more than one recreational drug in 27% of the cases. Most presentations were related to cocaine (38%), cannabis (37%), and amphetamines/methamphetamine excluding MDMA (12%). A drug screening was available in 108 cases (51%). The most commonly analytically detected substances were cannabis (23%), cocaine (22%), and benzodiazepines (19%). There was one intoxication with a novel substance, presenting with hallucinations, chest pain, dyspnea, and palpitations after self-reported use of MDMA; using LC-MS/MS 2C-B could later be identified. The majority of patients (40%) had impaired consciousness (GCS <15) at presentation and/or pre-hospital, 11% were unconscious (GCS <8). Other frequent symptoms were tachycardia (35%), nausea/vomiting (29%), anxiety (27%), and agitation (24%). Most intoxications (55%) were of minor severity and there were no fatalities. Severe complications included 4 acute myocardial infarctions (cocaine involved in 3 of them), 1 case with multiple organ failure (cocaine monointoxication), psychosis (18 cases), and seizures (14 cases). Most patients (72%) were discharged
Mechanisms of cytotoxicity in metamizole-associated neutropenia

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Objective: Metamizole, a non-opioid analgesic prodrug, rarely causes potentially life-threatening neutropenia and agranulocytosis. Currently, the mechanisms underlying metamizole-induced neutropenia (MIN) are only poorly understood. While immunological mechanisms are discussed, certain features are compatible with direct metabolic toxicity on granulocyte precursors in the bone marrow. Therefore, our objective was to investigate possible mechanisms toxicity by the main metamizole metabolites 4-methylaminoantipyrine (MAA), 4-formylaminoantipyrine (FAA), 4-aminoantipyrine (AA), and 4-acetylaminoantipyrine (AAA) in granulocytes and granulocyte precursors.

Methods: We treated HL60 cells (a promyelocytic cell line) and isolated human neutrophil granulocytes with different concentrations of metamizole metabolites (1 µM to 200 µM) with or without components of an oxidative system composed of horseradish peroxidase (HRP) and hydrogen peroxide (H₂O₂). We assessed the adenylate kinase release as a marker of cytotoxicity and the cellular ATP content as a marker of energy metabolism.

Results: MAA, FAA, AA, and AAA (up to 200 µM) alone were not cytotoxic and did not affect the ATP content in HL60 cells or granulocytes. In the presence of H₂O₂, MAA was not toxic for HL60 cells. H₂O₂ (100 µM) depleted the ATP content of HL60 cells by >95% and showed a minor cytotoxicity. This cytotoxicity was concentration-dependently increased by MAA and AA, whereas FAA and AAA were not cytotoxic under these conditions. In the presence of HRP and H₂O₂, AP depletion by H₂O₂ (>90%) and increased cytotoxicity by MAA and AA were detectable, but attenuated compared to H₂O₂ alone. In the presence of oligomycin, which depleted the cellular ATP by approximately 60%, MAA was not cytotoxic. Determination of the time course revealed that ATP depletion was completed between 3 h and 12 h and that cytotoxicity started at 12 h. In granulocytes, H₂O₂ depleted the cellular ATP content by approximately 80% and MAA was not cytotoxic.

Conclusion: MAA and AA are cytotoxic only in the presence of H₂O₂, whereas FAA and AAA are not cytotoxic. Cytotoxicity of MAA and AA seems to be related to the H₂O₂-induced cellular ATP depletion, which may render cells more sensitive. The ATP depletion must be >90% before cytotoxicity is initiated. Granulocyte precursors appear to be more sensitive than granulocytes, which corresponds well with the clinical observations.

Methods: Propofol infusion rates required to achieve changing target brain concentration (6 to 4 to 5 mg/L) throughout a 15 min operation for a virtual male patient (70 kg, 170 cm, 36 y) were obtained with the model of Schnider et al. [1] as implemented in the BasePrimera pump ( Fresenius Kabi, Germany). This subject was then simulated 10000 times under the estimated TCI dosage scheme, using the comprehensive population model with between-subject variability developed by Eleveld et al. [2] to describe plasma propofol concentrations in 660 patients. Median concentration with 90% prediction interval (P90) were calculated and compared to the target brain concentrations at equilibrium according to the TCI prediction. The percentage of virtual patients reaching propofol levels above 15 mg/L (maximum allowed in TCI) was also estimated.

Results: The figures show median with P90 of the Eleveld model and TCI predicted concentrations along with the aimed target levels. Median (P90) concentrations of 5.6 (3.7–8.1), 3.7 (2.6–5.3) and 4.6 (3.3–6.5) mg/L were calculated when the target levels of 6, 4 and 5 mg/L, respectively, were achieved according to TCI predictions. Furthermore, 12% of the virtual patients were found with concentrations exceeding 15 mg/L within the first minute of propofol infusion.

Conclusions: These results show the potential for a closed-loop control of blood concentration to improve automated anesthesia delivery. A proportional-integral-derivative (PID) controller based on real-time propofol measurement to optimize infusion rate is currently under development.

References

Methods: Direct oral anticoagulants: are they safer than vitamin K antagonists?

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Introduction: A significant fraction of the Swiss population is treated with anticoagulants. Bleeding complications are frequent, counting for about 10% of adverse drug reaction-related hospitalizations. After decades of exclusive use of vitamin K antagonists (VKA), direct oral anticoagulants (DOACs) are now available and their use is increasing. According to the published randomized controlled trials, DOACs are at least as effective as VKA, but might be safer.

Objectives: This study aimed to evaluate whether DOACs are safer than VKA by comparing their respective consumption with the number of hospitalizations for bleeding complications in an emergency department over the past years.

Methods: We retrospectively collected data from all patients treated with DOACs or VKA who were admitted to the Emergencies of CHUV for bleeding with externalization (any site) between 2011 and 2015. The severity of these hemorrhages was graded. Patient characteristics were recorded. The consumption data of DOACs and VKA were recorded. The consumption data of DOACs and VKA were investigated and compared to the number of hospitalizations for bleeding complications in an emergency department.

Results: The consumption data of DOACs and VKA were investigated and compared to the number of hospitalizations for bleeding complications in an emergency department. The consumption data of DOACs and VKA were investigated and compared to the number of hospitalizations for bleeding complications in an emergency department. The consumption data of DOACs and VKA were investigated and compared to the number of hospitalizations for bleeding complications in an emergency department.
Pharmacists for the years 2011 to 2015. Spontaneous reporting of bleeding events under DOACs and VKA to Swissmedic was extracted from the Vigilyze database. 

Results: A total of 779 admissions for bleeding events were recorded, among which 250 in patients treated with DOACs or VKA. Only 15 cases were associated with DOACs and were compared with a sub-sample of 50 among the 235 cases of the VKA group. Patients in the VKA group were slightly older (73.9 vs 76.4 years; NS), with higher comorbidity Charlson scores (2.16 vs 1.46; NS), and lower renal function (44 vs 57 ml/min/1.73 m²; p = 0.006). They had more often drug interactions (pharmacokinetic: p = 0.008; pharmacodynamic p = 0.004). The bleeding events did not differ significantly in their location, severity and management. The DOACs market share is growing with a number of DOACs units sold outpacing the VKA in 2015. The number of spontaneous reporting of DOACs-associated bleeding events to Swissmedic is higher than that of VKA since 2013.

Conclusion: The results tend to confirm a safer benefit of DOACs compared to VKA. However, VKA are prescribed to patients in less good condition and thus more at risk of bleeding, which may accentuate the difference in incidence of bleeding events. The over-representation of DOACs in the Swissmedic database might be due to reporting biases.

Prevalence of polypharmacy in the Swiss HIV Cohort Study (SHCS) 

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Introduction: Highly active antiretroviral drugs (ARVs) have transformed HIV infection from a deadly disease into a manageable chronic condition. As a consequence, HIV-infected individuals live longer and become older, affected by age-related comorbidities leading consequently to polypharmacy and a higher risk of drug-drug interactions (DDIs) [1]. There is currently a lack of real-life clinical data on the extent of polypharmacy and DDIs. Moreover, the information on drug-gene interaction and pharmacogenetics (PGx) are scarce. In that context, we aim to describe the prevalence of polypharmacy and PGx-labeled drug prescription in the Swiss HIV Cohort Study (SHCS).

Methods: We have initiated a large-scale prospective observational study within SHCS at the occasion of patient’s biannual cohort visits that implies the systematic documentation of all co-medications, along with plasma levels measurements of antiviral drugs and co-medications at risk of problematic DDIs. Patients are contacted by post one week before their SHCS visits and are invited to report all their current medications in a record form. Drugs with PGx recommendations are identified according to the American and European authorities together with the evidence-based expert opinions aggregated by the Clinical Pharmacogenetics Implementation Consortium (CPIC) [2].

Results: Data available at present from TDM routine service have shown that the most prescribed therapeutic classes are central nervous system and cardiovascular drugs representing 32% and 20% of the prescription, respectively. The proportion of patients receiving at least one non-HIV co-medication is of clinical importance, with a high prevalence of lipid-lowering agents (7%). On 10’030 prescriptions, 7.1% and 14.3% had a CPIC label grade A or B, respectively, affecting several therapeutic classes. Few drugs (1.2%) are recommended or required to be associated with a PGx test according to FDA as well. These results are in accordance with previous studies [3, 4].

Conclusion: In the growing healthcare challenge of personalized medicine and treatment optimization, research efforts must be pursued to improve the quality of ARVs prescriptions, especially with regards to potential DDIs.

Systematic review of case reports on drug pharmacokinetic assessment in patients under hemodialysis

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Introduction: Besides tailored clinical trials in pediatric and adult patients on intermittent hemodialysis (HD), individual case reports on pharmacokinetic (PK) assessments provide an important source of information about drug dialysability and dose adjustments required in this vulnerable population. As there is no systematic guidance available for such PK studies, we aimed to provide a review of current clinician-initiated PK assessment and reporting practices.

Methods: We performed a systematic review of case reports on individual drug PK in HD patients published between 2000 and 2016. We evaluated them for their completeness regarding essential information on patient, drug and HD therapy related factors that may influence PK. We also reviewed the use of PK calculations of relevance in HD patients, in particular dialysis clearance CLDIA, off-dialysis clearance CLoff, and amount of drug removed by HD, as suggested by available regulatory and methodological recommendations for PK assessment in this population.

Results: A total of 88 papers were retained in this review. The majority of case reports concerned non-renally eliminated drugs with QDR=0.7 (60%), and 85% of studied drugs were anticancer and anti-infective agents. Thirty-one case reports (35%) reported at least 50% of
relevant components in HD patients. CL\text{off} was calculated in 33% of case reports, of which only 10% used the recovery gold-standard method. CL\text{app} was calculated in 31% and the amount of drug removed by HD, which is important to calculate appropriate dose adjustments, was assessed in only 20%. Nineteen percent of studies simply reported a reduction ratio of drug concentrations before and after HD session.

Conclusions: Clinician-initiated PK assessments in HD patients are of definite usefulness for the community, but frequently lack important information to allow for interpretation and translation of results to other patients. Additionally, calculations methods to estimate drug dialysability are rarely used to characterize PK information in relevance in HD patients. Limited PK data collected in a single patient could be further leveraged by taking into account published PK information in combination with PK modeling. Checklist and guidance for easy-to-implement PK calculations and pharmacometric modeling can be useful to further enhance publication of individualized dosing evaluations in pediatric and adult HD patients.

Determination of transepithelial transport of ticagrelor in human intestine using in vitro Caco-2 cell monolayer assay

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Introduction: Ticagrelor is the first drug of a new non-thienopyridine oral antiplatelet agents category. Determination of drugs’ affinity for P-glycoprotein (P-gp) efflux transporter is essential for estimation of drugs oral bioavailability and potential drug-drug interactions.

Method: In the current study, the intestinal permeability of ticagrelor as well as its potential P-gp mediated active transport was assessed. To this end, bidirectional transport of ticagrelor was performed using in vitro Caco-2 (human epithelial colorectal adenocarcinoma) monolayer model in presence and absence of the potent P-gp inhibitor valsaparod.

Results: Ticagrelor presented high influx permeability with an apical-basolateral apparent permeability coefficient (P\text{app}) of 6.0(10\textsuperscript{6} cm/s. On the other hand, mean efflux ratio (ER) of 2.71 was observed for ticagrelor describing a higher efflux permeability compared to the influx component. Valsaparod showed a significant inhibitory effect on the efflux of ticagrelor suggesting involvement of P-gp in its oral disposition. Co-incubation of the P-gp inhibitor decreased the efflux P\text{app} of ticagrelor from 1.60(10\textsuperscript{-5} cm/s to 1.13(10\textsuperscript{-5} cm/s and decreased its ER by 70%. Results are presented in following table:

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<th>app P\text{app} (cm/s × 10\textsuperscript{-5})</th>
<th>Inh P\text{app} (cm/s × 10\textsuperscript{-5})</th>
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Conclusion: These results suggest a high permeability and a moderate active transport of ticagrelor by P-gp across the Caco-2 cell monolayer. However, in case of co-administration with an inhibitor of P-gp, a striking impact on pharmacokinetics of ticagrelor appears unlikely in clinical conditions and does not seem to cause bleeding events in patients.

Potential drug-drug interactions at hospital admission: comparative performance of two drug interaction screening programs and clinical relevance

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Introduction: Drug-drug interactions (DDIs), which can lead to drug toxicity or diminished therapeutic effect, can be prevented by the use of DDI screening programs. The aim of our study was to evaluate the frequency of DDI at hospital admission by using two DDI screening programs, and to assess their clinical relevance.

Methods: Patients admitted to an internal medicine and infectious diseases ward at Geneva University Hospitals between March and end of May 2016 were interviewed by a pharmacist/clinical pharmacologist for medication reconciliation. This was part of the national pilot program "Progress: medication safety at transitions in care". The medication list was systematically screened by Lexi-Interact\textsuperscript{3} and by the program from the Compendium Suisse des medicaiments to detect potential DDI. All cases were independently reviewed by three pharmacists/clinical pharmacologists to evaluate the clinical relevance of detected DDI.

Conceptual evaluation of urea rebound in pediatric hemodialysis patients by a physiology-based pharmacokinetic simulation study

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Introduction: Pediatric hemodialysis (HD) dosing and monitoring strategies are mainly derived from adult studies utilizing pre- and post-HD urea plasma concentration measurements. Accuracy of such HD evaluation approach depends on extent and duration of post-HD urea rebound, which occurs due to redistribution of urea from slowly perfused (peripheral) to quickly perfused (central) body compartments. The goal of this urea kinetic simulation study was to evaluate the expected urea rebound in pediatric HD patients.

Methods: Realistic pediatric HD prescription parameters and demographics were calculated over body weight (BW)-bands of 5 kg from a large registry database (DaVita) with ≥20 patients and >130 HD sessions per BW-band. Typical urea concentration-time profiles during and after HD sessions were simulated applying published urea kinetic data\textsuperscript{1,2} and implemented by physiologically-based affected pharmacokinetic models of results to other patients. Additionally, calculations methods to estimate drug dialysability are rarely used to characterize PK information in relevance in HD patients. Limited PK data collected in a single patient could be further leveraged by taking into account published PK information in combination with PK modeling. Checklist and guidance for easy-to-implement PK calculations and pharmacometric modeling can be useful to further enhance publication of individualized dosing evaluations in pediatric and adult HD patients.

References:

HepaRG cells.

Results: A total of 64 patients were interviewed, 58% were men. The mean age was 65 years old. A mean of 78 drugs per patient per day were taken (range: 0 to 19), including “as needed” medication. The most frequently used drugs were paracetamol, acetylsalicylic acid (cardiologic indication) and esomeprazole. A total of 132 potential DDI were detected by the Compendium software, and 314 potential DDI were detected by Lexi-Interact® (no severity filter added). The mean number of DDI detected by each software was 2.2 and 5.0 respectively (range: 0–17 and 0–33 respectively). The majority were pharmacodynamic DDI (80%) and 70.7% respectively. The three independent pharmacists/clinical pharmacologists judged a total of 87 DDI as being clinically relevant, representing approximately one third of all detected DDI by Lexi-Interact®.

Conclusion: Admitted patients are potentially subject to DDI as detected by DDI screening programs but not all of them are clinically relevant, and the different screening programs show variability in their performances.

Introduction: Hemorrhagic cystitis (HC) is one of the common complications of busulfan-cyclophosphamide conditioning regimen during allogeneic hematopoietic stem cell transplantation in children. In a retrospective analysis, a higher incidence of HC was observed in pediatric patients with higher sulfolane levels. We therefore hypothesized that sulfolane might increase the activity or expression of cytochromes P450 (CYP), which are involved in the first step of the metabolism of CY into its urotoxic metabolite acrolein.

Method: Different concentrations of sulfolane ranging from 0.5 to 5 µM were incubated with differentiated HepaRG (passage 19) cells seeded on 24-well plates at a density of 2×10^5 cells/cm^2 in a medium composed of phenol-free Williams medium E supplemented with 2 mM GlutamaxTM, 50 µM hydrocortisone hemisuccinate, 5 µg/ml insulin, 100 µM penicillin and 100 µg/ml streptomycin at 37°C, 5% CO2. Negative and positive controls with rifampicin (10 and 50 µM), omeprazole (50 and 100 µM) and phenobarbital (500 and 1000 µM) were used. Final concentration of DMSO during the time of induction was 0.1% in all conditions. After 72 hours of incubation with medium changes every 24 hours CYP activity was assessed by incubating a phenotyping cocktail composed of midazolam 5 µM (CYP3A4), S-mephenytoin 50 µM (CYP2C19), bupropion 50 µM (CYP2B6), phenol red-free Williams medium E. Reactions lasted 3 hours, after which incubation media and plated cells were collected for metabolite quantification by LC-MS/MS and gene expression analyses by RT-qPCR.

Results: HepaRG exposed to different levels of Su showed significant differences neither in CYP activity compared to controls, as measured by the velocity of metabolite production normalized to the total protein content, nor at the level of gene expression. For CYP2B6, induction by 2 fold was observed only at the mRNA level but did not exhibit increased activity while phenotyping with the probe drug. Known inducers of CYPs like phenobarbital, rifampicin, and omeprazole exhibited induction. Data from these experiments did not indicate a significant impact of sulfolane on CYP activity and expression in HepaRG cells.

Conclusion: The association between sulfolane levels and the incidence of HC in pediatric patients receiving busulfan-cyclophosphamide conditioning regimen prior to hematopoietic stem cell transplantation does not seem to involve CYP modulation.

Pharmacokinetics of transdermal etofenamate and diclofenac in healthy volunteers

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Background and aims: Little is known about the course of the plasma concentration and the bioavailability of non-steroidal anti-inflammatory drugs (NSAIDs) contained in dermal patches. In order to obtain more information about this subject, we determined the plasma concentration-time profile of diclofenac epomelamine (from a commercially available dermal patch) and of etofenamate (from a prototype dermal patch) in 24 healthy human subjects. In order to calculate the bioavailability, we compared drug exposure following patch application to exposure after i.m. application of diclofenac or etofenamate in the same subjects.

Methods: Subjects were treated using a parallel design (n = 12 per stratum) with a single dermal patch (removed after 12 hours) followed by (after 48 hours) 8 consecutive dermal patches every 12 hours to reach steady state conditions. The patches contained 10 mg/g diclofenac (Flector®; weight 14 g, 140 cm^2) or 50 mg/g etofenamate (patent EP 1833471; weight 14 g, 140 cm^2). The i.m. applications contained 75 mg diclofenac (Voltaren®) or 1 g etofenamate (Ribulfam®). Plasma concentrations were determined using a validated LC/MS method. Bioavailability was calculated as the ratio of the AUCs with dose adjustment.

Results: One subject treated with etofenamate developed an allergic contact dermatitis; otherwise the patches were well tolerated. After the first patch, C_max was 0.81 ± 0.38 (95% CI) ng/mL (reached 12 hours after patch removal) for diclofenac and 31.3 ± 8.5 ng/mL for flufenamatem (reached at patch removal), the main metabolite of etofenamate. Etofenamate was not detectable. After repetitive dosing, trough plasma concentrations after the eighth dose were 1.72 ± 0.72 (95% CI) ng/mL for diclofenac and 48.7 ± 14.8 ng/mL for flufenamatem. C_max for the i.m. applications were 1790 ± 280 (95% CI) ng/mL for diclofenac and 6810 ± 1450 ng/mL for etofenamate (measured as flufenamatem). Bioavailabilities (single dose) relative to i.m. applications were 0.22 ± 0.09% (95% CI) for diclofenac and 1.15 ± 0.13% for flufenamatem.

Conclusions: Etofenamate is rapidly converted to flufenamatem and has a higher bioavailability (as flufenamatem) than diclofenac after topical administration. The bioavailability of both drugs is low compared to i.m. application. The plasma concentrations reached are well below the IC50 values for COX-1 and COX-2 inhibition of these drugs, explaining the absence of dose-dependent toxicities after dermal application.

Multiplex liquid chromatography-tandem mass spectrometry assay for the simultaneous monitoring of Bosentan and Macitentan and their metabolites, together with Sildenafil and Tadalafil in patients with pulmonary arterial hypertension

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Introduction: Among the last generation endothelin receptor antagonists (ERAs) only Macitentan has shown a reduction in morbidity-mortality endpoints in pulmonary arterial hypertension (PAH) as compared to placebo. Moreover, compared to the previous ERA Bosentan, Macitentan may have higher clinical efficacy due to: (i) enhanced safety profile, (ii) less liver toxicity, (iii) reduced drug-drug interaction potential and (iv) improved tissue penetration properties as well as ER affinity [1]. Therefore, stable PAH patients currently on Bosentan may benefit from a switch to Macitentan. Yet, Bosentan moderately induces cytochromes CYP3A4 and CYP2C9, both enzymes also implicated in the biotransformation of Macitentan into its active metabolite. Then, switching from Bosentan to Macitentan may explain transient subtherapeutic drug levels in patients, which have never been investigated before. Possible adverse effects may however be attenuated in patients under bi-therapy with PDE5-inhibitors. The
Tailoring a clinical decision support tool to a hospital’s needs
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Introduction: A large number of commercially available Clinical Decision Support Systems (CDSS) exist. Most commonly, they are embedded in an electronic prescribing software program and their quality is variable. According to the software developer, the embedded CDSS used in our hospital has approximately 21'000 “severe” or contraindicated drug-drug interactions depicted, based on trade-names and generic names. Such alerts “pop-up” automatically during the prescribing process.

Methods: Automatically generated warnings regarding drug-drug combinations which could result in patient harm (“severe”), or which were contraindicated according to the drug label were assessed prospectively during routine patient care by pharmacologists, pharmacists and internists between May 2015 and September 2016. Unsatisfactory warnings were recorded in a local electronic spreadsheet and reported to the company along with the requested alteration every 3–4 months.

Results: During the 16-month period, 137 problematic alerts regarding severe or contraindicated drug-drug interactions were identified and reported to the company. Of these, 60% were changed by the company as requested, within an average of 59 days. The following reasons for not adopting the experts’ requests for optimization were given: technical difficulty, difference of opinion and inability to undertake country-specific changes to the database.

Conclusion: Close co-operation between treating physicians, pharmacologists, pharmacists, IT-specialists and the software company is needed to tailor a CDSS to a hospital’s needs and quality standards. The process is time- and resource-consuming and does not achieve complete implementation of local expert’s desired customizations.

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