



30^e Internistendagen

ABSTRACTBOEK

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Abstractboek**

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I ORAL PRESENTATIONS

O1.01

Febris e fungo

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Case: A 57-year old male without relevant medical history presented with fever attacks since six months. These attacks occurred once or twice a week and were accompanied by dyspnoea and coughing. Furthermore, he experienced progressive dyspnoea d'effort. Physical examination, laboratory results, including C-reactive protein and D-dimer, and chest X-ray were normal. Blood cultures were negative. Patient was instructed to keep a detailed record of his complaints.

It turned out that the fever attacks only occurred on Monday and Friday evenings; days on which mushroommycelium was grafted at the compost factory he worked for.

For a provocation test, patient was admitted to the hospital after a day's work. At 11 pm he developed fever (40.1°C). At that moment, he was hypoxic (pO₂ 7.8 kPa; normal: 11.0-14.4 kPa) and a high resolution CT showed subtle ground glass attenuation. Bronchoalveolar lavage showed lymphocytosis (53%; normal: 1-17% (smoker), 3-32% (non-smoker)) and decreased CD4+/CD8+ ratio (0.9; normal: 2.3 ± 0.2).

Diagnosis: Patient was diagnosed with acute extrinsic allergic alveolitis (EAA), also called hypersensitivity pneumonitis. In EAA, the inflammatory response of the alveolar mucosa is a hypersensitivity reaction of type 3 (immune-complex-mediated) or type 4 (T lymphocyte-mediated) to an inhaled agent.

Management: When diagnosed early in its course, the disease is reversible. In this case, the patient experienced no more fever, dyspnoea or coughing after he quit his job.

Clinical relevance: Besides highlighting an unusual cause of febris e causa ignota, this case underlines the high value of extensive anamnesis in patients with unexplained symptoms.

‘Body packer syndrome’ toxicity due to marihuana

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Case: A 23-year-old patient with an unremarkable medical history visited the Emergency Department with dizziness and drowsiness. Two days earlier he ingested five packets of marihuana, with a total weight of 30 grams. Patient had normal vital parameters, but was soporific (E3M6V5). He was evidently intoxicated, and the symptoms fitted the sedative-hypnotic toxidrome. Urinalysis for drugs of abuse was positive for marihuana only. An X-ray revealed two packets in the left upper abdominal quadrant. The patient was admitted for observation. The next day, the patient was too soporific (E3M6V4) to hold a conversation. A CAT-scan showed only three packets, all in the stomach. Subsequently, patient underwent surgical removal of three whole packets as well as the remains of one ruptured packet. The patient recovered without sequelae and was discharged from hospital after three days.

Discussion: Marihuana is an uncommon substance of packets, but a ruptured packet can cause severe, potentially lethal intoxications. In our case, underestimation of the risk of an ongoing marihuana overdose, and unfamiliarity with bodypacking resulted in delayed surgery, even though at presentation in the Emergency Room, a ruptured package was considered due to the presence of severe symptoms. Observation should only be performed in patients without symptoms. Surgery is the appropriate treatment in any bodypacker in whom a ruptured packet is considered based on symptoms of intoxication, potentially supported by toxicological test. Endoscopic treatment is discouraged due to high risk of packet rupture and ongoing intoxication as a result.

Complete arterio-venous re-endothelialization of growth-factor preloaded rat and human kidney scaffolds using human pluripotent stem cell-derived endothelium

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Background: The bioengineering of a replacement kidney has been proposed as an approach to address the growing shortage of donor kidneys for the treatment of chronic kidney disease. One approach being investigated is the recellularization of kidney scaffolds. In this study, we present several key advances towards successful re-endothelialization of whole kidney matrix scaffolds from both rodents and humans.

Methods: Human and rodent kidneys were decellularized with 1% SDS and 0.1% triton-X to obtain kidney scaffolds. Kidney scaffolds were then pre-loaded with vascular growth factors. Human induced pluripotent stem cells (iPSC) were differentiated into endothelial cells in large scale culture and were reseeded in preloaded kidney scaffolds via a novel arterio-venous delivery system.

Results: Based on the presence of preserved glycosaminoglycans within the decellularized kidney scaffold, we show improved localization of delivered endothelial cells after pre-loading of the vascular matrix with VEGF and angiopoietin 1. Using a novel simultaneous arterio-venous delivery system, we report the complete re-endothelialization of the kidney vasculature, including the glomerular and peritubular capillaries, using human iPSC-derived endothelial cells. Using this source of endothelial cells, it was possible to generate sufficient endothelial cells to recellularize an entire human kidney scaffold, achieving efficient cell delivery, adherence and endothelial cell proliferation and survival.

Conclusion: These major advances move the field closer to a human bioengineered kidney.

A pulmonary-renal syndrome secondary to thiamazol

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Case: A 21-year old Caucasian female, with Down's syndrome and M. graves, developed a cough, shortness of breath, fatigue, anemia and impaired renal function. Recently thiamazol was stopped due to the anemia. The patient was suspected to have a pneumonia and was treated with intravenous antibiotics, fluid and oxygen support. Despite treatment she deteriorated, developing respiratory failure and was admitted to the ICU for mechanical ventilation. The patient required high ventilator pressures and developed hemoptysis and diffuse bilateral consolidation on chest X-ray. Her renal function further deteriorated with glomerular erythrocyturia and proteinuria and persistently high inflammatory markers. Due to this decline a pulmo-renal syndrome was suspected. Additionally laboratory tests showed an elevated MPO ANCA. Kidney biopsy was performed and showed a pauci immune crescentic glomerulonephritis. Subsequently, a diagnosis of MPO-ANCA-associated microscopic polyangiitis vasculitis secondary to thiamazol with renal and pulmonary involvement was made. She was treated with high dose methylprednisolone for three days, followed by high dose prednisone daily. There was an immediate response with improvement in respiratory and renal situation, therefore no additionally anti-inflammatory drugs were required.

Discussion: Literature shows multiple case reports of MPO-ANCA-associated vasculitis due to antithyroid drugs (both PTU and thiamazol) with varying dosages and onsets. There is no clear correlation between the MPO-ANCA titre and the severity and number of organs involved.

Conclusion: MPO-ANCA-associated vasculitis is a rare but potentially life threatening complication of antithyroid drug use.

Case report: Pembrolizumab and acute kidney injury

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Introduction: Immunotherapy in non-small cell lung cancer (NSCLC) has improved prognosis. Pembrolizumab, an IgG₄ monoclonal antibody to PD-1, is available as first line therapy. Nivolumab has been used for NSCLC as second line therapy, since 2015. With the increasing use of immunotherapy, knowledge of the side effects is amendable.

Case: A 76-year-old patient presented with acute kidney failure (AKI). She had a history of chronic kidney disease stage 3b, diabetes mellitus type 2, and COPD. She was diagnosed with NSCLC with metastasis to the lymph nodes and adrenal gland and treated with pembrolizumab 200mg iv every 3 weeks. After the fourth infusion she presented with nausea, vomiting and AKI (eGFR declined from 57 to 4ml/min/1.73m²). Urine sediment showed red blood cells 25-50/field; no dysmorphic red blood cells; white blood 5-10/field and proteinuria was 0.2g/24h. Renal biopsy showed chronic tubulointerstitial nephritis (TIN) with 40-50% interstitial fibrosis and tubular atrophy, and acute tubular necrosis. The nephritis was attributed to pembrolizumab because the relation in time between start and AKI and by exclusion of other causes. Prednisone 140 mg intravenously (2 mg/kg) was started followed by oral prednisone tapering. There was no rechallange of Pembrolizumab. Renal function recovered to a certain extent (eGFR 26 ml/min/1.73m²).

Conclusion: AKI is a severe side-effect of cancer related immunotherapy. Close prolonged monitoring of kidney function is mandatory because this kidney failure may occur up to months after infusion of immunotherapy. Prednisone therapy may contribute to recovery of kidney function as has been described in other medication induced TIN.

ACE-inhibitor-induced angioedema successfully treated with C1-esterase inhibitor (Cinryze®)

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Case: A 70-year-old male with chronic obstructive pulmonary disease and chronic renal insufficiency was referred to the emergency department on suspicion of ACE-inhibitor-induced angioedema. He had swelling of the tongue and face without rash or pruritus and had started taking enalapril, an angiotensin-converting enzyme (ACE) -inhibitor two days ago. The general practitioner had administered 1 mg of epinephrine, 2 mg of clemastine and 8 mg of dexamethasone intramuscular. The angioedema progressed and began to involve the soft palate, uvula and neck. The patient was hardly able to speak and experienced dysphagia. On physical examination there were signs of larynx edema and the intensivist and anesthesiologist were consulted for evaluation of the need for intubation. We administered 1000 units of complement C1-esterase inhibitor (Cinryze®), which effectively reversed the angioedema within 30 minutes. Patient was observed on the intensive care unit for one night and intubation was finally not necessary. ACE-inhibitor was discontinued and registered as contra-indicated for this patient.

Discussion: ACE-inhibitor-induced angioedema shares clinical features with hereditary angioedema (HAE) caused by C1 esterase inhibitor deficiency, which are both bradykinin-mediated. In HAE treatment with C1-esterase inhibitor is proven to be effective, but evidence for treatment of ACE-inhibitor-induced angioedema is lacking. However, especially in patients who present with severe progressive angioedema that is threatening the airway it may be beneficial when started within six hours of onset of symptoms.

Conclusion: This case shows that C1-esterase inhibitor was effective in reversing ACE-inhibitor-induced angioedema and can prevent invasive measures like intubation or emergency airway puncture.

Hemorrhages: don't forget the (vitamin) 'C'

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A 61-year old Caucasian male, with a medical history of paranoid psychosis, hypertension and recurrent venous thromboembolism was admitted to the emergency room with painful muscles and weakness after a fall. He was experiencing psychosis for which he was treated in custody. As a result, he refused the use of medication. Radiographic examination by a surgeon revealed no fractures. We received a consult due to a deep normocytic anemia (hemoglobin 3.2 mmol/L) with normal platelet count and renal function. At physical examination, we saw a pale and cachectic patient. Inspection of the lower extremities revealed peripheral edema with widespread hematoma, multiple scattered ecchymosis, petechia and diffuse perifollicular purpura. Remaining physical examination was unremarkable. Additional blood tests revealed a folic acid deficiency (3 nmol/L), a normal vitamin B₁₂ and a mild leukopenia. Coagulation and liver tests were normal. Radiographic examination showed no (recurrent) venous thromboembolism. Laboratory evaluation confirmed the suspected diagnosis of scurvy (vitamin C showed a severe low value of 2 µmol/l) explaining the widespread hemorrhages. Dietary modification, ascorbic acid (500mg per day) and folic acid (0.5mg per day) were started. His muscle weakness and anemia improved dramatically within 2 days and 3 weeks respectively.

Conclusion: The cause of our patient's vitamin C deficiency, leading to structural instability of collagen, was attributed to a diet without fruit and vegetables for months. This case highlights the importance of a detailed history when evaluating unknown physical findings. Clinicians should be aware of this potentially fatal but easily curable disease that still exists!

Hallucinations and delusions with an unexpected cause

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A 53-year old, otherwise healthy man presented himself with delusions, hallucinations and memory loss. Apart from slightly elevated protein in his CSF, no other abnormalities were found, MRI scanning of his brain was unremarkable and intoxications were not detected.

He was treated with high dose methylprednisolone for a suspected limbic encephalitis, however, without a response. He gradually deteriorated, progressing to a comatose state. Intubation was performed and he was mechanically ventilated.

A new MRI scan of the brain showed diffuse white matter lesions which was thought to reflect acute disseminated encephalomyelitis (ADEM), probably caused by an infection or malignancy. However, after thorough investigation, no infection could be detected and no malignancy was found. Paraneoplastic antibodies were negative.

The only clue was an elevated LDH, which rose day by day, mildly increased liver enzymes and hepatosplenomegaly. A biopsy of the liver was performed, showing B cell lymphocytosis, that could either be malignant or reactive. Soon thereafter, our patient died due to a distributive shock. Autopsy revealed an intravascular lymphoma with localizations in nearly all organs, including the central nervous system. Intravascular large cell lymphoma (ILCL) is an extranodal manifestation of a diffuse large B cell lymphoma. It is a rare diagnosis and mostly found on autopsy as patients present with non-specific clinical manifestations and further evaluations are mostly inconclusive. Our case shows that it is important to recognize psychiatric symptoms as presenting manifestation, as only prompt chemotherapeutic treatment enhances survival.

Healthcare costs of patients on different renal replacement modalities – analysis of dutch health insurance claims data

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Background: Renal replacement therapy (RRT) is an expensive therapy, however, comprehensive cost estimates in the The Netherlands are based on one study from the 1990s. More recent studies in other countries lack a complete overview of all RRT modalities, especially of living donor kidney transplantation (LDKT). We present average healthcare costs for Dutch patients for 7 treatment modalities, including LDKT.

Methods: Dutch health insurance claims data of 2014 were used to identify adult RRT patients. The average annual healthcare costs were analyzed for 5 dialysis modalities (in-center haemodialysis, home haemodialysis, continuous ambulatory peritoneal dialysis (CAPD), automated peritoneal dialysis, multiple dialysis modalities in a year (mix dialysis group) and 2 transplant modalities (LDKT and deceased donor kidney transplantation (DDKT)).

Results: Total average annual healthcare costs ranged from €77,566 for CAPD patients to €105,833 for the mix dialysis group. Costs for kidney transplant recipients were €85,127 in the year of transplantation and rapidly declined in the first and second year after successful transplantation (resp. €29,612 and €15,018). A DDKT resulted in higher costs (€99,450) in the year of transplantation compared to an LDKT (€73,376).

Conclusion: This study presents comprehensive cost estimates of 7 different RRT modalities, including different dialysis and kidney transplantation modalities, using Dutch health claims data. CAPD patients have the lowest costs compared to other dialysis modalities. Costs in the year of an LDKT are 25% lower than those of a DDKT. Notably, after successful transplantation, annual costs decline substantially to a level that is approximately 14-19% of annual dialysis costs.

A soldier with recurrent fever

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Introduction: hereditary periodic fever syndromes are presenting with recurrent episodes of fever and other specific symptoms and are mostly diagnosed in early childhood. We present an uncommon presentation of periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA). Case: An 18-year-old man presented at the infectious diseases outpatient clinic with episodes of fever and pharyngitis. These episodes progressively occurred since his early childhood, initially diagnosed as recurrent viral infections and occurred every four weeks only since the last year. He had shown normal growth development and was otherwise healthy. The symptoms heavily hampered his training for army officer. Physical examination and blood results were normal. The typical cyclic pattern and oropharyngeal symptoms made us suspect PFAPA. Therefore, we re-examined him at the emergency ward during a new fever episode and objectified high fever, pharyngitis and aphthous stomatitis. Blood results showed increased CRP and IgD level. Serological tests and blood culture were negative. These findings met the criteria of PFAPA by K.T. Thomas. He was started on colchicine 1 mg per day and had no fever episode ever since. He successfully proceeded his military training.

Discussion: PFAPA is a rare syndrome and mostly diagnosed in childhood. In most cases symptoms cease years before adulthood, only this patient still suffered from fever episodes at the age of eighteen. When the cyclic pattern developed, the syndrome was finally diagnosed. There is a high rate of patients successfully responding to colchicine prophylaxis, strongly enhancing quality of life.

Future screening tool for pre-dialyses patients in the decision-making process pro or against renal replacement therapy. A prospective observational study

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Background: The prevalence of end stage renal disease increases, partially because of senescence. Many of these elderly patients are frail and have multiple comorbidities and some have low performance scores and/or cognitive dysfunction. In this group, renal replacement therapy (RRT) may possibly not increase survival and attribute to quality of life. This study investigates whether a screening tool may help in the decision-making process pro or against RRT.

Methods: In this prospective observational study 90 elderly pre-dialysis patients were screened with the Charlson co-morbidity Index (CCI), Davies comorbidity score, Groningen Frailty Indicator (GFI), Karnofsky score and the mini-mental state examination (MMSE) in combination with the clock drawing test to determine eligibility for RRT. Age and serum-albumin levels of the patients, as well as a surprise question (“Would you be surprised if this patient died within the next year?”) answered by the treating nephrologist were taken into account to determine the advisable treatment option.

Results: According to currently suggested decision protocol, conservative treatment was preferable in 31 (34.4%) patients. This is an increase of 19 (21.1%) patients compared to the standard treatment decision making process, which is based on the opinion of the physician and wishes of the patient (NcNemar: $p < 0.001$).

Conclusions: After a complete screening, significantly more patients would be advised not to start with RRT. The 77 patients from this study that started RRT will be followed for 3-5 years to determine whether this screening method correctly predicts eligibility for RRT, based on outcome.

‘Not everything is what it seems to be’

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Case: A 33 year old female was seen at the outpatient clinic because of persistent proteinuria (1.6g/L/12hours) after labour of her third child three months before. Her medical history mentioned pre-eclampsia during her first pregnancy. The second and third pregnancy had no complications. She had no complaints of edema. Family history was negative for kidney diseases. Physical examination showed a blood pressure of 110/70 mmHg, no periorbital/peripheral edema or skin/joint abnormalities. Blood results showed good kidney function (eGFR 120ml/min), normal albumin levels and normal inflammation parameters. Urinalysis in a portion showed proteinuria (8.3g/L) without significant albuminuria (9.5mg/L), leucocyturia or erythrocyturia. 24 hour urinalysis showed a total protein of 2.75g of which only 17.2 mg was albumin. There were no Bence Jones proteins found.

This remarkable finding raised the suspicion of factitious proteinuria after which urinalysis was repeated during outpatient consultation. Again proteinuria (5.5g/L) with negligible albuminuria (73mg/L) was found. Protein electrophoresis showed proteins in the urine that were not detectable in the blood. Therefore, it must be a protein that comes into the urine after filtration in the kidney. It showed similarities in structure with chicken protein with electrophoresis. The patient had no explanation for these findings. After consultation of her general practitioner, she appeared to be under treatment by a psychiatrist because of severe depression and anxiety disorders. The proteinuria was classified as “factitia”.

Conclusion: Proteinuria without albuminuria or Bence Jones proteinuria should always raise caution for “extrarenal” (e.g. factitious) proteinuria. Protein electrophoresis may provide more information concerning the origin.

Acute hepatitis E-viral infection as a cause of fulminant hepatitis in two non-immune compromised patients

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Case: A 74- and 71-year old male presented with icterus, fatigue, and dark urine since weeks. Both had elevated liver enzymes, with total bilirubin of 6 and 12 and alanine aminotransferase of 44 and 25 times the upper limit of normal. PT was elevated with 15.4 respectively 12.9 seconds. Hepatitis E virus (HEV) IgM and IgG were tested positive, consistent with acute HEV-infection. The first case recovered spontaneously in three months. The second case was treated with ribavirin due to progressive hyperbilirubinemia. His HEV-genotype was 3. Six weeks after ribavirin initiation, liver function rapidly recovered and HEV RNA levels dropped from 153×10^3 to <20 IU/mL.

Discussion: The seroprevalence of HEV is $\pm 27\%$ in the The Netherlands. A Dutch study found that amongst those with hepatitis symptoms, HEV-infection was the most common causative agent, with higher rates than hepatitis A, B, C, CMV and EBV viruses. While HEV-genotypes 1-2 are most prevalent in developing areas, genotypes 3 and 4 are most prevalent in western countries. In a HEV-3 dominant study amongst patients with acute fulminant hepatitis, HEV IgM was only detected in 0.4% of cases, with none being HEV-RNA positive. However, in a HEV-4 dominant study, 6.5% respectively 3.3% of acute fulminant hepatitis cases were tested positive for HEV IgM and HEV-RNA. While not much experience exists with treating acute HEV, all patients with severe acute HEV-infection were successfully treated with ribavirin in a recent study.

Conclusion: HEV is a common cause of acute hepatitis, but a rare cause of fulminant hepatitis.

Clinical practice of hepatitis B screening in patients starting with chemotherapy for haematological and solid tumours: a survey of Dutch haematologists and medical oncologists

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Background: Reactivation of hepatitis B virus (HBVr) during chemotherapy can lead to acute liver failure and delay of treatment. Most international guidelines advice universal screening for HBV before start of chemotherapy for haematological and solid tumours. This survey was performed to evaluate the clinical practice of Dutch haematologists and medical oncologists regarding screening of HBV.

Methods: A digital survey concerning HBV screening procedures was sent to all oncologists and haematologist of three Dutch provinces (North-Holland, South-Holland and Utrecht).

Results: Sixty-six responses were received (27% response rate) of whom 15 (23%) were haematologists, 14 (21%) haemato-oncologists, 32 (48%) oncologists and 5 (8%) residents. Forty-one percent of the specialists have a standard protocol for HBV screening, with a remarkable difference between haematologists (80%) and oncologists (6%). The majority of haematologist/haemato-oncologists (55%) screen all patients, the others screen high-risk patients. By contrast, none of the oncologists perform universal screening but the vast majority screens high-risk patients (84%). Sixteen percent of the oncologists do never screen for HBV. High-risk medication, ethnicity and high-risk behaviour were the most commonly used factors to identify high-risk patients. Eleven (17%) responders witnessed one or more HBVr during chemotherapy.

Conclusion: Universal HBV screening before start of chemotherapy is not common practice for Dutch haematologists and especially medical oncologists. Oncologists usually only screen patients who they consider high-risk patients. However, literature shows that it is difficult to recognize patients at risk for HBV infection. Awareness of best screening practice is necessary to reduce the risk of HBVr during chemotherapy.

A cascade of itraconazole-induced drug-drug interactions leading to a drop in blood pressure and acute kidney injury

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Case: We present a 47-year old man visiting our outpatient clinic for resistant hypertension. Despite treatment with nifedipine, enalapril, amiloride and hydrochlorothiazide his blood pressure remained ~160/100mmHg.

One year after his first visit he presented with dizziness, and malaise. In the preceding week his general practitioner prescribed itraconazole for an alleged fungal infection. His blood pressure was 121/77mmHg.

Laboratory results showed acute kidney injury (AKI) (eGFR 48ml/min) with a normal potassium (4.3mmol/l) and no proteinuria. Renal ultrasound was normal. Serum nifedipine-level was 262.5ug/l three hours after taking his medication (T_{max} 1.6-4.2 hours; therapeutic levels 25-150ug/l).

We subsequently replaced nifedipine by amlodipine and discontinued amiloride. Two months later the blood pressure was 135/85mmHg and the eGFR recovered to baseline (90ml/min). A report to the The Netherlands Pharmacovigilance Centre Lareb was made.

Discussion: Itraconazole inhibits CYP3A4, which metabolises nifedipine, and thereby increases the bioavailability of nifedipine. Despite the broad therapeutic range of nifedipine, this drug-drug interaction led to a toxic nifedipine-level and subsequent abrupt normalisation of blood pressure. Nifedipine-levels in this case were much higher than in earlier literature-reports.

AKI is a novel effect of this interaction. Our hypothesis is that the increased peripheral vasodilation, due to toxic nifedipine-levels, in combination with the use of diuretics (hydrochlorothiazide) enhanced the nephrotoxic effect of ACE-inhibition (enalapril).

This case illustrates that a pharmacokinetic drug-drug interaction of nifedipine and itraconazole can lead to a toxic nifedipine-level with hemodynamic consequences and consequently induces an increased effect of the pharmacodynamic drug-drug interaction between diuretics and ACE-inhibitors, resulting in AKI.

Acute kidney injury (AKI) in patients receiving high-dose flucloxacillin

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Background: Flucloxacillin is indicated in (suspected) *S. Aureus* infections. It is predominantly eliminated renally through tubular secretion and glomerular filtration. Cases of interstitial nephritis are reported, but the incidence, risk factors and nature of acute kidney injury (AKI) following flucloxacillin administration is unknown.

Methods: Patients receiving high-dose flucloxacillin (≥ 6 grams daily for >24 hours) from January 2017 until June 2017 were included. We retrospectively collected data on baseline, clinical and laboratory parameters. Patients with AKI were further analyzed.

Results: 24 of 149 patients (16%) receiving high-dose flucloxacillin developed AKI. Baseline characteristics (gender, age, co-morbidity, and renal function) did not differ between groups. About one-third received coincident nephrotoxic medications (29% received tobramycin, 23% a NSAID, and 32% RAS blockade) without differences between groups. In the AKI group, hypotension was more prevalent (25% vs. 10%) and flucloxacillin concentrations prior to AKI were significantly higher (median, IQR: 58, 40-76 vs. 30, 4-46 mg/l). Based on clinical parameters (clinical course of kidney function, presence of eosinophilia, fractional sodium excretion, urine osmolality), prerenal disease and acute tubulus necrosis (ATN) appeared to be the most common cause for the AKI whereas interstitial nephritis occurred less frequently.

Conclusion: AKI, often due to ATN, is common following high-dose flucloxacillin administration. Beyond prerenal factors such as hypotension or sepsis and other nephrotoxic medication, high levels of flucloxacillin might play a direct role in ATN. Kidney function and flucloxacillin concentrations should be closely monitored in patients receiving high-dose flucloxacillin therapy.

10 years of islet transplantation in The The Netherlands: from type 1 diabetes to chronic pancreatitis

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Pancreatic islet transplantation is performed at the Leiden University Medical Center since 2007. Starting as an experimental procedure, it is now increasingly commonplace. Here we describe the indications, procedure, and outcomes of pancreatic islet transplantation in The The Netherlands.

Methods: Indications for allogeneic islet transplantation included patients with severe beta cell failure, such as type 1 or cystic fibrosis-related diabetes, in combination with severe hypoglycemia-related problems and/or progressive complications. Islet autotransplantation was performed in patients who required pancreatectomy for non-malignant pancreatic disease (i.e. chronic pancreatitis). Islet isolation was performed through combined enzymatic and mechanical digestion of the pancreas, followed by gradient density separation. The final product was tested for function and safety, after which the islets were infused through the portal vein under local anesthesia. Immunosuppression, when indicated, included T-cell depletion, prednisolone, mycophenolate and tacrolimus.

Results: 35 patients (21M/14F, age 51 ± 10.3 years) underwent 55 allogeneic and two autologous islet transplantations. Islet graft function occurred in 34/35 of recipients with 46% of patients becoming insulin independent. Over time islet function declined, with insulin independence in 14% and partial islet function in 89% of patients after 47.9 ± 30.0 months (range 4-123). HbA1c was reduced from 66.8 ± 16.8 to 52.8 ± 16.2 mmol/mol ($p < 0.001$). In addition, patients with severe hypoglycemic events decreased from 39% to 6%.

Conclusion: Pancreatic islet transplantation restores endogenous insulin production in patients with diabetes due to severe beta cell failure or after pancreatectomy, leading to marked improvement in glycemic regulation and hypoglycemic events. Long term insulin independence is achieved only in a minority.

Not so Good

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Case: We present a 72-year-old female known with Barrett's, lichen planus (LP) and a type-AB thymoma. A hypogammaglobulinemia is seen with the thymoma, known as Good Syndrome. After thymoma resection, the hypogammaglobulinemia persisted, as did her anaemia. In the year following she was recurrently admitted to the hospital with dyspnoea, night sweats and peaking fever. Further testing revealed a complete depletion of the B-cells and a non-specific interstitial pneumonia (NSIP). Patient was treated with intravenous immunoglobulin, to which she initially showed a great response with a decrease in symptoms, correction of the anaemia and recovery of the NSIP. Unfortunately, she later developed an aplastic anaemia, multiple thrombosis and pneumocystic jiroveci pneumonia (PJP). She eventually died of an unexplained neurologic catatonic state.

Discussion: Autoimmune disease (AD) is frequently seen in thymoma patients, however only few have Good Syndrome. It is an adult-onset immunodeficiency; with a high mortality of 41%. The occurrence of AD in thymoma patients is high, over half develop AD; most likely due to malfunction of the thymus medullary selection process, causing auto reactive T-cell release. Myasthenia Gravis is the most frequently described. However, other AD such as Hashimoto thyroiditis, Systemic Lupus, LP, aplastic anaemia and Good syndrome have been seen.

Case: In our patient the Good syndrome, aplastic anaemia and LP can be linked to the thymoma, as the NSIP and PJP. A cause for the recurrent thrombosis was not found; testing for paroxysmal nocturnal haemoglobinuria was negative, which has also been described in combination with Good Syndrome.

Legionellosis-associated rhabdomyolysis with acute kidney failure and hypercalcemia

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Case: A 50-year old male presented because of dyspnea and anuria. Laboratory evaluation showed renal failure (creatinine 1755 $\mu\text{mol/L}$), rhabdomyolysis (CK 95581 U/L) and signs of inflammation (CRP 451 mg/L). Chest x-ray revealed spotty consolidations in the left lung and urinary antigen testing turned out positive for *Legionella pneumophila*. Treatment with ciprofloxacin was initiated and the patient required haemodialysis for three days. Because of severe hypocalcemia (1.72 mmol/L), calcium was supplied. He recovered and was discharged after 12 days with a creatinine of 158 $\mu\text{mol/L}$ and normal calcium levels, without the need for additional calcium.

Two weeks after discharge he was re-admitted because of a severe hypercalcemia (3.99 mmol/L). ECG showed a life-threatening short QT-interval (280ms). After excluding the most probable causes, a diagnosis of delayed hypercalcemia during the recovery phase in rhabdomyolysis-induced renal failure was made. The calcium normalized after several days of hyperhydration.

Discussion: *Legionella pneumophila* infection is a recognized but rare cause of rhabdomyolysis. Rhabdomyolysis in itself is frequently complicated by hyperkalemia and hyperphosphatemia, which leads hypocalcaemia due to ectopic calcium phosphate depositon. In the recovery phase, these deposits mobilize and can lead to delayed life threatening hypercalcemia.

Conclusion: Physicians should consider Legionella pneumonia in patients with pneumonia and signs of rhabdomyolysis and renal failure. Early diagnosis and early initiation of treatment with quinolones are associated with improved clinical outcome.

A severe delayed hypercalcemia can complicate the recovery after rhabdomyolysis-induced renal failure. Prolonged monitoring of serum calcium should be performed, even if hypocalcemia was present initially.

Facial paralysis as a first manifestation of ANCA-associated vasculitis

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A 24-year-old woman who underwent a total thyroidectomy due to a papillary carcinoma 6 months earlier, presented to the emergency department with arthralgia in all extremities.

Recently she was treated at the department of ENT because of persistent mastoiditis despite antibiotic therapy. A computed tomography showed mastoid effusion on the left side without involvement of bony structures, a mastoidectomy was performed. Additional physical examination showed facial weakness that was attributed to local infection or damage from the operation.

The patient was admitted to the internal medicine ward for further analysis and treatment of her arthralgia. Laboratory tests showed the presence of PR3-ANCA, indicating small-vessel vasculitis. Urine analysis showed signs of glomerulonephritis with intact eGFR. Additionally a positron emission tomography-computed tomography was performed and showed inflammation of the joints, ENT-area and a severe pulmonary involvement.

Because of the pre-existent facial nerve palsy a more thorough neurological examination was performed after admission. This showed involvement of the facial nerve, hypoglossal nerve and possibly the glossopharyngeal nerve. Magnetic resonance imaging of the brain showed no enhancement of meninges or ischemic changes in brain tissue. A lumbar puncture showed a leukocytosis with normal protein level and glucose. Presumably, involvement of multiple cranial nerves occurred as a consequence of ischemic injury in vasculitis, although pachymeningitis cannot be ruled out.

Patient was treated with seven sessions of plasmapheresis, Prednisolon 60 milligrams and Cyclophosphamide. However, after switch to azathioprine maintenance a relapse, presenting with tracheostenosis, occurred after which treatment with rituximab was initiated.

Measuring actual daily movement in patients with complicated Type 2 Diabetes Mellitus by using accelerometry

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Background: Type 2 Diabetes Mellitus (T2DM) is a lifestyle related disease, and physical activity (PA) is a main target for intervention. Although both insufficient PA and sedentary behaviour are strongly associated with increased cardiovascular risk in T2DM, the information on actual daily PA in patients with (complicated) T2DM is scarce.

Methods: In 98 T2DM patients treated in secondary care, PA was measured during 7 consecutive days with a Fitbit Flex, worn around the wrist. This device records the number of steps per minute, a measure of intensity of movement.

Results: The median age was 69⁶¹⁻⁷³ years, 76% used insulin and 75% had microvascular complications. A large majority of patients (85%) did not meet the goal of ≥ 10.000 steps per day and 44% of the patients fulfilled the criteria for 'limited activity/ sedentary behaviour' (i.e. < 5000 steps per day). There was a significant inverse association between percentages of micro- and macrovascular complications and number of steps per day. Only 5% of patients had ≥ 150 minutes per week of moderate to vigorous PA. Of the total waking hours per day, 76% (11h 41m) were spent at 0 steps per minute of which 7 hours were spent in prolonged sedentary bouts of at least 30 consecutive minutes.

Conclusion: The large majority of T2DM patients treated in secondary care are sedentary and do not adhere to the recommended levels of PA. Implementation of routine measurements should be considered as a starting point to improve lifestyle.

Prevention of infections in immune compromised patients; a mixed-method study evaluating healthcare professionals' opinions and practices

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Background: Immune compromised patients (ICP) form a growing group in healthcare. Studies showed that impaired awareness of patients and healthcare professionals (HCP) about infection prevention poses risks to ICP. No universal vaccination guidelines for ICP are currently available.

Methods: We performed a mixed-method study to evaluate daily practice and attitude of HCP to prevent infections in ICP. Twelve senior workers and two patients were interviewed. Data was framed to a questionnaire and distributed to HCP. 689 HCP (43%) responded, 269 HCP treated at least two ICP per week and were eligible for analysis.

Results: Half of the HCP state that the indication for vaccination is insufficiently addressed in current guidelines. Reimbursement is a barrier to vaccinate. 60% of the patients are considered as mild-moderately ICP during first visit. Influenza vaccine is addressed in 47%, while live-attenuated vaccinations only in 10%. HCP score their own knowledge a 7 (scale 1-10) and knowledge of their patients a 5. Nurses discuss travel plans more often than physicians. 53% of ICP that travel are referred to a specialized travel clinic, 39% are educated by their HCP. To decrease the number of infections, according to HCP one should vaccinate (13%), take extra in-hospital measures (16%) and/or educate ICP (40%).

Conclusion: There is an unmet need on clarity about vaccinations in guidelines for ICP. One should extend efforts to second line care since the majority is already an ICP at first visit. Knowledge and policy should be improved by education of both HCP and patients.

Anti-inflammatory dietary recommendations based on the relation between food and the gut microbiome composition in 1424 individuals

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Background: The gut microbiome plays an essential role in maintaining intestinal health. As microbes thrive on nutrients, the question arises whether we can nourish a protective, anti-inflammatory gut flora. In this study, we investigated the effect of 176 dietary factors on the gut microbiome of 1424 individuals across four cohorts comprising the general population, and patients with Crohn's disease, ulcerative colitis, and irritable bowel syndrome.

Methods: For every participant one stool sample was collected. Dietary intake data was derived from Food Frequency Questionnaires filled out on the day of faecal sampling. To reconstruct taxonomic and functional structure of the stool samples, shotgun metagenomic sequencing was performed. Cluster analyses were conducted to identify which dietary patterns were associated with microbial taxa and pathways. In addition, association analyses of individual food categories with individual microbial species and pathways were performed. Analyses were conducted separately for each cohort, followed by a weighted meta-analysis.

Results: We identified 74 food items associated with 98 taxa and 194 pathways (FDR<5%). Overall, the consumption of a plant-based diet was associated with an increase in short chain fatty acid (SCFA) producing bacteria. A pattern comprising plant proteins, vegetables, fruits, muesli, nuts, and fish was associated with increased *Roseburia hominis* and *Faecalibacterium prausnitzii* abundance, and increased levels of bacterial carbohydrate fermenting pathways.

Conclusion: We show that specific food groups are associated with the abundance of gut bacteria capable of increasing SCFAs that have anti-inflammatory effects, inferring that certain foods can exert mucosal protection by inducing gut bacteria.

Hepatitis E in the immunocompromised patient

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Introduction: Hepatitis E virus is increasingly being recognized as a risk factor for the development of acute and chronic liver failure. Delay in diagnosis can be fatal and timely recognition can save lives and prevent unwarranted complications.

Cases: A 64 year old patient known with Granulomatosis with polyangiitis (GPA) who was been treated with rituximab developed elevated liver enzymes. Diagnostic work-up for hepatitis showed negative viral serology including that for hepatitis E. He recovered spontaneously and a drug induced liver injury was suspected. Two years later he developed rapidly progressive cirrhosis. PCR for hepatitis E was high and this was in retrospect also positive at the initial presentation. The patient died of cirrhosis related complications few months after the diagnosis.

The second case involved a 32 year old patient who was been treated with mycofenolaat mofetil for limited GPA. She developed fulminant hepatitis with rapidly progressive liver failure. PCR for the hepatitis virus showed a high viral titer. Immunosuppression was stopped and she was treated with ribavirin and vitamin K and fully recovered.

Conclusion: In the immunocompromised patient, elevation of liver enzymes should always lead to thorough evaluation for hepatitis, including hepatitis E. Negative serology does not exclude an active hepatitis E-virus infection and PCR should be performed even in the absence of IgM and IgG. If untreated, acute hepatitis E can lead to rapidly progressive liver failure. Immunosuppression can lead to chronic hepatitis E infection and this can in turn lead to rapidly onset liver cirrhosis.

Glycemic control in women with gestational diabetes: how does it affect the perinatal outcomes?

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Background: There is inconclusive evidence to support any specific glycemic treatment targets in gestational diabetes. At OLVG insulin therapy is initiated if repeated fasting glucose values are ≥ 5.3 mmol/L and/or repeated 1.5 hour postprandial values are ≥ 7.0 mmol/L. This study aimed to objectify the association between these glycemic treatment targets and adverse perinatal outcomes.

Methods: This was a retrospective cohort study of 406 singleton pregnancies complicated by gestational diabetes. Outcomes include perinatal complications (large for gestational age, macrosomia, small for gestational age, shoulder dystocia, neonatal hypoglycemia and hyperbilirubinemia). Women and neonates with perinatal complications were compared to those without. Multivariate logistic regression analysis, stratified by confounders and effectmodifiers, was used.

Results: The risk of perinatal complications were increased for those with a fasting glucose value ≥ 5.3 mmol/L at 32 weeks of gestation (adjusted OR 2.0, 95% CI 1.02 – 4.11) and for those with 1.5 hour postprandial glucose values ≥ 7.0 mmol/L at 32 and 36 weeks (adjusted OR 2.73, 95% CI 1.36 – 5.50 and adjusted OR 2.16, 95% CI 1.06 – 4.41). Of 406 pregnancies complicated by gestational diabetes, 137 (33.7%) neonates had perinatal complications.

Conclusion: A fasting glucose value ≥ 5.3 mmol/L at 32 weeks and 1.5 hour postprandial glucose value ≥ 7.0 mmol/L at 32 and 36 weeks is significantly associated with perinatal complications. This could imply that treatment of these women should be tightened.

Hair cortisol analysis reveals a retrospective diagnosis of Cushing's disease in a patient with apoplexy of a pituitary adenoma

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A 31-year old woman was referred to our outpatient clinic after a recent diagnosis of apoplexy of a pituitary macroadenoma not previously identified. Her medical history reported morbid obesity, type 2 diabetes, and hypertension. Physical examination showed a phenotype typically suggesting Cushing's syndrome: moon face, acne, facial hirsutism, central obesity, quadriceps atrophy. Laboratory testing, however, showed panhypopituitarism: cortisol 9.00am <28nmol/L (240-700nmol/L), TSH 3.3mE/L (0.4-4.0mE/L), FT4 6pmol/L (10-22pmol/L), LH 2E/L, FSH 4E/L, estradiol <44pmol/L. We performed hair cortisol analysis, as a measure of long-term cortisol levels, which showed a cyclic though persistently elevated cortisol level of 25.0pg/mg on average (healthy controls 0.7-10.5pg/mg) over the last two years. These results are compatible with the diagnosis of Cushing's disease cured by pituitary apoplexy. Pituitary apoplexy is a well-known but infrequent clinical syndrome, in the majority of cases seen as first presenting symptom of a pituitary adenoma. Apoplexy in ACTH-secreting adenomas is exceedingly rare, accounting for <5% of apoplexy cases. Hemorrhage and/or infarction in apoplexy frequently causes loss of function of a ACTH producing adenoma. In case of apoplexy as a presenting sign of a pituitary adenoma, resolution of clinical signs of Cushing's disease confirms the retrospective diagnosis of an ACTH-producing adenoma. However, hair cortisol analysis can confirm previous hypercortisolism directly after apoplexy, thereby enabling adequate anticipation on remission of Cushing's disease.

Conclusion: we report a patient presenting with panhypopituitarism following pituitary apoplexy. A history of morbid obesity, hypertension, and specific Cushingoid features suggested Cushing's disease, which was retrospectively confirmed by hair cortisol analysis.

Reversible acute kidney failure induced by liraglutide

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A 57-year-old woman, with a history of type 2 diabetes mellitus, was admitted because of acute kidney failure (creatinine 951 $\mu\text{mol/L}$), lactate acidosis (lactate 9.7 mmol/L , pH 7.20) and severe hypoglycemia (glucose 0.8 mmol/L).

Physical examination showed a blood pressure of 165/75 mmHg and no signs of dehydration. Ultrasonography showed no post-renal obstruction. Since the ratio of alfa-1-microglobulin/creatinine in the urine was elevated, we considered acute interstitial nephritis the most likely cause of acute kidney failure.

Her diabetes, due to morbid obesity (BMI 56 kg/m^2), was treated with metformin and insulin. Before admission, insulin NPH was replaced by insulin degludec/liraglutide combination during ten days. Six days before admission insulin degludec/liraglutide was stopped because of abdominal complaints. In the hospital, she was treated with continuous hemodialysis during two days. Her kidney function recovered completely within seven weeks after cessation of liraglutide. Therefore, we attributed the acute kidney failure to the liraglutide use, as this was the only newly prescribed drug and we found no other causes of reversible acute kidney failure.

This is the first case report on acute kidney failure due to the side-effect of an insulin/GLP-1-agonist combination drug. Moreover, this side-effect is not mentioned in the medication leaflet. Other GLP-1-agonists, such as exenatide, have also been reported to cause kidney failure. Since acute kidney failure, for which dialysis is needed, is a severe adverse event, physicians prescribing GLP-1-agonists should be aware of this side-effect.

A case of thyroid storm with ventricle fibrillation after discontinuation of block and replace therapy in Graves' disease

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Case: A 53-year old male with a history of Graves' disease was brought into our Emergency Department (ED) after a witnessed out-of-hospital cardiac arrest. After resuscitation and two defibrillations, he had return of circulation and was awake and speaking upon arrival. Primary assessment showed a persistent sinus tachycardia of 140 bpm without signs of acute myocardial ischemia. We learned that the patient had discontinued thiamazol and levothyroxine three weeks earlier in preparation of radioactive iodide therapy. We restarted thiamazol with addition of propranolol. Shortly after, he went through eight sequences of ventricle fibrillation and was defibrillated promptly. We diagnosed him with thyroid storm, for which he was sedated, intubated and treated with propylthiouracil, propranolol, hydrocortisone, and potassium iodide. The patient made a quick recovery and was detubated after two days with a sinus rhythm of 93 bpm. We performed a thyroidectomy on day ten, which was complicated by bilateral recurrent laryngeal nerve damage, aspiration pneumonia and hypocalcaemia.

Conclusion: Thyroid storm is a rare complication of thyrotoxicosis with high mortality rates. Atrial arrhythmias are common, but only a handful cases of ventricular arrhythmias are known. Fast rising T₃ levels in Graves' disease are suggested to contribute to a complicated clinical course, but overall T₄ or T₃ levels are not associated. Diagnosing thyroid storm is essential, as it implies aggressive treatment and monitoring. This case illustrates the potential risk of discontinuation of block and replace therapy and the challenges in decision making. A multidisciplinary approach to these patients is advised.

Transient thyroiditis after parathyroidectomy for tertiary hyperparathyroidism

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Case: A 32-year-old male was hospitalized for parathyroidectomy because of tertiary hyperparathyroidism due to chronic renal failure. He had no personal or family history of thyroid disease. During thorough surgical neck exploration and palpation of areas around the thyroid gland, three parathyroid glands were successfully removed. The fourth gland was not detected.

The second post-operative day the patient developed tachycardia (108 beats/min). Physical examination demonstrated a restless patient. Exploratory blood tests only showed a C-reactive protein of 147 mg/l (n=<10 mg/l). One day later, additional blood analysis showed disturbed thyroid function (TSH:0.03 mU/l, n=0.3-4.2 mU/l, FT4:64.3 pmol/l, n=12-24 mU/l). Iodide-123 uptake scan showed a remarkable low uptake (6-hours:0.7%, 24-hours:1.2%), suggestive for thyroiditis. The patient was symptomatically treated with metoprolol. Within six weeks thyroid function normalized and remained normal during two years of follow up.

Discussion: The described patient unexpectedly developed thyrotoxicosis. The thyroid scan was compatible with thyroiditis. An infectious or auto-immune origin seemed unlikely. As previously described, thorough palpation and traction of the thyroid gland may cause follicular damage with release of preformed hormone, resulting in transient thyrotoxicosis. The incidence varies from 20-30% in patients after surgery for primary hyperparathyroidism and is dependent on the degree of exploration, variation in size/shape of thyroid and amount of intraoperative trauma.

Symptoms are mostly mild or absent, spontaneous resolution occurs in the majority of patients within six weeks. In patients with suggestive symptoms after parathyroidectomy, postoperative thyrotoxicosis should be considered and thyroid function tests are recommended. Treatment should be symptomatic with β -blockers.

Hyperthyroidism in a patient with testicular germ cell tumor

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Case: A 36-year old man, with a history of infertility, visited the general practitioner because of weight loss and palpitations. Laboratory tests showed a plasma level of thyroid-stimulating hormone (TSH) of 0.01 mU/l (n=0.3-4.2 mU/l) and free thyroxine (FT₄) 36 pmol/l (n=12-22 pmol/l). Thyroid scintigraphy showed a homogeneously increased activity of the thyroid gland, so a diagnosis of Graves' disease was made. Thyreostatic treatment was started.

Three days before the scintigraphy, he was operated upon by the urologist for a painful testicle. A poor risk nonseminoma testis was diagnosed (choriocarcinoma) with pulmonary and abdominal metastases demonstrated by CT scan. Laboratory tests showed α_1 -foetoproteine 3.6 μ g/l (n < 20 μ g/l), LD 683 U/l (n < 250 U/l) and β -HCG 5.100.000 U/l (n < 2U/l).

Additional tests showed TSH-R antibodies 0.25 U/l (n < 0.4U/l), not corroborating the diagnosis of Graves' disease. Thiamazole was discontinued. We postulated the high serum levels of β -HCG as the cause for the hyperthyroidism. This was confirmed by the decrease in serum levels of β -HCG and the normalization of thyroid function after starting chemotherapy. One month after treatment the serum β -HCG had dropped to 119.295 U/l and thyroid function was normalized. The patient also reattained hyperthyroidism when his β -HCG rose to >1 million U/l at recurrence. At retreatment again normalization of thyroid function occurred.

Conclusion: Human chorionic gonadotropin is family of glycoprotein hormones, including TSH. There is a similarity between the β -subunits of HCG and TSH. As a result, β -HCG has weak thyroid-stimulating activity and can cause hyperthyroidism.

Raynaud phenomenon caused by cold agglutinin disease with very low antibody titers: a cold case is best solved in winter time

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Case: A 64-year-old man without a mentionable medical history was referred to our tertiary center for treatment resistant Raynaud's phenomena. Previous evaluation had shown no secondary causes. At evaluation in our hospital in the winter season, apparent hemolysis (Hb 7.5 mmol/l, haptoglobin <0.2) was present, yielding the clinical suspicion of cold agglutinin disease (CAD). Remarkably, direct antiglobulin test showed auto-I antibodies at very low titers (C3d: 1:16) and IgM cryoglobulin was only weakly positive, which would generally not be considered to cause CAD *in vivo*. Therefore, we decided to confirm CAD *in vivo* by a cooling challenge of his hand. Plethysmography confirmed a Raynaud's attack at 25°C and capillary blood showed a normal blood smear before, but clear hemagglutination after cooling. Patient confirmed that his Raynaud's attacks were indeed always followed by nausea and hematuria. Although Hb levels had consistently been normal in the preceding five years, blood had never been drawn in winter time. In bone marrow aspirates, a small monoclonal B-cell and plasma cell population was found, which carried MYD88 mutation, suggestive of an underlying lymphoproliferative disease. Upon these findings, treatment with Rituximab was started which subsequently led to symptom reduction.

This case demonstrates that very low titers of cold-induced monoclonal IgM antibodies are not always harmless and may indeed lead to a clear case of CAD. We emphasize that when the clinical suspicion is high and laboratory tests are inconclusive, a cold provocation test may help to confirm this treatable and potentially serious cause of Raynaud's disease.

Pylephlebitis (abdominal Lemierre's syndrome) as complication of diverticulitis, a rare but clinically relevant finding

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Case: A 61-year old Caucasian male, with a medical history of testicular cancer 30 years ago, visited the emergency department with a 3 week lasting fever, abdominal pain, loss of appetite and nausea. Before presentation he was treated with 3 courses of antibiotics without improvement.

On presentation he was febrile with a tachycardia with normal blood pressure. The left abdominal region was tender on palpation. Laboratory tests showed a CRP of 109 mg/l (<5) without leukocytosis and normal kidney and liver function. Urine analysis showed a positive nitrite test and > 400 leucocytes/uL. Our differential diagnosis was pyelonephritis or diverticulitis with abscess. A computed tomographic scan showed sigmoid diverticulitis with extensive thrombosis of the mesenteric veins with intra- and extraluminal gas extending up to the portal confluence with non-occlusive portal vein thrombosis. These findings were consistent with pylephlebitis; an infectious suppurative thrombosis of the portal vein associated with abdominal infection, in this case diverticulitis.

Our patient was treated with broad spectrum antibiotics and low molecular weight heparin. Blood cultures showed *Bacteroides fragilis*, the most common pathogen of pylephlebitis. The clinical course was uneventful and he was discharged with oral anticoagulants.

Conclusion: Pylephlebitis is a rare complication of diverticulitis with high mortality and is comparable with Lemierre's syndrome associated with infections of the head and neck region. Pylephlebitis requires timely treatment with broad spectrum antibiotics to prevent embolic abscess formation in distant organs, such as the liver. The use of anticoagulation is controversial but early start is reported to be beneficial.

The use of ^{18}F Fluorocholine PET-CT in Primary Hyperparathyroidism

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Background: Preoperative localization of hyperfunctioning parathyroid tissue in primary hyperparathyroidism is necessary for minimal invasive surgery, which is preferential to cervical exploration. Conventional imaging techniques, ultrasound and Tc99m-sestamibi (MIBI) scans, have a sensitivity between 60-80%. Recent literature shows promising results for ^{18}F Fluorocholine PET-CT (FCH PET-CT) in detection of hyperfunctioning parathyroid tissue in inconclusive or negative conventional imaging.

Methods: Patients from four centers with biochemical primary hyperparathyroidism who underwent a FCH PET-CT in our facility were analyzed retrospectively. Our facility for nuclear medicine has a regional function in performing PET-CT. FCH PET-CTs were interpreted by different nuclear medicine physicians and binomially scored as positive or negative, and retrospectively correlated with histological outcome. The number of lesions and the locations were reported. Surgery was performed based on expert opinion of a multidisciplinary team. Results were compared to other imaging modalities, surgical and pathological findings and biochemical follow-up.

Results: 24 patients were studied, disclosing 28 lesions. Mean calcium and PTH levels were 2.86mmol/l (± 0.17) and 18.2pmol/l (± 10.7). Histology showed adenoma and/or hyperplasia in 24 cases, no parathyroid tissue was identified in four cases. Per lesion the FCH PET-CT outcome was scored based on histology as true positive, false positive or false negative. 67.9% of the FCH PET-CT positive lesions were true positive, 10.7% false positive and 21.4% false negative, respectively.

Conclusion: FCH PET-CT contributes in identifying adenomas or hyperplasia in about two-thirds of the cases with biochemical hyperparathyroidism and negative conventional imaging.

Reduction of unnecessary laboratory testing in a general internal ward using six simple clinical rules

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Background: Laboratory testing has been over-utilized for years with a huge number of unnecessary lab tests being done in clinical internal wards. The elimination of unnecessary laboratory testing is becoming more and more important in the control and management of the rapid growth of healthcare costs.

Therefore, we investigated the number of laboratory testing and defined simple clinical rules in order to reduce laboratory measurements without compromising the quality of care.

Methods: Prospective observational study including adult patients (>18 years) in a general internal ward of the Jeroen Bosch Hospital in 's-Hertogenbosch. Primary goal of the study was 10% reduction in laboratory testing by using six simple clinical rules (i.e. day after admission no lab (unless), no more than 2 blood collections per week (unless), no C-reactive protein measurement after initial decrease, no measurement of urea, sodium/potassium when creatinin is ordered, no daily kidney function in case of renal failure).

Results: From January 2015 until April 2015 one hundred twenty-eight (n=128) patients were included in this observational study. In these patients 784 blood collections were observed.

Furthermore, 3109 laboratory tests were ordered.

After implementing six simple clinical rules, one year later we again measured the number of blood collections and ordered laboratory tests (January 2016 until April 2016). In 122 consecutive patients, on average 31% reduction of blood collections was observed. Lastly, there was a 22% reduction in laboratory tests ordered.

Conclusion: Using six simple clinical rules lead to a significant reduction in laboratory testing without compromising patient care.

An underdiagnosed complication of treatment with metformin for diabetes mellitus

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Case: A 73 year old patient with a cardiac history and diabetes mellitus type 2, treated with metformin for over 8 years, was seen at our hospital with a symptomatic megaloblastic anemia with hemolysis (hemoglobin 5.1 mmol/L, mean corpuscular volume 115 fL, reticulocytes 22 x10⁹, haptoglobin undetectable low, LD 1069 and an undetectable vitamin B12-level). I.m. vitamin B12 supplementation was started after which the reticulocytes and later the hemoglobin-level were rising. One week later oral folic acid was added. One month later, laboratory investigation showed a normal hemoglobin and no signs of hemolysis. Since parietal cell and intrinsic factor antibodies were negative, vitamin B12 was switched to oral supplementation and calcium supplementation was added.

Discussion: Many studies have linked long term metformin use with vitamin B12 deficiency and therefore (megaloblastic) anemia and peripheral neuropathy. This deficiency tends to be associated with dosage and duration of metformin use. Approximately 10% (up to 30%) of patients taking metformin have signs of a reduced vitamin B12 absorption, but literature shows few described cases of megaloblastic anemia due to metformin-associated vitamin B12-deficiency, with suggest this deficiency is underdiagnosed. The exact mechanism of which metformin leads to low vitamin B12 levels is unclear. Knowing that ileal vitamin B12 absorption is a calcium-dependent process and that metformin has an effect on calcium-dependent membrane action, one study showed that the malabsorption of vitamin B12 induced by metformin can be reversed with increased intake of calcium.

Patients' experiences with discussing do-not-resuscitate preferences

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Background: The present debate on asking patients in advance about their do-not-resuscitate (DNR) preferences is gaining further relevance with a patient population that is more severely ill and lives longer than ever before. However, data on patients' experiences with advance DNR decision-making in a Dutch hospital setting are limited.

Methods: During two different days, we interviewed all hospitalized patients in the general internal medicine units in the Amphia Hospital, Breda, The Netherlands. We asked 6 questions to investigate how often DNR preferences were discussed by a medical doctor at admission in the emergency department, and furthermore the feelings and beliefs of patients about this question.

Results: In total 63 patients participated in the study with a median age of 73 years (range 18- 95) and 48% males. Forty-one percent had a DNR status. Less than 8% of patients (n=5) experienced talking about DNR preferences in the emergency department as unpleasant (18-65 years: 13%; >65 years old 5%). The majority (n=54; 86%) of patients felt that DNR preferences should be discussed in advance (18-65 years: 79%; >65 years old 90%). Furthermore, 59% (n=37) has thought about their DNR preferences even before admission to the hospital (18-65 years: 50%; >65 years old 64%).

Conclusion: This study shows that the majority of patients have a positive attitude towards discussing DNR preferences in advance. Discussing DNR preferences at admission at the emergency department provides a possibility to respect the wishes of patients and can therefore be part of good medical practice.

A young woman with hypomagnesaemia, hepatitis and abnormal kidneys

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Case: A 20-year-old female with no medical history, presented with fever, cough and muscle cramps. She denied use of medication or drugs. Physical examination was unremarkable. Laboratory tests showed hypomagnesaemia (0.31 mmol/l), hypokalemia (2.6 mmol/l) and elevated liver enzymes (gGT 231, AF 184, ASAT 17, ALAT 14 U/l, bilirubin 32 umol/l). There was urinary loss of magnesium (fractional excretion 17%) and potassium (31 mmol/L). The initial diagnostic work-up focused on the combination of liver enzyme abnormalities and fever. Hypomagnesaemia and hypokalemia were thought to be due to Gitelman's syndrome. Infectious hepatitis, autoimmune hepatitis and storage diseases were ruled out. A PET-CT showed hypodense abnormalities and small cysts in both kidneys. A renal biopsy was normal. The fever and cough disappeared spontaneously and were ascribed to a transient viral infection. Based on the combination of hypomagnesaemia, raised liver enzymes and abnormal kidneys, a genetic analysis for mutations in the hepatocyte nuclear factor-1 β (*HNF1 β*) gene was performed. A heterozygous pathogenic mutation was found. *HNF1 β* encodes for a transcription factor, which regulates many target genes. More than 50 different *HNF1 β* mutations have been reported. It is an autosomal dominant multisystem disease involving the kidneys, urogenital tract, pancreas, liver, brain, and parathyroid gland. Even within families, expression of the phenotype varies considerably. This is probably attributable to the functional promiscuity of *HNF1 β* .

Conclusion: Unexplained hypomagnesaemia due to renal loss of magnesium, in particular when combined with renal abnormalities should prompt the physician to consider genetic disease due to a mutation in *HNF1 β* .

Variation in treatment and survival of older patients with non-metastatic breast cancer in five European countries

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Background: Older patients are poorly represented in breast cancer research. We compared treatment strategies and survival outcomes between European countries and assessed whether variance in treatment patterns may be associated with variation in survival.

Methods: Population-based study including patients aged ≥ 70 with non-metastatic breast cancer from cancer registries from the The Netherlands, Belgium, Ireland, England and Greater Poland. Proportions of local and systemic treatments, five-year relative survival and relative excess risks (RER) between countries were calculated.

Results: 236,015 patients were included. The proportion of stage I breast cancer receiving endocrine therapy ranged from 19.6% (The Netherlands) to 84.6% (Belgium). The proportion of stage III breast cancer receiving no breast surgery varied between 22.0% (Belgium) and 50.8% (Ireland). For stage I breast cancer, relative survival was lower in England compared to Belgium (RER 2.96, 95%CI 1.30-6.72, $P < .001$). For stage III breast cancer, England, Ireland and Greater Poland showed significantly worse relative survival compared to Belgium.

Discussion: There is substantial variation in treatment strategies and survival outcomes in elderly with breast cancer in Europe. For early stage breast cancer, we observed large variation in endocrine therapy but no variation in relative survival, suggesting potential overtreatment. For advanced breast cancer, we observed higher survival in countries with lower proportions of omission of surgery, suggesting potential undertreatment.

Hypereosinophilia caused by paraneoplastic GM-CSF production in large cell carcinoma of the lung

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Case: A 61-year-old woman, with a history of a thymoma, was referred because of a microcytic anaemia (haemoglobin 6.9 mmol/L) without any symptoms. Additional laboratory tests showed a remarkable leucocytosis and eosinophilia of 20.3 and $5.5 \times 10^9/L$, respectively. A bone marrow biopsy showed marked hypereosinophilia, however no evidence for clonal aberrations (BCR-ABL, FIP1L1-PDGFRa, JAK2) was found. A CT-chest/abdomen, which is part of the analysis of hypereosinophilia, revealed enlarged mediastinal lymph nodes and a pulmonary mass suspected for lung carcinoma. Three weeks after the first presentation she was admitted for further investigation. Laboratory investigation showed progressive eosinophilia of $27 \times 10^9/L$. Prednisolone was started with no effect (after 4 weeks eosinophils increased to $57 /L$). A histologic biopsy of a supraclavicular node revealed the diagnosis of metastatic large cell carcinoma of the lung.

To explain the observed hypereosinophilia, an immunological work-up was initiated which showed high serum GM-CSF levels (227 pg/ml). This supported our hypothesis that the lung tumor cells produce GM-CSF which led to the hypereosinophilia. Because of poor performance status the patient was not eligible for chemotherapy or immunotherapy.

Discussion: Paraneoplastic GM-CSF production of lung carcinoma is rare and has been described in very few case reports before. Paraneoplastic leucocytosis with high G-CSF levels is seen more frequently in lung carcinoma and is associated with poor prognosis.

Clinical relevance: In the evaluation of hypereosinophilia paraneoplastic GM-CSF production should be considered. Therefore a CT-chest/abdomen should be part of the work-up of hypereosinophilia.

Increased overall survival after introduction of structured bedside consultation in *Staphylococcus aureus* bacteraemia

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Background: *Staphylococcus aureus* bacteraemia (SAB) is a common and severe disease. In 2012 a structured bedside consultation (SBC) was introduced at Rijnstate Hospital. We analysed the effect of this SBC on the overall survival of patients with a SAB.

Methods: We performed a retrospective cohort study, including all patients over 18 years with a SAB from 2009 until 2017. The cases preceding versus after implementation of SBC in 2012 were compared.

Results: In total 613 episodes of SAB were analysed, 234 cases before and 379 cases since SBC. In 484 patients at risk for a complicated course, there was no significant difference in the 30day-mortality (23.3% versus 18.4%, $p=0.18$), however an increase in 365day-survival was seen (55.2% versus 64.8%, $p=0.04$). Overall, more patients received adequate therapy, both in the first two weeks (67.8% versus 86.7%, $p<0.001$), as in a complicated SAB (70.5% versus 93.2%, $p<0.001$). In 21% of patients with TEE following a negative by TEE following a negative or inconclusive TTE an endocarditis was diagnosed. In 65% the metastatic infection seen on the PET-scan was a new diagnostic finding.

Conclusion: Structured bedside consultation is highly beneficial for the overall survival in at risk patients with a SAB. Moreover, the additional value of TEE and the PET-scan was shown. We strongly advise compliance to SBC in all patients with SAB and the use of both TEE and PET-scans in these patients.

Cool

An uncommon but severe cause of bilateral pneumonia. Honey, are the kids all right?

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Case A 32-year old Ethiopian man with a history of smoking marijuana was presented at our Emergency Department with fever, hemoptysis and dyspnea since 4 days. Physical examination showed tachypnea, high fever (39.8°C) and generalized papulovesicular skin lesions on head, torso and extremities. Laboratory studies demonstrated inflammation, thrombocytopenia, hyponatremia, acute renal failure, elevated LDH, CK and liver enzymes. Rapid HIV testing was negative. Urine testing demonstrated proteinuria, erythrocyturia and low urine sodium. Arterial blood gas showed hypoxia, elevated lactate and normal anion gap metabolic acidosis with respiratory alkalosis. Chest radiograph demonstrated bilateral diffuse spotty nodular interstitial lesions. Treatment with intravenous fluids, antibiotics (ceftriaxone; ciprofloxacin), glucocorticoids and antiviral therapy (acyclovir) was initiated. Patient was admitted to the Intensive Care where intubation and invasive ventilation were needed for 4 days. Additional information revealed that his child had chickenpox a few weeks earlier. The diagnosis varicella zoster pneumonia was made with positive IgM and positive PCR for varicella zoster virus in sputum and skin lesions. Additional testing for autoimmune disorders, bacterial superinfections and tuberculosis was negative. Treatment with antiviral therapy was continued for 14 days. At follow up 2 weeks after discharge his clinical condition was improved and chest radiograph was normalized.

Discussion: In immunocompetent adults chickenpox may be accompanied by pneumonia with overall mortality between 10 and 30 percent, increasing to 50 percent when respiratory failure is present. Risk factors include male sex and cigarette smoking.

Conclusion: This case demonstrates that pneumonia is a severe complication of varicella zoster infection in adults.

Preventive measures of high-altitude illness at the Annapurna circuit: an observational study among mountainbikers in Nepal

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Background: With every ascending meter travelling through mountainous terrain, the risk of high-altitude illness (HAI) increases. Risk factors for HAI are rapid ascent, younger age and vigorous exercise. The use of preventive and therapeutic measures is important in managing HAI. We performed an observational study on risk factors for, and effects of preventive measures on HAI.

Methods: We included participants of a mountainbiking expedition at the Annapurna circuit in Nepal. Participants reached a maximum altitude of 5417 meters in 4 stages. Before each stage pulse, blood pressure and oxygen saturation were measured. Participants completed a questionnaire on acute mountain sickness (AMS).

Results: We included 21 participants (91.5% male) with a median age of 38.9 years. Their mean preceding annual training distance was 4.190 km. During ascent, oxygen saturation decreased with increasing altitude (average 97.5% at 790 meter to 82.7% at 4450 meter) while average AMS-score, pulse frequency and systolic blood pressure increased (average score of 0.6 to 3.8, 68 to 72 strokes per minute and 133mmHg to 140mmHg respectively). There were two incident cases of HAI (one AMS and one pulmonary edema). The average AMS-score during ascent was lower (0.6 vs. 2.0) and oxygen saturation levels were higher in altitude-acclimatized participants (95.9% to 90.9%). Preventive acetazolamide users had similar trends.

Conclusion: Rapid ascent to high-altitudes imposes a serious risk of HAI. Acetazolamide might have some favorable effects on oxygenation and symptoms in high altitudes, but altitude training and acclimatization appear to be the best preventive measures.

Identification of vulnerable older patients in the Emergency Department: how about the gut feeling?

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Background: Older patients have an increased risk for adverse health outcomes during and after hospitalisation. Timely identification, preferably in the Emergency Department (ED), followed by patient-tailored interventions decreases this risk. A comprehensive geriatric assessment (CGA) to identify these patients in the ED is not feasible, but the clinical judgment of physicians and nurses might serve as a quick impression of vulnerability and as a first step of a CGA.

Methods: A two-week prospective pilot study was conducted. All consecutive patients aged ≥ 70 years presenting in the ED between 9AM-10PM were eligible. Patients were assessed for vulnerability with the Safety Management System (Dutch: VMS-score) for vulnerable elderly, a risk assessment tool to identify older patients at risk for functional decline. Clinical impression was recorded using a single question ('Do you consider this older patient to be vulnerable?'), appraised by the attending physician and nurse in the ED. Sensitivity and specificity were calculated for both clinical impressions compared to the VMS-score.

Results: Of 130 enrolled patients, with a median age of 77.0 (IQR 72.8-82.0) years, 59 were vulnerable according to the VMS-score. The physician's clinical impression of vulnerability was 91.5% sensitive and 39.4% specific. The clinical impression of the nurse had a sensitivity of 86.4% and a specificity of 45.1%.

Conclusion: The clinical impression of vulnerability is a simple question which can be useful as a first step in the identification of vulnerable older ED patients, although both physicians and nurses tend to overestimate the presence of vulnerability.

Stiff as a board

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Case: A 85-year old woman was referred to the emergency department with dyspnoea, difficulty swallowing and severe neck pain. She had a history of M. Alzheimer and hypertension. Physical examination showed signs of respiratory insufficiency, trismus and severe hypertonia of the neck musculature (opisthotonus). Further neurological examination was normal and blood results showed a C-reactive protein of 159 mg/L and white blood cell count $16.8 \times 10^9/L$.

Seven days prior to admission, the patient was diagnosed with a traumatic fracture of metacarpal V of the right hand after a fall. Besides surgical treatment she received an injection with tetanus toxoid. Nonetheless with this admission tetanus was expected and with signs of respiratory insufficiency she was admitted to the ICU.

The (ICU) treatment consisted of 5 pillars: 1. Effective surgical wound management in combination with metronidazole, 2. Neutralising the Clostridium toxin with immunoglobulin (human tetanus immunoglobulins (3000 IU) intramuscular for two days), 3. Suppression of muscle cramps with benzodiazepines, 4. Treatment of sympathetic hyperactivity with labetalol and 5. supportive ICU care with early tracheostomy. After 3 weeks the severity of muscle spasms had diminished substantially and she was weaned from mechanical ventilation. After 6 weeks in our ICU she was transferred to the ward for further revalidation, another 10 days later she left the hospital.

Because tetanus does not confer immunity after recovery, she also received active immunisation.

Conclusion: Although tetanus has become a forgotten disease in developed countries, tetanus still exists. With early diagnosis and aggressive treatment the prognosis increases.

Salbutamol as a cause for lactic acidosis

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Case: A 23 year old female with a history of hyperventilation, a borderline disorder, and possibly asthma, visited the emergency department because of a collapse after inhalation of salbutamol, a selective β_2 -agonist. She complained of dyspnea and she felt not well at all. Physical examination showed tachypnea and no other abnormalities. Laboratory evaluation showed not a respiratory acid-base disorder, but a metabolic acidosis (pH: 7.31, pCO₂: 3,6 kPa, base excess: -11.1 mmol/l, anion gap: 23) and a very high lactate level of 12.4 mol/l (ref. <1.6 mol/l). There were no signs of shock, tissue ischemia, or liver dysfunction. 2 hours later, the acidosis was spontaneously resolved (pH: 7.44, lactate: 1.1 mol/l) and there was no longer hyperventilation. Lactic acidosis was probably caused by salbutamol toxicity. Salbutamol treatment was stopped, also because the diagnosis of asthma was not sure.

Discussion: Lactic acidosis is often a sign of severe illness with hypoxia or tissue hypoperfusion. Another cause of lactic acidosis, namely β -agonist toxicity, is much less recognized. The exact mechanism is unclear. β -agonists may increase lipolysis, glycolysis and glycogenolysis. This increases pyruvate which is then converted to lactate. In our patient, salbutamol caused dyspnea instead of relieving asthmatic complaints.

Conclusion: Physicians should be aware that β -agonists can be toxic and can cause acute hyperventilation due to metabolic acidosis. It resolves spontaneously with tapering or cessation of β -agonists.

Patients' disease perception and physicians' and nurses' first clinical impressions predict 30-day mortality and other adverse outcomes in older emergency patients

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Background: After an emergency department (ED) visit, older patients run a high risk for adverse outcomes. Thus far, no reliable tools are available to predict these outcomes. The objective of this study was to assess the discriminatory value of disease perception, self-rated health, first clinical impression and the surprise question (SQ) with respect to 30-day mortality and other adverse outcomes in older ED patients.

Methods: We performed a prospective multicentre cohort study in older (≥ 65 years) medical ED patients. Patients, nurses and physicians filled out questionnaires concerning their disease perception, self-rated health and first clinical impression. Area under the curves (AUCs) of receiver operating characteristics (ROCs) were calculated.

Results: The first clinical impression of nurses and physicians provided the best discriminating value for 30-day mortality (AUCs 0.71 – 0.75). Loss of independent living was most adequately predicted by nurses (AUC 0.81). Disease perception and self-rated health of patients were less predictive for 30-day mortality (AUCs 0.64 – 0.69). The discriminating value for other adverse outcomes was lower (AUCs 0.60 – 0.67).

Conclusion: Disease perception, self-rated health and clinical impression are predictive for mortality and other adverse outcomes in older ED patients. Our findings may be useful as a clinical tool to predict adverse outcomes in older ED patients, in order to personalize clinical diagnostic procedures and treatment.

Effect of elevated hemoglobin A1c on complication rates after bariatric surgery

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Background: Diabetes mellitus type 2 (DM2) is a metabolic disorder with long-term complications. Bariatric surgery is one of the treatment options for DM2. The guidelines do not provide any hard recommendations regarding preoperative glycemic regulation. Furthermore, little is known about the relationship between an increased glycated hemoglobin (HbA1c) and postoperative complications after bariatry. The aim of this study is to know whether an increased preoperative HbA1c is a risk factor for postoperative complications.

Method: We retrospectively reviewed a database for patients who underwent a laparoscopic sleeve gastrectomy or a laparoscopic gastric bypass. The analysis was about all types of complications. The two cohort were divided according to the preoperative HbA1c ($>$ or \leq 42 mmol/mol).

Results: The data from 500 patients were collected: 250 patients in both groups. There were 31 complications (12.4%) in the group with a preoperative HbA1c \leq 42 mmol/mol and 50 (20%) in the group with a preoperative HbA1c $>$ 42 mmol/mol ($p=0.057$). The preoperative HbA1c is a predictive risk factor for patients younger than 52 (OR=1.031 95%CI(1.009-1.053) / $p=0.005$) but not for those older than 52 (OR=1.009 (0.985-1.033) / $p=0.48$). Furthermore, the HbA1c usually normalizes within 1 year after surgery (mean 41.39 mmol/mol 95% CI: 40.30 - 42.47). The weight loss in patients with an increased preoperative HbA1c is limited($p<0.001$) and the length of stay is prolonged for patients with complications($p<0.001$).

Conclusion: In this study an increased preoperative HbA1c ($>$ 42mmol/mol) is a greater risk for postoperative complications in bariatric patients younger than 52 years.

Integrated Assessment of Lifestyle and Pharmacological Management: Blood Pressure, Lipid and HbA1c Control in The DIAbetes and LifEstyle Cohort Twente (DIALECT)

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Background: Cardiovascular risk management is paramount in type 2 diabetes mellitus (T2DM). However, targets for blood pressure (BP), low density lipoprotein cholesterol (LDLc) and glycated hemoglobin (HbA1c) are often not reached. We evaluated whether integrated assessment of lifestyle and pharmacological management can identify the window of opportunity for improving target achievement.

Methods: This cross-sectional analysis was performed on baseline data from the DIAbetes and LifEstyle Cohort Twente (DIALECT-1, n=450, age 63 ± 9 years, 57% men, diabetes duration 11⁷⁻¹⁸ years). Patients were divided according to BP (≤140/85, or ≤130/80 in case of albuminuria), LDLc (≤2.5 mmol/l) and HbA1c (<53 mmol/mol) on target (OT), or not on target (NOT).

Results: BP, LDLc and HbA1c targets were achieved by 53%, 76% and 36% of patients respectively. Adherence to lifestyle guidelines was as follows: BMI 5%, physical activity 59%; vegetables 7%; fruit 28%; legumes 7%; nuts 14%; dairy 19%; fish 36%; tea 8%; fats 66%; red meat 12%; processed meat 2%; alcohol 71%; sweetened beverages 34%; sodium 12%. In BP-NOT, 38% of patients already used 3+ antihypertensives. In patients with LDLc-NOT, only 8% used high intensity statins. In patients with HbA1c-NOT, 78% used insulin and 37% used >90 units insulin/day.

Conclusion: Integrated assessment of lifestyle and pharmacological management demonstrated a different window of opportunity for each treatment target. Particularly in BP and HbA1c treatment, where progressive insulin resistance prohibits pharmacological efficacy, there is ample opportunity for lifestyle intervention. We advocate incorporating monitoring of lifestyle management in routine care.

Early Detection of Hypoglycaemia in Type 1 Diabetes Using a Wearable Device Measuring Heart Rate Variability

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Background: Patients with type 1 diabetes (T1D) are at risk of potentially hazardous hypoglycaemia. Changes in heart rate variability (HRV) patterns can be observed at the initiation of a hypoglycaemic event due to sympathetic nervous system activity. The present study aimed to investigate whether HRV-changes detected by a wearable device have the potential to alert for an upcoming hypoglycaemic events.

Methods: Patients with T1D were asked to wear the a VitalConnect HealthPatch heart rate monitor during five consecutive days. Hypoglycaemic events were defined as glucose <3.9 mmol/l by finger stick measurement and verified by continuous glucose monitoring. Parameters of HRV included Standard Deviation of the R-R intervals (SDNN), Square Root of the Mean Standard differences of Successive R-R intervals (RMSSD) and Low and High Frequency ratio (LF:HF).

Results: Twenty patients were included (12 women, mean (\pm SD) age 43 ± 11 years, diabetes duration 26 ± 11 years). This analysis was performed on 39 hypoglycaemic events among 10 subjects. The median subject-normalized LF:HF was 0.31 (IQR, 0.17-0.63) 30 minutes before hypoglycaemia and increased to 0.37 (0.18-0.63) during hypoglycaemia. The median RMSSD decreased from 40 (24-59) to 35 (25-45) before an hypoglycaemic event. Twenty events showed a clear detectable increase in LF:HF preceding hypoglycaemia, 18 a decrease in RMSSD, and 11 events were not preceded by a change in HRV.

Conclusion: Hypoglycaemic events are being preceded by changes in HRV that can be detected by a wearable device. Wearable patches measuring real time HRV seem promising devices for early detection of hypoglycaemic events.

‘Sweet after sourness’

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Introduction: A diabetic keto acidosis (DKA) is a medical emergency and sometimes admission to an Intensive Care Unit is needed for restoring homeostasis. We present a case with an additional source of metabolic dysregulation.

Case report: a 38-year-old unconscious man was admitted to our hospital. There was a history of type 2 Diabetes Mellitus, for which he used Metformin. 5 days before admission he complains about muscle aches, he was coughing and vomiting. Eventually he was found unconscious in his bed. Glucose test strip noted “high”.

Physical examination: Airway: not obstructed. Breathing: Respiratory Rate 30/min Saturation 100% with 10L/min oxygen. Bilateral rhonchi. Circulation: RR 115/80 mmHg Pulse 100/min reduced capillary refill. Disability: E3M5V3 Exposure: Temperature 34°C. Arterial blood sample: pH 6.72 pCO₂ 16 mmHg Bicarbonate 2 mmol/L Lactate 2 mmol/L Glucose 54 mmol/L Venous blood sample: Creatinine 215 mmol/L Phosphate 2.26 mmol/L Potassium 5.5 mmol/L Sodium 126 mmol/L Chloride 94 mmol/L. Anion-gap 27 Urine: Ketone 3+ X-thorax: lobar infiltrate. Urine Legionella antigen test positive. Working diagnosis: DKA evoked by Legionella Pneumonia.

Follow up: despite massive rehydration (10L Sodium Chloride 0.9% and 400ml Sodium Bicarbonate 8.4%) the pH only slightly improved (pH 6.85) There was no urine production. We hypothesized that the persistent acidosis was of renal origin and started CVVHD. After 5 days CVVHD could be discontinued. There was a complete recovery of renal function but the patient remained insulin dependent.

Conclusion: persistent metabolic acidosis in DKA after adequate treatment warrants further examination for a second diagnosis.

A rare cause of spontaneous hypoglycemia

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A 85-year old woman was brought to our emergency department because of a spontaneous symptomatic hypoglycemia (2.2mmol/l) without a history of diabetes. At presentation, she had normal vital signs. Laboratory evaluation showed no inflammation and normal kidney, thyroid and liver function. Adrenal insufficiency was excluded. Additional laboratory results showed a hyperinsulinemic state with an insulin level of 4380pmol/l and C-peptide of 1.2nmol/l without circulating oral hypoglycemic agents. CT scan, MRI-scan and endoscopic ultrasonography of the pancreas were normal. Hyperinsulinemic hypoglycemia without any evidence for an insulinoma or drug abuse can be caused by rare causes, such as pancreatic β -cell hyperplasia, nesidioblastosis or insulin auto-immune syndrome (IAS). In our patient, insulin antibodies turned out to be strongly positive (titer >50mU/l) corresponding with IAS. IAS, or Hirata disease, is a very rare cause of hyperinsulinemic hypoglycemia, characterized by circulating autoantibodies to endogenous insulin in individuals without earlier exposure to exogenous insulin. The mechanism of hypoglycemia is the sudden release of insulin, bound to these antibodies. Treatment consists of frequently low caloric meals, which limits the rise in postprandial insulin secretion and binding to antibodies. Additionally, treatment with steroids or rituximab can be considered, with conflicting results.

We treated the patient with diet and steroids: although hypoglycemic episodes did not disappear, they were less pronounced and not life-threatening anymore.

In conclusion, the patient was diagnosed with IAS, which should be considered in the differential diagnosis of spontaneous hypoglycemia in non-diabetic individuals. Distinction from pancreatic pathologies is crucial to prevent unwarranted procedures and interventions.

The complete disappearance of a long-lasting goiter

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Case: A 65-year old woman had an euthyroid goiter for decades, which was interpreted as multinodular. Six years ago, she was diagnosed with Hashimoto thyroiditis (HT) after developing hypothyroidism with positive anti-thyroid peroxidase antibodies. Afterwards the goiter slowly increased, without complaints. However, one year ago a sudden deterioration occurred with rapid growth of the goiter, very firm consistency, hoarseness, vocal cord paralysis and life-threatening stridor. Based on this clinical image, an anaplastic thyroid carcinoma was suspected. Nevertheless, further examination, including histological biopsy, revealed a diffuse large B-cell lymphoma (DLBCL), stage I. Treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristin and prednisone) led to quickly vanishing clinical features and complete remission on scintigraphy. Moreover: to our great surprise the goiter that existed for decades completely disappeared. Therefore, it is our hypothesis that the pre-existing goiter should be considered as an indolent lymphoma which led to the abovementioned clinical presentation after dedifferentiation into a DLBCL.

Discussion: Epidemiological studies suggest a relation between HT and primary thyroid lymphoma (PTL), with a reported 40-80 times increase of risk of developing PTL. Of all PTL 50-80% are of the DLBCL type. However, HT is associated with the more indolent mucosa-associated lymphoid tissue (MALT) lymphoma. Dedifferentiation into DLBCL might occur and worsens the prognosis.

Conclusion: We report a case of Hashimoto thyroiditis and long-lasting goiter, the latter completely disappearing after being identified and treated as Non-Hodgkin Lymphoma. Clinicians should consider lymphoma in the differential diagnosis of goiter, especially in case of coexisting Hashimoto thyroiditis.

Central hypocortisolism unmasked by thyroid hormone replacement

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Case: a 70-year old male patient who was being treated for central hypothyroidism and hypogonadism due to pituitary cystic macroadenoma was admitted to the Internal Medicine ward because of symptomatic hyponatremia. He had been experiencing headache, dizziness and confusion, as well as muscle pains and decreased exercise tolerance. Laboratory analysis showed decreased serum sodium levels of 115 mmol/L, with otherwise unremarkable biochemistry. Thyroid hormone was adequately supplemented (TSH 0.083 mU/L ; fT4 13 pmol/L). Urinalysis showed increased sodium excretion, which did not respond to fluid restriction and sodium supplementation. Fasting cortisol levels, which had been 0.52 µmol/L before starting thyroid hormone supplementation 4 months previously, were found to be markedly decreased to 0.09 µmol/L. Upon administration of hydrocortisone his sodium level rose to 135 mmol/L, leading to resolution of the symptoms. Subsequent MR imaging of the pituitary region showed any no growth or change of the known cystic mass.

Discussion/conclusion: thyroid hormone replacement therapy can unmask concurrent adrenal insufficiency in patients with primary and secondary hypothyroidism by increasing the basal metabolic rate, leading to increased cortisol demand. Even though hypocortisolism had seemingly been excluded in this case, 4 months of thyroid hormone supplementation nevertheless revealed a symptomatic hyponatremia due to cortisol deficiency. Physicians should always be alert to the possibility of new-onset hypocortisolism not only before, but also after starting thyroid hormone replacement therapy in patients with primary and secondary hypothyroidism, even when the hypothalamic-pituitary-adrenal axis seems intact at first glance.

Why a rare form of diabetes mellitus, kidney dysfunction and renal cysts may be of interest to a clinical oncologist

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Case: A 58-year old woman presented with abdominal distension, cachexia, ascites and axillary and supraclavicular lymphadenopathy. Her medical history included diabetes, kidney dysfunction and renal cysts attributed to Hepatic Nuclear Factor (HNF1beta) Maturity Onset Diabetes of the Young (MODY-5). Further examination revealed metastatic serous ovarian cancer stage IV. She was treated with paclitaxel/carboplatin followed by complete debulking.

Discussion: The phenotype of HNF1betaMODY is caused by heterozygous inactivating mutations/deletions in the gene encoding for the hepatic transcription factor HNF1beta, and has traditionally been described as 'diabetes and renal cysts'. HNF1beta plays an important role in organogenesis, explaining why liver and genitourinary abnormalities also occur. HNF1beta is downregulated in most cases of serous ovarian cancer suggesting that HNF1beta may have a tumor suppressive role in this tumor type. To our knowledge, there has been one other case report of a woman with HNF1betaMODY and ovarian carcinoma. She also developed chromophobe renal cell carcinoma, which has been linked to HNF1beta inactivation.

Relevance: It is currently unknown whether HNF1betaMODY predisposes to serous ovarian carcinoma. We hypothesize that a germline inactivating mutation in the HNF1beta gene predisposes to serous ovarian carcinoma, as a second somatic hit of the wild type allele may result in loss of function of the HNF1beta protein which has been associated with his tumor type.

Multiple Sclerosis associated Diabetes Insipidus – in search of a bright spot

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Case: A 54 year old female patient with a history of progressive multiple sclerosis was admitted with a staphylococcus aureus bacteremia due to decubitus of her hip. She was successfully treated with intravenous flucloxacillin. During admission she suffered from severe polydipsia and polyuria. In the absence of intravenous fluid suppletion, excessive water intake or the use of diuretics, her daily urine production exceeded 4 liters. Blood tests showed normal electrolytes and kidney function (Na 137 mmol/l; K 4.1 mmol/l, Ca 2.48 mmol/l, Ureum 4.5mmol/l, creatinine 27 umol/l, glucose 5.4 mmol/l). As a lack of excessive water intake ruled out psychogenic polydipsia, central or renal diabetes insipidus was expected. However, urine analysis did not confirm these diagnoses as urine osmolality was 651 mOsmol/kg.

Due to persistent polyuria and polydipsia, urinary analysis was repeated. This time, serum osmolality repeatedly exceeded urine osmolality (serum 286 mOsm/kg, urine 224 mOsm/kg). On suspicion of central diabetes insipidus a water restriction test was scheduled but could not be fulfilled due to hemodynamic instability. MRI of the brain revealed an absent posterior pituitary bright spot suggestive for central diabetes insipidus. The result of the ADH measurement is still pending. The patient was successfully treated with desmopressin after which urine production normalized (<2 liters per day), the polydipsia diminished and the serum sodium level remained within normal range.

Conclusion: Multipel sclerosis is associated with central diabetes insipidus. In case of a clear clinical suspicion, a single urine osmolality measurement is not sufficient to rule out this diagnosis.

Propylthiouracil (PTU) induced pancytopenia

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A 49-year old woman was referred to our outpatient clinic with new onset pancytopenia. She reported tiredness and several hematomas and petechiae in the past weeks. She had a medical history of Graves' disease, for which block and replace therapy with thiamazol and levothyroxine was started fourteen months before. However, after a few weeks of treatment, thiamazol was switched to propylthiouracil (PTU) after the development of a skin rash.

At physical examination the patient had multiple petechiae. Laboratory tests showed a haemoglobin of 6.8 mmol/L, a platelet count of $107 \times 10^9/L$, and a white blood cell count of $2.3 \times 10^9/L$ (neutrophils $1.3 \times 10^9/L$). The TSH level was 1.71 mU/L and the free T₄ level was 16.0 pmol/L.

As pancytopenia was described as an uncommon side effect of PTU, both PTU and levothyroxine were stopped. Complete blood count was checked weekly. Within two weeks, the haemoglobin level increased to 8.3 mmol/L, the platelet count to $200 \times 10^9/L$, and the white blood cell count to $5.6 \times 10^9/L$, and therefore no bone marrow biopsy was indicated. After stopping medication for Graves' disease, thyroid function remained stable.

Conclusion: Pancytopenia is a rare but potentially severe complication of propylthiouracil (PTU), but can recover quickly after stopping PTU.

Experimental inhibition of hepatic bile salt flux: a novel approach to ameliorate cholestasis and metabolic dysfunction

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Background: Bile salts, mediators of fat solubilization in the intestine, are now recognized as signalling molecules that regulate energy metabolism and immune responses by activation of their receptors (FXR and TGR5) in muscle, adipose tissue and immune cells. Hepatic bile salt uptake is determined by NTCP and OATP-isoforms, which control bile salt flux from blood towards bile.

We hypothesized that inhibition of hepatic bile salt transport delays clearance of circulating bile salts. In this way, prolonged bile salt signalling via blood may ameliorate cholestatic liver disease and different facets of the metabolic syndrome.

Methods: NTCP and OATP-deficient mouse models were used to understand the consequences of inhibited bile salt flux. NTCP-mediated transport was pharmacologically blocked using myrcludex B. Hepatobiliary effects of NTCP-inhibition were investigated in obstructive and genetic cholestasis models. Also, dynamic versus chronic effects of bile salt manipulation were studied in models of diet-induced obesity.

Results: Inhibition of NTCP caused conjugated bile salt elevation in blood. Cholestatic injury was reduced after NTCP-inhibition. Transient plasma bile salt elevations were well tolerated, and reduced plasma ALT and/or ALP levels were found. Furthermore, NTCP-inhibition protected mice against deleterious effects of a high-fat diet, reflected by reduced body weights and (liver) adiposity. Fasting plasma GLP-1 levels improved, however, glucose tolerance was not altered. Furthermore, transient NTCP-inhibition lowered plasma HDL/LDL-cholesterol.

Conclusion: Targeting hepatic bile salt uptake by NTCP shows promising effects in the fields of cholestasis and (lipid) metabolism, which sets the stage to investigate prolonged bile salt signalling in clinical trials.

Breathtaking Liver Cirrhosis

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A 68-year old man presented to the pulmonology department with chronic dyspnea during light exercise. His medical history included stable alcoholic liver cirrhosis. Assessment 3 years earlier had revealed no cardiac explanation for dyspnea. Pulmonary function test showed normal pulmonary volumes, but the diffusion capacity for carbon dioxide was only 52% of predicted. A high resolution computed tomography scan showed no normovolemic chronic obstructive pulmonary disease or other pulmonary abnormalities as cause of the low diffusion capacity. Exercise assessment revealed severe exercise intolerance (maximum rate of oxygen consumption 63% of predicted) with deoxygenation from 91 to 75% SAO₂, indicating a right-to-left shunt. Echocardiography ruled out severe portopulmonary hypertension as potential cause of this shunt. Contrast echocardiography demonstrated an extracardiac right-to-left shunt. The diagnosis hepatopulmonary syndrome with intrapulmonary vascular dilatations was established, graded as moderate to severe based on an alveolar-arterial gradient of 7.3kPa and arterial oxygen tension of 8.0kPa.

Intrapulmonary vascular dilatations are frequently observed in patients with chronic liver disease. In this population, an imbalance in the release of vasoactive mediators and reduced hepatic clearance lead to the formation of pulmonary vascular dilatations. The increased blood flow through these dilated capillaries induces a ventilation-perfusion mismatch with a physiologic shunt of mixed venous blood into the pulmonary veins. Therapy consists of supportive measures such as supplemental oxygen, but liver transplantation is the only definitive treatment. Awareness of this frequent complication of chronic liver disease is necessary for supportive therapy and timely consultation with a liver transplantation center.

An uncommon case of gastrointestinal blood loss

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Case: A 35 year old male presented with acute profuse bright red rectal blood loss. His medical history included varicose veins as well as a mild mitral insufficiency which was found during analysis after the sudden death of his father. Hemoglobin was 6.8 mmol/l, there was no kreatin ureum mismatch. Colonoscopy was performed which showed no active bleeding but did show diverticulosis. Despite the patient's young age, a diverticular bleed was considered to be the most likely diagnosis. We initially planned to manage the bleeding conservatively. The blood loss recurred however with hematemesis. During gastroscopy, a small diverticulum was seen in the duodenal bulb. With the use of the Waterjet a pulsating bleeding was provoked. The defect was closed somewhat successfully using four clips. On CT angiography, a dissected aneurysm of the celiac trunk 18mm in size was found with a small fistula to the stomach. The defect was coiled succesfully and without complications.

Discussion: We believe the aneurysm as well as the patient's (family) history to be in line with a diagnosis of Vascular type Ehlers Danlos Syndrome (EDS). Genetic analysis is pending as of the writing of this abstract. EDS is often left undiagnosed until a major vascular event or autopsy. Several events in this patient's medical history could have prompted further investigation to EDS. While there are no specific therapeutic options, life-style and reproductive counselling are mandated

Increased abundance of gut microbial virulence factors and pro-inflammatory pathways during Crohn's disease exacerbations

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Background: Crohn's Disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract characterized by alternating periods of exacerbation and remission. The pathophysiological mechanisms that trigger an exacerbation remain largely unknown, but accumulating evidence suggests that pro-inflammatory changes in the gut microbiome play an important role. In this study, we aim to identify microbial features associated with the onset and progression of CD exacerbations.

Methods: We collected 196 stool samples of CD patients (one stool sample per patient) in 2013-2014. Microbial profiles were generated using whole genome shotgun metagenomic sequencing on the Illumina HiSeq platform. Microbial taxonomy, pathways and abundances of virulence factor genes were determined using specialized software and the Virulence Factor Database. All clinical records were reviewed two years after sampling, to relate each stool sample to the disease activity chronology. Microbiome profiles were correlated to disease activity using logistic regression and linear models.

Results: Of the 196 CD patients, 24 patients were having an exacerbation during stool sampling, while 172 were in remission. During an exacerbation, 160 microbial pathways were differentially abundant, including a decrease in the production of the anti-oxidant vitamin B2 (FDR=0.03). In addition, microbial virulence factors linearly increased before an exacerbation and decreased after an exacerbation, including *flaA* Flagella, *flhB* Flagellar Biosynthesis Protein and *flhF* Flagellar GTP binding Protein (FDR<0.01).

Conclusion: We found that flagella virulence factors, associated with bacterial adhesion and invasion, increase during a CD exacerbation and decrease after an exacerbation, and could therefore be interesting targets for translational microbiome-based drug research.

Co2I

Severe diarrhea 3 months after adjusting antihypertensive therapy

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Case: a 68 year old woman with hypertension was admitted to our hospital several times within two months because of severe watery diarrhea, nausea and progressive weight loss (12 kilograms). Infectious causes and exocrine pancreatic insufficiency were ruled out, celiac serology was negative. A colonoscopy was performed without abnormalities a gastroscopy revealed thickening of the duodenal folds; microscopy showed villous atrophy, crypt hyperplasia and intra epithelial leucocytosis. Furthermore there was no indication for Whipple's or lymphoproliferative disease. Despite negative celiac serology and a negative HLA DQ2-8 celiac disease was diagnosed. After two weeks of a strict gluten-free diet the patient returned with continuous severe diarrhea.

Discussion: when clinical suspicion of celiac disease arises suggested diagnostics are serology and duodenal biopsies. When encountering a patient with villous atrophy but negative serology it is important to re-assess your diagnosis and consider amongst others inflammatory bowel disease, giardiasis, immunodeficiency related disorders, intestinal lymphoma and Whipple's disease. Furthermore a review of medication should be done, in particular the use of olmesartan should be considered. Olmesartan is suggested to increase the pro-apoptotic effect that angiotensin-II appears to have on the intestinal epithelium in the duodenum. The patient discussed here started using olmesartan 4 months earlier. During her last hospital admission olmesartan was replaced by valsartan after which her complaints gradually diminished; she's slowly gaining weight again over the last months.

Conclusion: *medication associated enteropathy* should always be considered with unexplained diarrhea.

Father, son and ferritin

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Case: A 78-year-old male was referred because of hyperferritinemia (7294ug/L; reference < 250ug/L). No symptoms were present, he had a normal BMI and cataract, diabetes and liversteatosis were absent. The transferrin saturation percentage was normal, as well as liver enzyme levels and ultrasound. P.Cys282Tyr and p.His63Asp variants in HFE-associated hereditary hemochromatosis were absent. The patients 33-year-old son presented elsewhere with complaints of fatigue. His ferritin level was 3334ug/l. MRI showed striking hepatic iron deposits. Genetic testing identified heterozygosity for HFE p.Cys282Tyr variant and the ferroportin (SLC40A1) gene variant p.Val162del. Ferroportin disease was diagnosed and careful phlebotomy was started. The father however, experienced syncope and anemia. Phlebotomy is well tolerated by his son.

Background: ferroportin disease (FD) is an autosomal dominant ironloading disorder caused by an heterozygote 'loss of function' variant of the ferroportin gene (SLC40A1). Multiple FD-associated pathogenic variations have been identified. In contrast to parenchymal iron loading in hereditary hemochromatosis, iron accumulation occurs mainly in reticuloendothelial macrophages (RES) of the spleen, liver and bone, which can best be visualized on MRI. Although the clinical manifestations are usually mild or even absent, RES iron overload may lead to hepatic fibrogenesis and carcinogenesis. Unlike classical hemochromatosis, FD patients are sensitive to the development of anemia upon phlebotomy, which is due to inhibition of iron release of the affected macrophages.

Conclusion: ferroportin disease should be suspected in case of unexplained hyperferritemia. It may have implications for relatives and iron depletion therapy must be personalized.

Secondary care experience of patients with multiple chronic conditions: a qualitative study

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Background: As the prevalence of multiple chronic conditions (MCC) increases, the coordination of care becomes more important. This study aimed to investigate patients' experiences, beliefs and understandings of the current secondary care for MCC.

Methods: We conducted 8 semi-structured, in-depth interviews with patients with MCC, who visited at least two physicians in Gelre hospitals for at least two appointments in the previous year.

Results: Being a patient with MCC in the hospital can be complex and keeping an overview required effort, according to the participants. Most participants would appreciate more coordination and communication. However, the exact needs seemed to differ. The multiple visits transformed them into experienced patients: based on the experiences and observations they developed strategies to sustain themselves in the hospital. Altogether, communication in the hospital submerged as an important, overarching theme. Different events and types of communication evoked specific feelings and expectations that were important for the patients' care experience as well.

Conclusion: An overview of the patient's care seems an essential element for a more coordinated, individualized approach of care. Future research might focus on ways to engage both healthcare professionals and patients in the improvement of care. It could aim on finding ways to create overview and coordination and define responsibilities, but also on clarifying what group of patients needs assistance. It might also investigate the effect of good and clean communication on reducing hassles. Overall, also in the future patients' care experience could play an important role to determine the direction of new interventions.

Drug-induced liver injury caused by atorvastatin

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Case: We report the case of a 54 year old women who presented to our clinic with fever, generalized aches and epigastric pain. The symptoms started 3 days before admission to our hospital. Two months earlier she was admitted to the coronary care unit due to myocardial infarction. Treatment with atorvastatin (40mg) and clopidogrel (75mg) was initiated at that time. A cardiac cause of her current symptoms was excluded. Laboratory results revealed a slightly elevated C-reactive protein. Liver function tests were all markedly elevated. Alanine amino-transferase (ALT) and aspartate-transaminase (AST) were more than ten folds of the normal upper limit. There was also cholestasis with elevated bilirubin, alkaline phosphatase (ALP) and γ -glutamyl transpeptidase (γ -GT). Abdominal ultrasound and CT scan revealed no abnormalities. Because liver function test continued to rise, extensive viral, bacterial and auto-immune blood tests were conducted. All laboratory results were negative. After cessation of atorvastatin, the general symptoms improved and the liver function test gradually recovered to the baseline after one month. The diagnosis drug-induced liver injury (DILI) due to atorvastatin was made. Pravastatin is known to be less hepatotoxic compared to other statins. Our patient therefore switched to pravastatin. After initiation of pravastatin liver function tests remained on the baseline.

Discussion: Although rare, statins have been reported to cause severe liver injury. This risk might be increased when other cytochrome metabolized drugs such as clopidogrel are used simultaneously. Pravastatin is the only statin not metabolized by the cytochrome system. Therefore it might be a safe alternative.

Differences in side effects among the generic variants of simvastatin, omeprazole and pantoprazole

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Background: The 'drug preference policy' ensures that pharmacists issue the cheapest variation of a generic drug. Although the active ingredient is required to be within an acceptable bioequivalent range compared to the brand-name product, patients may report differences in side effects. The aim of this study was to compare the incidence of side effects among the variants of three common generic drugs.

Methods: All adult patients who visited the Alrijne Hospital Pharmacy between April 1st 2015 until October 1st 2015 and were issued either generic omeprazole, pantoprazole or simvastatin were included in the study. After 8 weeks, a survey was sent that showed pictures and names of all the generic variants and patients were asked to select the variant they had been using and to report possible side effects. Occurrence and severity of side effects were investigated and compared between the different variants of all three generic drugs.

Results: 1904 patients were included and 470 returned the survey. The odds ratio of the prevalence of side effects in general between the 2 most common generic variants of omeprazole, pantoprazole and simvastatin were respectively 1.05 (CI 0.17 to 6.59), 1.23(CI 0.40 to 3.76) and 1.47(CI 0.36 to 6.01). The distribution of side effects differed per variant.

Conclusion: We could not establish any significant difference in the prevalence of side effects in general among the variants of three commonly prescribed generic drugs. To determine if generic drugs are fully interchangeable, a more detailed study of the distribution of side effects is needed.

Hypercalcemia associated with Marjolin's ulcer

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A 61-year old female with chronic suppurative wounds, on which she had been operated multiple times, presented with complaints of pain, nausea, weight loss and lethargy. On physical examination she was cachectic and had extensive wounds and scarring of the buttocks and groin.

Laboratory tests showed a serum level of calcium corrected for the serum albumin level of 4,3 mmol/l (2,15-2,55 mmol/l), with a serum level of phosphate of 0,72 mmol/l (0,7-1,4 mmol/l) and a normal renal function.

Serum levels of parathormone, PTH-related peptide (PTH-rp), total protein, M-protein, free light chains ratio, vitamin A, 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D were normal. Also, 24-h urinary calcium excretion was normal. Thus, we could not identify any endocrinological or drug induced mechanism as the cause for her hypercalcemia.

A PET-CT scan showed FDG uptake in the buttocks and groin, consistent with inflammation, as well as osteomyelitis of the ischium bone.

A literature search was performed on hypercalcemia occurring in osteomyelitis. One case report described hypercalcemia by secretion of PTH-rp due to Marjolin's ulcer, a neoplastic transformation of chronic wounds, with development of squamous cell carcinoma from chronic osteomyelitis.

Bone tissue was therefore sent to pathology, showing a moderately differentiated squamous cell carcinoma. In contrast to the data in literature we did not find elevated serum levels of PTH-rp. Possibly, other humoral factors and/or cytokines (e.g. GM-CSF, G-CSF, Il-1, Il-6) may lead to hypercalcemia independent of PTH-rp production. The exact mechanism of hypercalcemia in our patient remains unclear.

Acute Epstein-Barr virus infection as cause of rhabdomyolysis in young adult male

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Case: A 18-year-old man presented in the emergency department with dyspnea and myalgia. He had an history of asthma, but did not use any medication recently. He denied any drugs use or extreme physical activity. On physical examination he had an increased respiratory rate and was wheezing on expiration. There was no fever present.

Laboratory investigations showed a strongly increased creatine kinase (CK) of 42140 U/L and an elevated LDH level. Renal function and liver tests were normal. Chest X-ray, electrocardiogram (ECG) and urinalysis showed no abnormalities.

The patient was admitted on the pulmonology ward with an asthma exacerbation. Internal medicine was consulted because of the elevated CK levels, which was interpreted as rhabdomyolysis. Further investigations into the cause of this rhabdomyolysis demonstrated an acute Epstein-Barr virus (EBV) infection with the ELISA positive for IgG and IgM (EBV-VCA). Other viral serology was negative, thyroid function and glucose levels were normal. The patient was given fluid infusion to induce diuresis and prevent renal failure. Within a few days CK levels decreased to 745 U/L and the patient could be discharged.

Discussion: Rhabdomyolysis due to an acute EBV infection was described before in literature. Most cases were seen in young adults and in some cases rhabdomyolysis led to acute renal failure. Remarkably in our patient renal function was not affected despite the high CK levels probably due to the short period between onset of symptoms and start of treatment.

TIRADS to reduce FNA in thyroid nodules

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Background: Dutch guideline of thyroid carcinoma of 2015 recommends to perform a fine needle aspiration (FNA) on every palpable thyroid nodule except for 100% cystic nodule found on ultrasound. This guideline states that the use of ultrasound is not reliable to rule out thyroid carcinoma.

In order to reduce the number of FNA in patients with thyroid nodules and to save healthcare costs, we searched for a new ultrasound protocol to optimize evaluation of thyroid nodules.

Methods: We performed a critically appraised topic addressing the question: can ultrasound differentiate between benign versus malign thyroid nodules? The literature search was performed in February 2017.

Results: We found three appropriate prospective studies on this topic. In these articles the use of Thyroid Imaging Reporting and Data System (TIRADS) was studied. TIRADS consists of 5 categories: normal thyroid tissue belongs to category 1 and a thyroid node that is highly suspicious for thyroid carcinoma to category 5.

The studies found that certain characteristics on ultrasound belong to low risk (TIRADS 2 and 3: 0% resp. 0,25-0,5% risk of carcinoma). On the other hand some characteristics on ultrasound are associated with a high risk for thyroid carcinoma.

Conclusion: Use of TIRADS is a reliable and an attractive diagnostic modality to determine the risk of thyroid carcinoma. When the ultrasound characteristics reflect benign (TIRADS 2 or 3) FNA is not indicated. With the use of TIRADS FNA can be reduced with 40-60%. We are planning to implement TIRADS in our hospital.

Fluid mimicking a tumor

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Case: A 71-year old man with no relevant medical history was seen at the outpatient clinic because of anemia and hypoalbuminemia. He had no actual complaints. On physical examination a cachectic and paly patient was seen without further remarks. Laboratory tests showed a hemoglobin 7,2 mmol/L, MCV 108fl, albumin 30 g/L and M-protein was found: type IgM kappa and lambda, 16 g/L. Beta-2-microglobuline was 4.12 mg/l . Abdominal ultrasound showed some ascites and fluid around the left kidney. Abdominal CT was performed and showed soft tissue around the left kidney with normal aspect of the kidneys. There was no lymphadenopathy or hepatosplenomegaly. Biopsy of the perirenal mass and also a bone marrow biopsy was planned. Histopathologic evaluation of the mass showed a low-grade B-cell non-Hodgkin's lymphoma with plasma cell differentiation matching with lymphoplasmocytic lymphoma. IPSS score was 2. Watchful waiting approach was chosen because of asymptomatic disease.

Discussion: The differential diagnosis of perirenal mass is broad and includes renal cell carcinoma with perirenal spread, lymphoma, leukemia, retroperitoneal fibrosis and metastases. In this case the fluid around the left kidney seen on ultrasound, eventually turned out to be a tumor. The cortex of lymphatic tissue is just as fluid dark on ultrasound. In this specific case it was confused with fluid. The occurrence of isolated lymphoma in the perirenal space is very unusual.

To highlight: in case of fluid around the kidneys on ultrasound without signs of kidney contusion or pyelonephritis, it is recommended to perform abdominal-CT to exclude perirenal tumor.

An unusual osmolal gap

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A 30-year-old woman was admitted to the hospital with severe heart failure, secondary to a non-compaction cardiomyopathy. Treatment included norepinephrine and enoximone through a peripherally inserted central catheter (PICC). Blood results showed a hyponatraemia (122 mmol/l), conceivably secondary to cardiac failure. However, the plasma osmolality was repeatedly elevated (345-566 mOsm/kg). An osmolal gap was present (164 mOsmol/kg) without metabolic acidosis. Ethanol was suspected, and indeed levels were elevated (2.39 g/l), but the patient was bedridden and medical history and room search for alcohol were negative. Furthermore, it accounted for merely 52 missing osmoles. To analyse the residual gap, gas chromatography was performed and demonstrated toxic propylene glycol levels (8.2 g/l), explaining the missing gap. Enoximone could be the suspect, since it contains solvents ethanol and propylene glycol, however we were puzzled by the lack of symptoms accompanying toxic levels. Therefore a sampling problem was suspected. Blood samples were taken from the PICC line, adjacent to the enoximone lumen. Due to low cardiac output, enoximone could accumulate near the exit ports. Additionally, ethanol can damage the polyurethane PICC line, thereby causing a lumen breach. Central and peripheral blood samples were taken simultaneously and showed a central to peripheral osmolal gap of 140 mOsm/kg, low peripheral propylene glycol levels and no ethanol. Our case highlights the importance of measurement errors due to blood sampling site. Especially the solvents used in enoximone can be misleading. A hyponatraemia in a patient with cardiac failure may just (not) be a simple as one might suspect.

Neither cancer, nor infection: idiopathic granulomatous mastitis

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A 44 year old women from moroccan descent, without relevant history, presented with chronic recurrent unilateral mastitis. A surgeon had already treated her with different antibiotics and drainage of abscesses. Since her mastitis was not improving and cultures of the pus remained negative, they were contemplating ablation.

She had two lumps with epithelial fistulas in the left breast, accompanied by redness for over six months. She did not breastfeed in the last year. Laboratory tests including inflammation parameters and ANA were normal. Ultrasonography and MRI of the mamma showed induration of the upper quadrants with diffuse edema. Histopathological findings were destruction of the glandular ducts with histiocytes and giant cells, without any indication of malignancy, matching a granulomatous inflammation. No signs of funghi or mycobacteria were seen. Granulomatous diseases such as tuberculosis and sarcoidosis were excluded by a normal X-ray, angiotensin converting enzyme and a negative interferon gamma release assay.

Idiopathic granulomatous mastitis is a benign inflammatory condition of the breast of unknown etiology. Literature reports positive responses to steroids suggesting an autoimmune condition. However, more than 50% of reported cases are initially mistaken for breast carcinoma and can cause unnecessary surgery which can result in slow wound healing and epithelial fistulas. Diagnosis is histologically confirmed by non-caseating granulomas in the breast and sterile microbiological cultures. It can be treated with corticosteroids, immunosuppressive agents or anti-inflammatory drugs. Considering side effects, our patient started with colchicine and the first results seem positive.

Clozapine-induced cardiomyopathy and interstitial nephritis

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A 44-year old female presented with fever and dyspnoea. Because of a schizoaffective disorder she stayed in a psychiatric clinic. She used clozapine for 2,5 weeks. Since 4 days she complained of muscle pains, fever and a sore throat. Subsequently she developed a cough and progressive dyspnoea. At presentation she was ill with tachycardia, low blood pressure, high fever and oxygen-dependence. Pulmonary auscultation revealed left-sided basal crackles and diminished breathing. Laboratory investigation showed inflammation, lymphopenia, thrombocytopenia and impaired liver biochemistry. Chest X-ray revealed left-sided pleural effusion and suspicion of pneumonia.

A presumed pneumonia was treated with antibiotics without clinical improvement. Extensive microbiologic investigation was negative and there was no serologic evidence for systemic disease. Cardiac ultrasound showed impaired left ventricular function. Patient was diagnosed with clozapine-induced cardiomyopathy. Clozapine was stopped and diuretic therapy was successfully started. Patient clinically recovered.

During admission she developed severe progressive kidney failure, despite stopping diuretics and careful fluid administration. Ultrasound and urinalysis were unremarkable. Kidney biopsy showed extensive interstitial nephritis. We initiated steroids after which kidney function started to recover. Cardiac (as demonstrated by ultrasound) and kidney function completely recovered after some weeks.

Clozapine is a widely used antipsychotic drug with particularly known hematologic and cardiovascular side effects. Cardiomyopathy can be caused by T-cell and eosinophil mediated inflammation. However, it is less known that other organs such as the kidney can also be involved in this auto-inflammatory process. In patients using clozapine presenting with inflammatory disease we should be aware of toxicity of this drug.

Severe neurological symptoms caused by hypomagnesemia induced hypocalcemia in a 69-year old male with GERD

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A 69-year old male presented to the emergency ward with a headache and dizziness. He had been admitted to the neurology ward with similar symptoms a week earlier, where he was diagnosed with hypotension of unknown origin. At discharge, blood pressure had normalized, but symptoms were still present and progressed over the next days. Clinical and neurological examination revealed no abnormalities. Routine laboratory studies showed a normal blood count, liver and kidney panel and CRP. Additional CT scanning of the brain showed no explanation for his symptoms. The patient was admitted to the neurology ward and observed. During observation his behavior changed. First, he became more aggressive, later he was in an apathetic state. Furthermore, he developed seizures and a vertical nystagmus. Additional diagnostics, including MRI, liquor puncture and EEG, were all normal and eventually the patient was thought to have Creutzfeldt Jacob disease. Specific testing was performed, alongside extensive laboratory studies, including all electrolytes. The first returned negative, but he turned out to have extensive hypomagnesemia (<0.10 mmol/L) and hypocalcemia (1.66 mmol/L, corrected). The cause of this extreme hypomagnesemia was thoroughly investigated, but eventually proved to be due to PPI use. Electrolytes were supplemented and his symptoms resolved.

This case reveals the intense symptomatology of electrolyte disturbances. In classic cases, Chvostek's and Trousseau's signs trigger the thought of hypomagnesemia and hypocalcemia. However, we should be aware that the absence of these signs in patients with extensive neurological symptoms does not exclude electrolyte disturbances as underlying condition.

Hypothyroidism induced hyponatremia: It exists

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Introduction: Severe hypothyroidism may induce hyponatremia through impairing urine dilution, possibly caused by elevated ADH levels. The elevation of ADH levels is attributed to a decreased cardiac output causing relative hypotension and arterial baroreceptor activity. In myxoedema coma case reports found high levels of ADH contributing to hyponatremia. Therefore, the results of urinalysis in hypothyroidism induced hyponatremia are similar to the results in hyponatremia due to SIADH.

Cases: Patient A, a 77 year old man presented at the ER with muscle weakness, malaise and oedema. Laboratory investigation revealed a symptomatic hyponatremia of 117mmol/l and serum TSH 61mU/l. Urinalysis results were compatible with ADH activity. Patient A was ultimately diagnosed with autoimmune hypothyroidism and myxoedema. After treatment of hypothyroidism the serum sodium concentration stabilised. Patient B, a 79 year old man was referred to the outpatient clinic because of renal insufficiency. He used amiodarone as treatment for ventricular tachycardias. At presentation there were no clinical signs of fluid overload. Laboratory investigation revealed an asymptomatic hyponatremia of 125mmol/l and serum TSH 140mU/l, Urinalysis results were suggestive of ADH activity. Patient B was diagnosed with amiodarone induced hypothyroidism and secondary asymptomatic hyponatremia.

Conclusion: Hypothyroidism is a relatively rare cause of hyponatremia. In case of severe hypothyroidism, hyponatremia may develop due to decreased capacity of free water excretion. The therapeutic consequences of hyponatremia secondary to hypothyroidism justify the measurement of TSH values in hyponatremic patients especially in patients with signs of ADH-activity.

Knowledge dissemination on drug-related falls: EUGMS task and finish group on fall-risk-increasing drugs

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Background: Falls are a public health priority due to their common appearance and accompanying injuries, reduced quality of life and substantial health care costs. Use of certain medication (fall-risk-increasing drugs) is one the major risk factor for falls. However, there is varying awareness among physicians and patients about drug-related falls. Moreover, the lack of knowledge is a major barrier to perform drug withdrawal interventions effectively. On behalf of the European union geriatric medicine society task and finish group on fall-risk-increasing drugs, we present preferential strategies to disseminate knowledge on drug-related falls in the The Netherlands as well as Europe.

Methods: Several expert meetings were held to (1) determine target groups, priorities, and strategy with regard to knowledge dissemination on fall-risk increasing drugs and (2) develop educational material. A patient focus group was held to determine patient preferences and needs.

Results: In 2017, educational video about drug-related falls to students, leaflet for older persons and e-learning to GPs and pharmacists was developed. These will be available in the The Netherlands through cooperating partners including Dutch Network Falls Prevention, VeiligheidNL, University of Amsterdam and Dutch institute of sustainable Medication use. A dissemination strategy is being unrolled, and a translation in other European languages is currently underway.

Conclusion: This co-operation on a European level with both experts and patients has resulted in several educational products, and different possibilities have been recognized to disseminate the knowledge. Besides generating new knowledge through studies, it remains essential to focus on implementation, and for this, knowledge dissemination is vital.

Fall-risk-increasing drugs: a systematic review and meta-analysis

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Background: Medication use is an important risk factor for falls. However, several frequently prescribed medication classes are still under debate as potential fall-risk-increasing drugs in the older population. The aim of this systematic review and meta-analysis is to evaluate the associations between fall risk and medications comprehensively.

Methods: Design: a systematic review and meta-analysis. Data sources: Medline, Embase, and PsycINFO. Key search concepts: 'fall', 'aged', 'causality', and 'medication'. Studies which investigated medications as risk factors for falls in participants ≥ 60 years or with a mean age ≥ 70 were included. A meta-analysis was performed using the generic inverse variance method, pooling unadjusted and adjusted odds ratios (OR) separately.

Results: In total, 402 studies were included in the narrative synthesis. Meta-analysis using adjusted ORs showed significant results (pooled OR [95% confidence interval]) for loop diuretics OR 1.36 (1.17-1.57), beta-blocking agents OR 0.88 (0.80-0.97), opioids OR 1.60 (1.35-1.91), antiepileptics OR 1.55 (1.25-1.92), antipsychotics 1.54 (1.28-1.85), antidepressants 1.57 (1.43-1.74), tricyclic antidepressants 1.41 (1.07-1.86), selective serotonin reuptake inhibitors 2.02 (1.85-2.20), benzodiazepines 1.42 (1.22-1.65), long-acting benzodiazepines 1.81 (1.05-3.16), short-acting benzodiazepines 1.27 (1.04-1.56) and polypharmacy OR 1.75 (1.27-2.41).

Conclusion: Psychotropics, opioids, loop diuretics, antiepileptic use, and polypharmacy were significantly associated with increased fall risk, whereas beta-blockers were significantly associated with decreased risk. Furthermore, recent studies indicate that specific drug properties, may affect fall risk and also drug-disease interaction may play a role. Thus, studies addressing these issues are warranted to obtain a better understanding of drug-related falls.

A case of familial Creutzfeldt-Jakob disease

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Case: a 77-year old Italian male with a history of diabetes, alcohol abuse and recently diagnosed neuropathy was presented at our emergency department because of confusion. Mental health declined fast and he had developed vision disorders.

At physical examination, vital signs were normal. There was a maximal Glasgow coma score, orientated patient; however bradyphrenia, lethargy and apathy were present as well as visual hallucinations. Laboratory test showed no abnormalities. It was first said to be a delirium due to start of Lyrica for the neuropathy but discontinuation did not solve the clinical symptoms.

During admission the situation deteriorated despite extensive treatment of the delirium with several antipsychotics. The patient was agitated, hallucinated and suffered from motoric disturbances.

A CT of the brain was normal. Liquor investigations (including Tau-protein) were unremarkable. Serology for HIV and Treponema Pallidum came back negative. A EEG showed slow occipital activity and epileptiform discharges which led to starting Keppra. The MRI did not provide further clues. Later during admission family stated that 2 members of his Italian family suffered from a rapid progressive brain disease with gait disturbances, said to be Creutzfeldt-Jakob disease.

Patient's health declined further and he developed an aspiration pneumonia due to swallowing disorder and palliative care was started. Post-mortem analysis showed positive stain for prion activity in the brain. Genetic analysis confirmed a case of familial Creutzfeldt-Jakob disease, it showed a mutation of prion gene E200 K, which to our best knowledge, was to date not described in the The Netherlands.

C038

How immune suppression can cause angry macrophages

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Case: A 53 year old male presented with nausea, vomiting, diarrhea, fever and icterus. His medical history included colitis ulcerosa (CU) for which he was treated with azathioprine.

Laboratory results showed pancytopenia (Hemoglobin 6.0 mmol/l, thrombocytes $89 \times 10^9/L$, leukocytes $1.2 \times 10^9/L$), high serum ferritin (6200 $\mu g/L$) signs of diffuse intravascular coagulation (PT 16 sec, D-dimer 2.21 mg/L, fibrinogen 0.9 g/L), elevated liver enzymes (total bilirubin 129 $\mu mol/L$, direct bilirubin 108 $\mu mol/L$, ASAT 174 U/L, LDH 914 U/L, AF 349 U/L, GGT 339 U/L) and high inflammatory markers (CRP 89 mg/L).

Serology of viral pathogens, including Epstein-Barrvirus (EBV) was negative. However, PCR for EBV was positive with a high viral load (120000 copies /ml). Imaging by CT of the abdomen showed splenomegaly and splenic infarction. Bone marrow examination revealed hemophagocytosis. Soluble IL2 receptor showed a value of >55000 pg/ml. The diagnosis EBV related hemofagocytic lymphohistiocytosis (HLH) was considered, since 7 of 8 diagnostic criteria were fulfilled. Patient was treated according to HLH-94 protocol with rituximab, high dose steroids and etoposide.

Discussion: We describe a case of primary EBV infection with the development of HLH in a patient who was treated with azathioprine for CU. Thiopurine exposure is an important risk factor for the development of HLH in patients with inflammatory bowel disease. Viral infections such as EBV should be considered as potential triggers. Chronic lymphopenia caused by thiopurine exposure is thought to suppress the host cellular-mediated immune response via suppressor T lymphocytes during primary EBV infection.

Coombs and copper

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Case: A 67-year old Caucasian male, with a medical history of obesity, was referred with anemia and thrombocytopenia. He had no symptoms, except dark urine and an improving cellulitis for which he recently finished antibiotics. Physical examination showed pitting edema of lower extremities. Laboratory tests showed a Hemoglobin of 7.0 mmol/L (8.5-11.0), thrombocytopenia of 99 10⁹/L (150-400) and liver test disorders, no signs of infection. Direct antiglobulin test (DAT) was negative. Vitamin deficiency and TMA were excluded. Because of progressive liver test and function disorders, our working diagnosis was secondary hemolysis due to liver failure. Other causes of DAT-negative hemolysis such as paroxysmal nocturnal hemoglobinuria, hemoglobinopathy, G6PD-deficiency, bone-marrow disease, toxic agents and membrane defects were excluded. Further work-up showed extensive liver cirrhosis due to Wilson disease, with high copper excretion, low ceruloplasmin and a one-sided Kayser-Fleischer ring. Other causes of liver failure were excluded. Wilson is an autosomal recessive disease, caused by a mutation in the ATP7B-gen, leading to copper stacking in the body. Hemolysis occurs due to oxidant damage by copper. Wilson has a fatal course without appropriate treatment. Our patient was referred to a liver transplant hospital for further evaluation and transplanted successfully after developing neurological damage, with recovery of symptoms and laboratory values.

Conclusion: DAT/Coombs negative hemolysis needs further diagnostic testing, consider secondary causes as liver disease, sometimes this could be the first clue to Wilson disease. Early detection and treatment will prevent serious damage.

Leukemia is not so Sweet

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A 64-year old woman without a past medical history was referred with weight loss and hematomas on arms and legs. Laboratory tests showed anemia, leukocytosis and thrombocytopenia. Bone marrow investigation revealed an acute myeloid leukemia (AML). Chemotherapy (daunorubicin and cytarabine) was started via a central venous catheter, as venous access was limited due to the painful hematomas. The following day fever and an erythematous rash were noted and treated as erysipelas with antibiotics (flucloxacillin). Chest x-ray revealed no infiltrates. Blood cultures remained negative. Deep venous arm thrombosis was excluded by ultrasound. The rash evolved into bullae and necrotic plaques. One week after presentation a skin biopsy showed neutrophilic infiltration in the dermis. The diagnosis Sweet syndrome was confirmed. Prednisone 30mg per day was started and her skin abnormalities disappeared. Prednisone was tapered and discontinued after three weeks. The patient's AML was treated successfully. Her skin abnormalities did not relapse.

Three different types of Sweet syndrome exist; classical, drug-induced and malignant. The malignant Sweet is mainly present in patients with hematological malignancies. Reports confirm a diagnostic delay, as the skin disorder can develop during or concurrently with the diagnosis of a malignancy. Treatment with prednisone is commonly used with a rapid response. Skin relapses are described, thus tapering is advised.

Always consider the diagnosis Sweet syndrome in a patient with a hematological malignancy and erythematous painful skin lesions. The diagnosis needs to be confirmed by histopathology. Treatment approach is to treat the underlying disease and if severe in combination with steroids.

Membranoproliferative glomerulopathy – a presentation of chronic lymphatic leukaemia

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A 67-year-old woman with a history of recent stroke presented at the outpatient clinic with hypertension and macroalbuminuria. She reported foaming urine but no edema. Physical examination was unremarkable apart from a blood pressure of 162/95mmHg. Laboratory examination showed an estimated glomerular filtration rate of 59 ml/min/1.73m² and albumin of 35.1 g/L. She had a normocytic anaemia of 6.1 mmol/L, normal range thrombocytes and leukocytes, leukocyte differential report was normal. M-protein IgG type kappa was slightly present (0.03 g/L). Urinalysis showed protein excretion of 6g/24 hours, 91% dysmorphic erythrocytes and Bence Jones protein type kappa. Ultrasonic examination of the kidneys showed no abnormalities. A kidney biopsy showed membranoproliferative glomerulonephritis (MPGN) with monoclonal kappa light chain depositions. This indicated monoclonal gammopathy of renal significance and prompted further bone marrow examination. The bone marrow biopsy showed no plasma cell neoplasia, but localisation of chronic lymphatic leukaemia (CLL).

MPGN secondary to monoclonal gammopathy has been described in haematological disorders such as monoclonal gammopathy of undetermined significance, Waldenström macroglobulinemia, lymphoproliferative disorders, and multiple myeloma. Within CLL patients, MPGN is the most common glomerulopathy and is sometimes the first presentation of CLL, as was the case in our patient. Treatment of the underlying haematological disorder can reduce albuminuria and improve renal function.

Our patient was given 4 courses of Rituximab, Fludarabine and Cyclofosfamide after which protein excretion decreased to <0.2g/24 hours and no CLL was detectable in the bone marrow anymore. This case underlines that MPGN can be a first presentation of a haematological disorder.

Cardiac lymphoma

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Introduction: primary cardiac lymphoma or secondary cardiac involvement in systemic lymphoma is a very rare disease.

A 67 year old man without relevant history, presented with pain in the left upper leg and left hip since two weeks. The pain was worsening. He couldn't move his left leg and wasn't able to stand up. He hasn't been unwell and didn't have fever. His weight was unchanged. Except shortness of breath no another complaints. Physical examination revealed thicker upper leg left and inguinal node on the left side. No additional abnormalities were found. Laboratory results were normal. The echo of the inguinal left showed a pathological node of 3.8cm. Histopathological examination of this node showed a diffuse large B-cell lymphoma (DLBCL). Additional bone marrow and crista biopsy confirmed the diagnoses DLBCL. PET-scan revealed FDG uptake in the lymphnodes left inguinal, in pelvis, abdominal, mediastinal and in the right ventricle. The right ventricle involvement has been interpreted as a secondary cardiac lymphoma. Further the spinal tap and histological examination showed also secondary CNS lymphoma (DLBCL). After treatment with 6 cycli of R-CHOP, all lesions inclusive the right ventricle lesion disappeared.

Discussion: The symptoms of cardiac lymphoma are nonspecific. It may present with heart rhythm disturbance, episodic syncope, VCSS or respiratory distress. However usually patient present with dyspnoea, chest pain or pericardia effusion. The right atrium and right ventricle are preferentially involved by systemic lymphoma. The most effective treatment is chemotherapy. Palliative surgery may be necessary when the blood flow is disturbed.

Cyclic thrombocytopenia: a rare cause of thrombocytopenia

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Case: A 61-year-old woman presented with thrombocytopenia and petechiae. She had no history of thrombocytopenia or bleeding episodes and did not use any medication. On physical examination there was no lymphadenopathy and no hepatosplenomegaly.

Laboratory investigations showed isolated thrombocytopenia (thrombocytes $38 \times 10^9/L$). Further laboratory investigations were within the normal limits. Other investigations to rule out secondary causes of thrombocytopenia were negative. Therefore the diagnosis immune thrombocytopenic purpura (ITP) was made. The patient was treated with daily prednisolone 1 mg/kg. Within days the platelet count increased up to $> 600 \times 10^9/L$. During the following months the platelet count fluctuated from severe thrombocytopenia to high platelet levels ($> 1000 \times 10^9/L$), not related to the prednisone dosage. Due to persistent platelet count fluctuations despite therapy, the prednisone was discontinued. However platelet fluctuations were still present. Bone marrow aspiration and biopsy demonstrated atypical megakaryopoiesis and no other pathology.

Clinical observation and weekly platelet measurements revealed an independent cyclic fluctuation in platelet count, consisting with a cyclic thrombocytopenia (CTP). Remarkably simultaneously measured thrombopoietin, megakaryocyte growth and development factor, levels also fluctuated, inversely proportional with the platelet levels.

Discussion: CTP is a rare condition, characterized by periodic rebound fluctuations in platelet count, not responding on corticosteroid treatment. Mostly no treatment is warranted. The exact pathogenesis of CTP and, whenever needed, most effective treatment is still unclear. Despite its rarity CTP should be included in the differential diagnosis of thrombocytopenia.

Acute myeloid leukemia presenting as acute T-cell leukemia

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Case: we present a 31-year-old woman referred to the emergency department with fatigue, shortness of breath, night sweats and abdominal pain in the right upper quadrant. On physical examination, there were decreased breathing sound in the lower left part of the thorax. Laboratory testing showed leukocytosis of $65 \times 10^9/L$ with 80% blasts, immunophenotyping concluded an acute myeloid leukemia (AML). X-thorax showed hilar and mediastinal lymphadenopathy with left sided pleural effusion. On CT-thorax/abdomen lymphadenopathy and pleural effusion was confirmed as well as lesions in the liver and mammae. Bone-marrow biopsy and pleural fluid analysis confirmed the diagnosis. Further immunophenotyping made clear there was an aberrant expression of CD7 (a T-cell-marker). The absence of CD3 excluded possibility of an acute T-cell lymphoid leukemia, while clinical evaluation and bone marrow morphology suggested otherwise. We treated her with idarubicin and cytarabine ("3+7") on which she accomplished complete remission and she will be prepared to receive an allogenic stem cell transplantation.

Genetic evaluation showed a translocation $t(10;11)$ which may lead to fusion of the AFI10 and CALM-genes and is associated with multiple different variations of leukemia. This suggests the genetic abnormality arises in early hematopoietic cells who can differentiate down several paths or that this translocation occurs down several lines with a hematologic malignancy as a result. Diagnosis of hematologic malignancies in the 2016 WHO-classification is largely based on genetics and molecular diagnostics. It is interesting that clinical presentation and bone marrow morphology can point in the wrong direction.

Rare extramedullary localization in chronic lymphocytic leukemia

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Case: A 57-year-old male with a history of ulcerative colitis was diagnosed with chronic lymphocytic leukemia (CLL), RAI stage 0. Cytogenetics revealed a 13q deletion with an unmutated IgVH status. There was no treatment indication. Two years later, the patient developed diarrhea. During colonoscopy a moderate to severe pancolitis was seen, suspected for an exacerbation of ulcerative colitis. Besides signs of active ulcerative colitis, biopsies showed diffuse lymphocytic infiltration suspected for a localization of CLL based on the immunohistochemical staining pattern (CD20+, CD5+, CD23+). The patient was administered mesalazine upon which the diarrhea improved. Repeated colonoscopies with biopsies after 3 and 6 months showed mild chronic active inflammation and no active inflammation, respectively. The lymphocytic infiltrates persisted. In 3 years, the leucocyte count gradually increased from $20 \times 10^9/L$ at diagnosis to $70 \times 10^9/L$ now. The patient is still asymptomatic and there is no anemia or thrombocytopenia. Follow-up CT scan 2 years after diagnosis showed progressive lymphadenopathy at both sides of the diaphragm with the largest lymph nodes measuring 17 mm. No hepatosplenomegaly was seen. So far, no treatment for CLL is initiated.

Conclusion: Gastrointestinal involvement in CLL without Richter transformation has rarely been reported in literature. We present a CLL patient who is still asymptomatic one year after colonic infiltration was detected. Current CLL staging and treatment guidelines do not take into account the presence of extramedullary localizations. The impact on disease course and prognosis is unknown. This case shows that asymptomatic patients with colonic involvement can be safely monitored without treatment.

Native aortic valve endocarditis with *Morganella morganii* in a patient with multiple myeloma and valvular amyloidosis

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Introduction: Patients with multiple myeloma (MM) are known to be immune incompetent and experience higher incidences of infectious diseases. However, infective endocarditis (IE) is rarely observed in patients with MM and *Morganella morganii* (*M. morganii*) has never been associated with IE.

Case: A 72-year-old female receiving 4th line treatment for MM presented with fever and concomitant confusion. Urinary culture revealed growth of *E. coli*, wherefore broad-spectrum penicillin and high-dose corticosteroids were initiated. However, blood cultures showed growth of *M. morganii*. Fluoroquinolone was added due to penicillin-resistance of the *Morganella* species. Two days after admission, the patient acutely deteriorated with hemodynamic instability. Gentamicin and high dose corticosteroid were added. Echocardiography showed marked aortic valve vegetation, leading to the diagnosis of bacterial endocarditis of the native aortic valve. One year prior to admission, echocardiography had shown structural normal heart and valves. Shortly after diagnosis, the patient died. At autopsy, vegetation with gram-negative rods in the native aortic valve was observed, confirming the diagnosis of *M. morganii*-endocarditis. Additional staining for amyloid confirmed advanced light-chain (AL) amyloidosis with extensive amyloid depositions of the aortic valve and valvular damage as complications of her MM.

Discussion: Our case suggests that IE with *M. morganii* was facilitated by the combination of the cardiac amyloidosis with valvular impairment and the profound immune deficiency caused by the several chemo-immunomodulatory treatment lines and the MM itself. This case further illustrates that awareness for rare opportunistic infections in an era with growing potential of combined chemo-immunotherapy is warranted.

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An unusual case of neuropsychiatric Systemic Lupus Erythematosus

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Case: a 59-year old Moroccan male with history of knee arthritis had been analyzed because of weight loss and decreased appetite for 4 months. Laboratory tests showed high erythrocyte sedimentation rate (ESR), microcytic anemia, and leucopenia. An extensive diagnostic work-up revealed no infection or malignancy. A high anti-ds DNA pointed towards an auto-immune disease. Then, the patient was hospitalized with acute onset of confusion, apathy, hallucinations, tremor, and pleuritis. A MRI scan showed aspecific hyperintensities of the cerebral white matter. Liquor protein levels were high, Polymerase Chain Reaction (PCR) and cultures for microbial pathogens were negative. There were no paraneoplastic neuronal antibodies detectable in peripheral blood. Electroencephalography (EEG) showed diffuse encephalopathy. The diagnosis systemic lupus erythematosus (SLE) was made in accordance with the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria: arthritis, serositis, leucopenia, positive ANA and anti-ds DNA tests, low serum complement, antiphospholipid antibodies, and a positive direct Coombs test. The neurologic symptoms were defined as neuropsychiatric SLE. The patient was treated with methylprednisolone 1000 mg per day intravenously. After three days he could have a normal conversation, and began to eat again. The treatment was continued with prednisone 60 mg/day and cyclophosphamide intravenously.

Discussion: Neuropsychiatric SLE may have a heterogeneous presentation including hallucinations and apathy. Cutaneous manifestations may be absent. SLE should be considered when a patient presents with a combination of somatic and psychiatric symptoms, even if a patient does not fit the characteristic profile. Brain imaging, liquor diagnostics, and specific auto-antibodies may point towards neuropsychiatric SLE.

Type IV allergic reaction after cosmelan treatment

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A 27-year-old otherwise healthy woman presented to the emergency department with a facial rash and oedema. She had been treated two days before with Cosmelan (Mesoestetic Pharmagroupâ), a cosmetic face mask that is advertised by the company to 'reduce and eliminate skin blemishes of melanic origin'. After application of the mask she experienced slow progression of swelling of the face and a burning sensation. A few hours before presentation her eyes and lips started to get swollen as well. She did not experience any shortness of breath.

Physical examination revealed severe oedema and erythema of the face, the forehead showed crustae with a yellow exsudate. She could barely open her eyes. Her tongue appeared normal and endoscopic examination of the larynx showed no swelling of the vocal cords. The patient was diagnosed with allergic contact dermatitis, a delayed type hypersensitivity reaction (type IV) due to Cosmelan.

She was initially treated with intravenous hydrocortisone and clemastine. After consultation with a dermatologist topical clobetasole was also applied.

After one night of observation and treatment the swelling was significantly diminished and the patient could be discharged. She was referred for allergy testing.

Allergic contact dermatitis can be evoked by thousands of substances. It is important to distinguish allergic contact dermatitis from irritant contact dermatitis, because severe allergic contact dermatitis should be treated with steroids and there can be a risk of anaphylactic shock.

Atypical pneumonia with dramatic sequelae

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Introduction: Atypical pneumonia accounts for up to 20% of community-acquired pneumonias. Immune phenomena have been described in atypical pneumonia, including hemolysis, cardiac disease, and central nervous system (CNS) involvement. In this case, we present a rare complication of *Mycoplasma pneumoniae* infection.

Case: A 39-year old male with a history of asthma was admitted to the hospital with bilateral pneumonia not responsive to 4 days of antibiotic therapy by the primary physician. Antibiotic treatment was intensified without response. Four days after admission the patient complained of loss of motor function in his lower extremities, rapidly followed by loss of sensibility and absent control of bladder and bowel function. Magnetic resonance imaging (MRI) showed signal abnormalities on level Th1 to Th9, consistent with transverse myelitis. Shortly thereafter, serology and PCR on sputum showed *Mycoplasma pneumoniae*. Antibiotic treatment was switched and the patient received pulse therapy with methylprednisolone during 5 days. Three days after initiation of methylprednisolone there was no improvement of CNS symptoms and plasma exchange was added. Follow-up MRI showed ongoing edema in the myelum therefore prednisolone was switched to dexamethasone and cyclophosphamide was added. Currently, after two weeks of therapy, there is minimal improvement in sensibility and still no improvement in motor function.

Conclusion: Transverse myelitis is a rare complication of *Mycoplasma* infection that clinicians treating pneumonia must be aware of. Pathogenesis is uncertain, possibilities include direct infection and an immune-mediated reaction by molecular mimicry. Therapy is directed to both and outcomes vary from permanent disability to complete recovery.

Pulmonary hypertension with an unexpected cause

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Introduction: The etiology of pulmonary hypertension (PH) is diverse. Here, we present a case in which PH led to discovery of an unexpected disease.

Case: A healthy 62-year old woman was admitted to the Intensive Care Unit with acute respiratory distress needing extracorporeal membrane oxygenation (ECMO). Chest X-ray was normal, CT-angiography showed right ventricular overload which was confirmed with transthoracic cardiac ultrasound (right ventricular pressure 82 mmHg) leading to the diagnosis of PH. Cardiac function was normal. Further work-up consisted of exclusion of connective tissue disease (negative patient history and serology), exclusion of lung disease and pulmonary embolism (COPD GOLD II with a history of smoking and dubious embolism on CT, both insufficient explanation of high right pulmonary arterial pressure). Additional diagnoses were *Pneumocystis jirovecii* pneumonia and Cytomegalovirus pneumonitis and retinitis leading to a suspicion of acquired immunodeficiency syndrome. Indeed, HIV serology was positive with a viral load of 7.7×10^5 copies/mL and CD4 count of 83×10^6 /L. She was treated with sildenafil and macitentan for PH and dolutegravir and emtricitabine/tenofovir disoproxil for HIV with favorable response. In retrospect, HIV infection was probably caused by contact with an infected needle during her work in a pharmacy in 1999.

Conclusion: HIV infection is a rare cause of PAH. Numerous HIV relating factors and host inflammatory cytokines can induce a procoagulant state and increase the expression of endothelial adhesion molecules and accumulation of inflammatory cells in the pulmonary arteries. HIV-testing must be included in the work-up of PH in the absence of known risk factors.

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An adult case with shigellosis-associated encephalopathy

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A 45-year-old man was presented at the emergency department with altered neurologic status and a one-day history of diarrhea and fever. The patient's sexual history revealed multiple male partners. As bacterial meningitis or viral encephalitis was suspected, treatment was started accordingly. Cerebrospinal fluid investigations only showed a slight increase of leucocytes and microbiological studies remained negative. Stool culture revealed *Shigella flexneri*, after which *Shigella* associated encephalopathy was suspected. The patient recovered quickly with antibiotic treatment. The incidence of *Shigella* infections in the Western world is rising due to sexual transmission among men who have sex with men. *Shigella*-induced encephalopathy is a notorious complication among children with a severe form known as the Ekiri syndrome, though rarely seen in adults. This is the second report of encephalopathy in an adult with *Shigella flexneri* enteric infection.

An adult with a primo varicella-zoster infection and pneumonia

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We present a 36-year-old woman who was born and raised in Hongkong but was living in the The Netherlands since she was 20. She complained of dyspnoea and had an itching rash with vesicals on face, trunk and extremities. She could not recall of ever having an episode of chickenpox. On physical examination there were partially dried up vesicles on face, trunk and both arms. She had a fever, was hypoxic and crackles over both lungs were heard on auscultation. Lab results showed a CRP of 51 and a hepatitis. Chest x-ray and CT revealed bilateral pulmonary infiltrates. PCR of a throat swab as well as vesical fluid was positive for varicella-zoster virus (VZV). She was admitted with a VZV primo-infection complicated by a pneumonia and hepatitis. She was admitted tot he ICU for one day because of pending exhaustion but intubation was not necessary. The patient was successfully treated with aciclovir. After four days she could be discharged in a decent clinical condition. Adult VZV primo-infections are uncommon in Dutch natives but occur more often in immigrants from countries with a temperate climate where less people are infected during childhood With the ongoing globalization it is important for healthcare workers in the The Netherlands to be aware that this infection also occurs in adults with a higher mortality and morbidity than in children.

Night fever

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Case: a 64-year old male was referred to the out patient clinic with a daily fever, night sweats and weight loss. The fever was preferentially present in the evening and night for the last six weeks. He had lost eight kilograms in weight. Before these symptoms started he had been on a holiday in Italy where he had been in contact with goats. The years before he had been in several countries in Africa.

Physical examination was unremarkable except for an enlarged spleen and a fever. Laboratory studies showed increased inflammatory parameters and liver enzymes. Blood cultures and extended microbiology studies including *Coxiella burnetii* serology were all negative. PET/CT-scan showed an enlarged spleen of 18 cm with enhanced FDG-uptake.

Because of clinical deterioration and a developing pancytopenia a histological biopsy of the spleen was performed. Standard hematoxylin and eosin staining showed the presence of abundant *Leishmania* parasites. PCR investigation to determine the subspecies is performed. The results are not yet known. This will tell us if he was infected during his recent stay in Italy or earlier in Africa. The patient is treated with liposomal amphotericin B with regression of his symptoms and improvement of his pancytopenia.

Case report: Scrub typhus

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Case: A 53-years patient presented with fever, myalgia and diffuse headache as most dominant symptom. His medical history was unremarkable without use of any medication. Seven days before the onset of symptoms he had returned from Cambodia. He was in Cambodia on holiday for 14 days, during which he stayed some days in a jungle. Physical examination revealed fever (T 38.9°C) with no further abnormalities, especially no rash or eschars. Laboratory investigation showed thrombocytopenia ($72 \times 10^9/L$), and mildly elevated liver enzymes. Microscopic blood examination for malaria was negative. Serologic tests for dengue and leptospirosis were negative. Further close questioning revealed that the patient also had visited rice fields during his trip in Cambodia. Regarding this new information, the possibility of scrub typhus was raised. IgM anti-*O. tsutsugamushi* was positive, thus confirming the diagnosis of scrub typhus. The patient was treated with doxycycline for seven days. The fever and other symptoms disappeared. The thrombocytopenia resolved.

Discussion: Scrub typhus is an infectious disease caused by the Gram-negative bacterium *Orientia tsutsugamushi*. It is primarily distributed throughout the Asian pacific rim. The vector and reservoir of *O. tsutsugamushi* are larval trombiculid mites, also called chiggers. While these mites typically are found in areas of heavy scrub vegetation, rice fields are an under-appreciated location where the biting of mites and transmission of *O. tsutsugamushi* occurs in the endemic areas. Furthermore the presence of rash and eschars are not mandatory for diagnosis of scrub typhus.

Evaluation of a continuous infusion protocol for vancomycin: checking protocol adherence and efficacy

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Background: It is known that dosing vancomycin is difficult, due to the interpatient variations and the risk of toxic and sub-therapeutic levels. No optimal dosing protocol has been yet found. In 2014, the Canisius Wilhelmina Hospital created their own detailed continuous infusion (CI) protocol, based on a loading and daily dose. The aim of this study was to perform an evaluation of this protocol, by: (i) determining the protocol adherence; (ii) checking protocol efficacy in both adherence group and non-adherence group and (iii) defining patient factors in the adherence group, associated with insufficient vancomycin levels.

Methods: Patients were enrolled, if treated with the vancomycin CI protocol between February 2014 and May 2017. Information was extracted from the patient files and the pharmacy records. Serum vancomycin concentration was taken daily and an adequate concentration was defined as 20-25 mg/L. Differences were assessed using the Chi-squared test, Fisher's exact test, unpaired T-test or Mann-Whitney U test.

Results: 88 patients were included. Thirty-six patients received protocol-care up to the first serum concentration (41% of total) and 25 up to the second serum level (29%). In the correctly dosed patients, 92% of the first serum concentrations were below range and 48% of the second. Younger age was associated with insufficient vancomycin levels (68 versus 80 years, $p=0.044$).

Conclusions: The protocol adherence was low and correct application of the protocol resulted in low serum concentrations. Thus, protocol adherence needs to be improved and higher doses are needed to improve the protocol efficacy.

A *Nocardia farcinica* mycotic aneurysm as a rare cause of subacute disseminated disease

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A non-immunocompromised 73 year old male was admitted with fever and skin lesions, one week following placement of left common iliac artery vascular graft. Endocarditis was suspected, but not proven despite multiple blood cultures and echocardiograms. Skin biopsy of the lesions suggested infection but no pathogen was found. Patient clinically improved on short treatment with vancomycin and cefuroxime

Several months later, he was re-admitted with recurrence of the skin lesions, now accompanied by back pain. Again blood cultures, skin biopsies and echocardiograms were unsuccessful in finding a culprit. Vertebral osteomyelitis was suspected, a biopsy of the vertebra was performed but histology did not bring about a diagnosis. Patient was referred to a tertiary center where a PET-scan was executed, which showed a mycotic aneurysm at the site of the vascular graft with also high uptake in the lungs, vertebrae L5 and S1, and peripheral blood vessels and soft tissue of the legs. The mycotic aneurysm, including the graft, was surgically removed. Culture of the graft revealed *Nocardia farcinica*. Patient was treated successfully with meropenem and TMP-SMX, based on susceptibility testing.

Even though *Nocardia* spp are a rare cause of disseminated disease, it should be suspected in patients with difficult-to-control infections where no pathogen is found, in particular when immunocompromised. *Nocardia* is hard to isolate through non-invasive measures and has a tendency to relapse despite appropriate therapy. Furthermore, even though two-third of patients with disseminated nocardiosis are immunocompromised, it can occur in healthy individuals, especially after placement of a foreign body.

Respiratory failure and rhabdomyolysis as presenting symptoms of Leptospirosis in a non-travelling patient

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Case: A 71 year old man was presented to the emergency room with shortness of breath, fever and myalgia. There were no expositions to Legionella, he had not travelled abroad. Physical examination revealed a patient with fever and respiratory failure.

Laboratory results demonstrated acute renal insufficiency, elevated liver enzymes with a remarkably elevated bilirubin (76 $\mu\text{mol/L}$) and creatine kinase of 9683 U/L. Arterial blood gas analysis showed a respiratory alkalosis, hypoxia and an elevated A-a gradient. Chest X-ray revealed diffuse consolidations. The patient was admitted to the ICU under the suspicion of a pneumoseptic shock with multi organ failure and was treated with cefuroxime, ciprofloxacin, vasopressive agents and was put on a mechanical ventilator.

All microbiological studies including CMV, EBV, HIV and mycobacterial PCR testing were negative.

There were no signs of liver failure and abdominal ultrasound was normal.

After 4 days, the patient slowly improved. As often, a detailed history led to the final diagnosis; the patient worked in a kitchen garden with stagnant water where rats were seen. Leptospirosis was confirmed by PCR.

The incidence in the The Netherlands is only around 30 patients/year, ' after travelling. Treatment consists of 7 days of benzylpenicillin and supportive measures.

Conclusion: Leptospirosis in the The Netherlands is rare, especially in non-travelling patients. It can cause fever, respiratory failure, renal insufficiency, jaundice and hemorrhagic diathesis. Rhabdomyolysis is frequently reported. Exposition to stagnant water should raise suspicion for Leptospirosis.

Does your dog bite?

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Case: A 38 year old man with no relevant medical history was admitted to the emergency department with abdominal pain, vomiting, and diarrhea. Patient had signs of cyanosis and petechia on his fingertips. Heart rate was 111 beats/min, blood pressure 140/100 mmHg and no fever. C-reactive protein was 450 mg/L, white cell count 26×10^9 , creatinin 248 $\mu\text{mol/L}$, and Hb 9.8 mmol/L. Notably, platelet count was 7×10^9 , and blood smear showed schistocytes. Direct coombs test was negative. D-dimer was strongly elevated (21 mg/L), fibrinogen was 2.0. A CT scan of the abdomen showed no abnormalities. As diagnosis we considered sepsis with disseminated intravascular coagulation (DIC) or thrombotic microangiopathy (TMA), such as thrombotic thrombocytopenic purpura (TTP), or shiga toxin-mediated hemolytic uremic syndrome (ST-HUS). He was transferred to the ICU and treated with ceftriaxone, inotropics and plasmapheresis. ADAMSTS 13 concentration was 26%, which made TTP highly unlikely. Patient fully recovered following this treatment regimen. Later, blood culture showed capnocytophaga canimorsus. The patient told us that he was bitten by his dog. Nevertheless, he still keeps the picture of the dog next to his bed.

Discussion: Capnocytophaga canimorus is a bacterial cause of fulminant sepsis caused by dog bites. It is highly rare, most common in immunocompromised patients and the fatality rate in case series is as high as 28-31%. Growth in culture is slow, blood cultures require a mean incubation period of six days. Treatment consists of a beta-lactam-beta-lactamase combination, cephalosporin or carbapenem.

Gardnerella Vaginalis infection in an immunocompromised male patient

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Case: A 69-year-old man was admitted to the emergency room suffering from severe pain in both hip joints and pelvic area whilst walking and standing up. The pain had started 1.5 weeks ago after a long walk and worsened over time. He had a medical history of diabetes mellitus and prostate cancer, cured by surgery and radiotherapy. Physical examination was unremarkable and laboratory results showed increased inflammatory markers, otherwise normal. A CT-scan of the pelvic area showed arthrosis of the symphysis and both hip joints, but no signs of metastasis or inflammation. The urine culture returned negative. After pain treatment the patient was discharged.

Six weeks later the patient returned because of increasing pain in both hips and the pelvic area, while being treated with prednison by his general practitioner. An MRI scan than revealed a septic arthritis of the symphysis pubis and abscesses, located in the pectineus muscle of both legs. Percutaneous drainage was performed. From cultures of both urine and abscess fluid, *Gardnerella Vaginalis* was identified using MALDI-TOF mass spectrometry. The patient was treated with oral metronidazole, after which he recovered fully and the pain disappeared.

Background: *Gardnerella Vaginalis* infection is a sexually transmitted disease which is rarely diagnosed in immunocompromised men. Few cases have been reported, most of them in HIV-positive patients. Like non-recurrent bacterial vaginosis in women, *Gardnerella Vaginalis* infection in men is well treated with metronidazole.

Conclusion: *Gardnerella Vaginalis* infection is rarely diagnosed in immunocompromised male patients and can cause severe septic complications.

Rickettsia typhi recrudescence during secukinumab treatment

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Case: A 48-year old man with a history of psoriasis for which he used secukinumab (interleukin-17A inhibitor) since 14 months, presented with coughing, fever, dyspnea, myalgias, severe headache and nights sweats. He had returned from a trip to Indonesia five months earlier. Except for fever, physical examination revealed no abnormalities. Bloodwork showed slight elevation of C-reactive protein (CRP) and liver enzymes. Computed tomography (CT) of the abdomen and thorax showed no signs of infection. Tests for malaria, HIV, hepatitis, tuberculosis, CMV, EBV, toxoplasmosis, brucellosis and leptospirosis were negative. The patient was admitted to the hospital; blood and urine specimens were obtained for culture. During admission high temperatures persisted and liver enzyme abnormalities increased. A brain CT was normal; cerebrospinal fluid analysis revealed normal white-cell counts, protein and glucose levels. The secukinumab was discontinued. Cefuroxime and gentamycin were administered and later switched to flucloxacillin due to positivity of 3/4 blood culture bottles with *Staphylococcus epidermidis* (deemed as contamination). PET-CT revealed the presence of cervical lymphadenopathy, avid hilar lymph nodes, an enlarged and activated spleen and activated bone marrow, suspicious for infection. A biopsied cervical lymph node was reactive. Serological assessment eventually revealed a positive IgG level for *Rickettsia typhi* (>1:256) with negative IgM. Treatment with doxycycline was initiated which resulted in full recovery.

Discussion: The incubation time of typhus infections is 1-2 weeks but recrudescence of epidemic typhus (*Rickettsia prowazekii*) can occur years later during immune suppression, known as Brill-Zinsser disease. This phenomenon has not yet been described for *Rickettsia typhi*.

Myobacterium malmoense tenosynovitis in a kidney transplant recipient

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A 74-year-old male kidney transplant recipient (21 years after transplantation) receiving triple immunosuppressive therapy presented with a recurrent painful swelling of the right wrist. He had no history of wrist trauma or overexertion. Physical examination revealed a tenosynovitis of the right wrist.

Two years prior to this presentation, he suffered a similar episode, which resolved after treatment with amoxicillin/clavulanate during 14 days. Despite this antibiotic regimen, he continued to have wrist pain. For diagnostic purposes a synovectomy and carpal tunnel release was performed.

Treatment with penicilline intravenously was initially started and later discontinued because synovial fluid obtained for microbiological analysis during synovectomy remained negative.

Biopsy of the synovium showed active chronic fibrinous inflammation with extensive granulomatous inflammation. The initial culture was negative for mycobacterium. And after 7 weeks of incubation a *M. malmoense* was identified in the culture.

Based on resistance testing treatment with rifampicin, azithromycin and ethambutol was started.

M. malmoense is a slow-growing nontuberculous mycobacterium (NTM) and requires an incubation time of 6-12 weeks before growth is observed. Clinical suspicion is essential for the diagnosis as histological and microbiological examinations require specific handling which is not routinely performed. Due to lack of clinical suspicion, diagnosis is often delayed and a negative history of trauma should not distract from the possibility of a NTM synovitis.

Conclusion: NTM infections should be considered in immunocompromised patients with treatment resistant tenosynovitis.

A diabetic ketoacidosis with an extraordinary twist

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Case: A 51-year-old Nigerian immigrant, with a medical history of diabetes mellitus, was presented at the emergency department with malaise and vomiting. On physical examination a moderately ill patient was seen. Laboratory results revealed a diabetic ketoacidosis (DKA) with a glucose level of 23.4 mmol/l, pH of 7.23 and bicarbonate level of 9.9 mmol/l. In addition, an Hb level of 5.9 mmol/l, thrombocytopenia of $71 \times 10^9/l$, elevated liver enzymes with a LDH of 775 IU/L and a normal haptoglobin level were observed. Kidney function was normal. Treatment with intravenous fluids, potassium and insulin was started. Thereafter the laboratory reported that malaria parasites were seen in the white blood cell differential count. A blood smear detected *Plasmodium falciparum* with a density of 12.5% of parasitized red blood cells. Treatment with intravenous artesunate was started. Initially, the patient reported no recent travel to Nigeria, later on this turned out to be one month ago. During admission the patient developed acute renal failure for which CVVH was started after which the kidney function recovered.

Discussion: This case illustrates an uncommon presentation of DKA, induced by a severe *Plasmodium falciparum* infection. It underlines the importance of malaria suspicion as a cause of acute illness in immigrants of malaria-endemic countries, even when patients report they did not travel for a long time. The pathogenesis of acute renal failure in malaria infection is complex in which hemodynamic and immunological factors play a role in the development of acute tubular necrosis, interstitial nephritis and/or glomerulonephritis.

Ossal lesions in secondary syphilis

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Case: A 57-year old female without relevant medical history presented with malaise, earache and hearing loss. Despite oral amoxicillin/clavulanic acid, she developed fever. Moreover, multiple erythematous maculae appeared on soles and palms. Physical examination revealed a new diastolic heart murmur. There were no clinical signs of otitis or mastitis and neurological examination was normal. C-reactive protein was elevated (210 mg/L), but blood cultures were negative.

Because of the combination of fever, a new heart murmur and the skin lesions, resembling Janeway lesions, endocarditis was suspected. However, transthoracic and transoesophageal echocardiography showed no valve vegetation.

Further diagnostic testing revealed the presence of treponemal antibodies and a positive rapid plasma regain (RPR) test (titer 1:128). The RPR test in cerebrospinal fluid was also positive. One month before, during regular control in the blood bank, serum RPR was negative. She was HIV negative. Thus, the patient was diagnosed with secondary syphilis with neurosyphilis.

In the diagnostic work-up, a PET/CT-scan was performed which, unexpectedly, showed localised high FDG-uptake in the skull, sternum, scapula and several ribs, without substrate on low dose CT-scan.

Discussion: We describe a case of a HIV-negative patient with ossal lesions in secondary syphilis. Although common in tertiary syphilis, bone involvement is rare in secondary syphilis. Only several other case reports describe PET-positive and/or lytic bone lesions in patients with secondary syphilis. The patient was successfully treated with penicillin. After two months, a PET/CT-scan was repeated. All bone lesions had disappeared.

A 52-year old male with severe, untreated cerebral malaria

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Presentation: A 52-year old male was presented at the emergency department after being found unresponsive at home by a neighbour. Communication with the patient was not possible due to his neurologic state. The patient had visited Ghana earlier that month and had not used malaria prophylaxis. At the time of presentation, he had been feeling unwell and had a severe headache for a week, yet refused to seek medical care.

Clinical findings: Upon presentation the patient was hemodynamically stable and had a glasgow coma score of 3-5-3. Physical examination did not show any other abnormalities; liver and spleen were not enlarged.

Diagnostic tests: Initial blood tests showed a mild anemia (Hb 7.5 mmol/L), leukocytosis (18.3 mmol/L), acute kidney failure (creatinine 132 umol/L) and metabolic acidosis (pH 7.29, lactate 12.7 mmol/L). Blood film examination showed presence of plasmodium falciparum. The parasite load was 4.4%.

Interventions: The patient was admitted to the ICU and was treated with fluid resuscitation, hydrocortisone and artesunate.

Clinical outcome and conclusion: Despite the aggressive initial treatment, the condition of the patient deteriorated rapidly after admission. He developed respiratory failure, anuric kidney failure and disseminated intravascular coagulation. Therefore the patient was intubated, put on continuous renal replacement therapy and received epinephrine. The parasite load had increased to 27.6% upon re-evaluation. We believe that the first parasite load was underestimated due to poor circulation. Preparations for exchange transfusion were made, but unfortunately the patient passed away during these preparations.

Case report: 'He is sleeping with the fishes'

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Case: A 69 year old man presented with an erythematous, painful, edematous right hand and fore-arm. Despite oral treatment with various antibiotics and corticosteroids symptoms worsened. The patient developed subcutaneous nodules and decreased movement of the right wrist. MRI revealed a tenosynovitis of the extensor digitorum longus, with inflammation of the subcutis and cutis. An excision biopsy of the extensor tendons was performed. Histology showed chronic granulomatous inflammation. Auramine, Ziehl-Neelsen stain, bacterial culture and mycobacterial PCR results were negative. Laboratory results, chest X-ray and a second biopsy were unremarkable. On the ¹⁸F-FDG-PET scan there were no other sites of high FDG uptake. Because no underlying cause was identified, a third excision biopsy was conducted by the plastic surgeon and deep muscle and tendon cultures were taken. These cultures revealed multiple colonies of *Mycobacterium marinum*. In conclusion our patient was suffering from a *Mycobacterium marinum* tenosynovitis. This fits with the fact that the patient was keeping a tropical aquarium. Treatment consisted of azithromycin and ethambutol for 5 months. After treatment the patient fully recovered.

Discussion: In most cases infectious tenosynovitis is caused by gram positive cocci. Although rare, infectious tenosynovitis can be caused by *Mycobacterium marinum* and is most often related to fish tank exposure. Long-term treatment with antibiotics is required.

Conclusion: This case illustrates that diagnosis of infectious tenosynovitis might be a daunting process. Persistence and conducting a thorough anamnesis can be of great value and rewarding for both patient and physician.

Backpain and fever in an immunocompromised patient returning from Mecca: A rare case of Salmonella aortitis

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Case: a 62-year old immunocompromised male was admitted with fever and abdominal pain without changes in defecation pattern. He visited Mecca a few weeks before. Medical history mentioned DM, M. Crohn treated with mercaptopurine and infliximab, ileocecal resection, Leriche's syndrome and diabetic CKD. Soon after admission bloodcultures grew Salmonella non-Typhi, treatment with ceftriaxone was initiated and immunosuppressive drugs were ceased. CT abdomen showed a cholecystitis; gallbladder drainage was performed. Antibiotics were switched to meronem after ESBL E.coli grew in the gallculture. Fourteen days after initiation of broadspectrum antibiotics he showed recurrent fever with concomitant abdominal- and back pain. Echo and MRI spine showed no abnormalities, meronem was withdrawn because of possible medication induced fever. Bloodcultures remained negative. Fever disappeared after 5 days and re-appeared after 9 days, on day 28th. Meronem was reinitiated, bloodcultures showed recurrent bacteraemia with Salmonella non-Typhi, which raised the possibility of a persistent focus. Also, there was persistent unexplained abdominal- and backpain. Urgent echo abdomen and echocardiography were normal. While waiting for PET-CT, CT-abdomen was repeated and now showed an infrarenal aortitis, mycotic aneurysm and covered rupture. Emergency surgery was performed with implantation of an aorta-bifurcation prosthesis, post-operative ceftriaxon was continued 6 weeks. He is currently on hemodialysis after occlusion of the left anastomosis.

Discussion: In patients with Salmonella bacteraemia in combination with fever, back- or abdominal pain, infectious aortitis should be considered. Particularly in immunocompromised or atherosclerotic hosts. Therapy ideally consists of endovascular aortic repair combined with long-term antibiotics. Mortality after surgery varies between 0-40%.

An unusual case of thrombosis, chest pain and a viral infection

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Case: A 27-year-old male with a history of an appendectomy presented to the emergency room with a left groin pain after a long cycling trip. The pain increased with pressure. Ultrasound and CT scanning showed thrombosis of the left testicular vein and a left-sided varicocele. A therapeutic dosage of rivaroxaban was prescribed for six months.

Four days later the patient developed a left-sided chest pain, increasing with deep breath. Vital signs were normal, including an oxygen saturation of 100%. Further physical examination was unremarkable. Blood results showed a mild leucocytosis ($11 \times 10^9/L$) with lymphocytosis (4×10^9), a CRP of 11 mg/L and slightly elevated liver enzymes. Angio-CT showed no sign of a pulmonary embolism, pericardial fluid or other abnormalities. The next day, the pain had substantially decreased.

Suspecting a case of pleurodynia epidemica, the doctor sent a faeces sample for PCR and it came back positive for Parechovirus.

On urologic follow-up, an echo of the kidneys, testicles and epidimytes showed no sign of malignancy. Thrombophilia screen was negative.

Conclusion: Thrombosis of the testicular vein is a rare event, associated with exercise, renal and testicular malignancies and with varicoceles. Thrombosis and varicocele are mainly left-sided because of stasis in the long testicular vein and, sometimes, “nutcracking” between the aorta and the superior mesenteric vein. There are indications of a thrombogenic effect of viral infections. We tentatively suggest a causal effect of the Parecho virus infection.

A *Clostridium perfringens* sepsis mimicking an acute hemolytic transfusion reaction

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Case: a 55-year old men was admitted 10 days after receiving his first cycle of chemotherapy (5-fluorouracil and irinotecan) for metastatic rectal cancer. He presented with painful swallowing and weight loss caused by a *Candida* infection. He was commenced on nystatine and enteral tube feeding. His analgesics were increased to relieve his abdominal pains caused by peritoneal metastases. After improving he received a second cycle of chemotherapy. We choose to transfuse our patient for a symptomatic anemia with an hemoglobin of 4.7mmol/l . After transfusion he developed a temperature of 38.5°C, but was otherwise stable. A second unit was withhold and blood cultures were taken. Laboratory investigation showed signs of hemolysis with an a LDH of 864U/l and an unconjugated hyperbilirubinemia. An acute hemolytic transfusion reaction was suspected and supportive care was administered. With increasing temperature as well as an increase of abdominal pain we also commenced our patient on piperacilline/tazobactam to cover him for a sepsis.

In the course of the evening he started vomiting blood and his hemoglobin dropped to 3.6mmol/l. We suspected bleeding from a Mallory-Weiss lesion and decided to transfuse a second unit of blood. This led to a second febrile episode and the patient condition deteriorated quickly. On his request we stopped all treatment and he died the same night. Post mortem the blood cultures came positive with an *Clostridium perfringens*.

Conclusion: a *Clostridium perfringens* sepsis can mimic an acute hemolytic transfusion reaction and should be considered in a patient with fever after transfusion.

A hidden guest in the chest

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Case: A 65-year old woman with a history of reumatoid arthritis, for which she used prednisolone and plaquenil, was presented at our Emergency Department with dyspnea, malaise, weight loss and a chronic wound of the foot. Physical examination showed a tachycardia (P120/minute) and peripheral edema. Laboratory studies demonstrated an anemia, inflammation, high nt-proBNP and cholestasis. Chest radiography demonstrated cardiomegaly. A bedside echocardiogram was conducted and revealed pericardial effusion without tamponade. Patient was admitted for pericardiocentesis which relieved the symptoms. Culture of the pericardial fluid and foot wound revealed a non-typhoidal Salmonella group D, while the blood cultures remained negative. Treatment with antibiotics was initiated.

During the hospital admission, the patient appeared to have several other complaints. A history of chronic wounds, oral ulcers, dysphagia and mononeuropathy of the right hand. Additional work up and the combination of symptoms met the criteria for polyarthritis nodosa, which was confirmed with histology. Treatment with steroids was started.

Discussion: This case illustrates an uncommon cause of pericardial effusion. Infections with non-typhoidal Salmonella are mostly restricted to gastrointestinal disease, cardiovascular manifestations may occur but are extremely rare. The importance of early detection is crucial, because non-typhoidal Salmonella pericarditis carries a high mortality rate.

Additionally, in any patient presenting with a Salmonella pericarditis/endocarditis, it is vital to consider an underlying predisposing condition like a systemic disease, immune deficiency or immunosuppressive treatment

Conclusion: This case demonstrates that pericardial effusion can be caused by non-typhoidal Salmonella group D. Additional testing for potential underlying predisposing condition is recommended.

A severe case of leptospirosis

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A 71-year-old man was admitted to the intensive care with respiratory failure and septic shock. Mechanical ventilation, vasopressive medication and renal replacement therapy had to be commenced immediately. He was ill for a few days, had a fever and had been complaining of myalgia. Dyspnea started the day of admission and had rapidly worsened. Because a chest X-ray showed bilateral consolidations, broad-spectrum antibiotics were started to treat pneumonia. Laboratory findings showed leucocytosis, thrombocytopenia, high levels of creatine kinase and increasing hyperbilirubinemia. Therefore, we added leptospirosis to the differential diagnosis as the cause of acute respiratory distress syndrome or intra-alveolar haemorrhage. This diagnosis was confirmed by PCR.

The patient had not been swimming in open waters, nor had he been travelling or been in contact with rodents. Source research revealed that water from the Rhine river he used for irrigation of his vegetable garden was the most likely cause of the infection.

Leptospirosis seems to be an emerging zoonosis in the The Netherlands. Warm weather conditions, and flooding rivers can lead to an increase in infections. Most patients have self-limiting flu-like symptoms, but leptospirosis may also cause a fulminant septic shock syndrome with multi-organ failure. Mortality in these cases rises to more than fifty percent.

Conclusion: This case illustrates the potential serious complications of leptospirosis and makes clear that infections not only occur after swimming in open water or contact with rodents, but may also be the result of using infected water for irrigation purposes.

Imported yellow fever virus (YFV) infection from Brazil: are we facing urban transmission?

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A 46-year-old Dutch male patient presented on our outpatient tropical department due to fever, headache, myalgia, vomiting and diarrhea. For his work as a missionary, he had stayed in Brazil, in particular in Mariporã, a municipality in Sao Paulo metropolitan region. His illness started one day before departure back home. Physical examination revealed no relevant additional abnormalities. Laboratory tests showed mild thrombocytopenia, marked elevation of hepatic transaminases with normal bilirubin and moderately decreased renal function. Leukocyte counts and coagulation markers were normal. Real-time PCR detected YFV in urine, whole blood and plasma on day 4 after the onset of symptoms. He had no history of YFV vaccination. Upon hospitalization, he showed rapid recovery after symptomatic treatment.

YFV infection is a serious disease, possibly leading to high-grade fever, severe jaundice and multi-organ failure, with a case-fatality rate of up to 30%. No specific treatment is available. A large outbreak of YFV infection in 2016/2017 with 777 documented cases in Brazil has recently ended. However, circulation of YFV in the Sao Paulo metropolitan area since October 2017 has heightened attention of the Brazilian authorities with increasing fears for the establishment of an urban instead of the usual sylvatic (forest) transmission cycle involving *Aedes aegypti* mosquitoes. Currently, cases are reported from urban regions, like parks, which to date were not regarded as risk areas. Apart from possibly required modification of national Brazilian vaccination guidelines, this case illustrates the urgent need for YFV vaccination before travel to affected areas.

Pneumocystis Jirovecii Pneumonia (PJP) in an otherwise immune competent patient

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Introduction: immune compromised patients are at risk of PJP. Immune competent patients admitted with PJP warrants additional analysis. In our case we will describe diagnostic difficulties and pronounce to be alert of a second diagnosis.

Case: a 50-year old man was presented with shortness of breath, dry cough and weight loss. He also noticed intermittent arthritis, cutaneous manifestations and progressive muscular weakness. Physical examination: Temperature 40°C Celsius Saturation 80% while on Oxygen 15L/min NRM. Respiratory rate 30/min, bilateral pulmonary crackles. No skin abnormalities. Blood sample: Lactate dehydrogenase 1000 U/L (reference < 450 U/L) Creatine Kinase 200 U/L (reference <170 U/L). CT thorax: Extensive ground glass opacities.

Follow-up: He was intubated and mechanically ventilated. Broncho-alveolar lavage: PCR on PJP positive. Cotrimoxazole and Prednisolone were started. Additional diagnostics: HIV negative, antinuclear antibodies and rheumatoid factor negative. His situation declined. CT thorax: rapid progressive interstitial phenomena. Eventually oxygenation was hardly possible and veno-venous extra corporal membrane oxygenation (VV-ECMO) was considered. In the meantime a clinically amyopathic dermatomyositis (CADM) was confirmed by anti-melanoma differentiation associated gene 5 antibodies (MDA5ab). CADM is characterized by muscle weakness and cutaneous involvement which associates a rapid progressive interstitial lung disease with high mortality. Urgent therapy is indicated. Despite Methylprednisolone, Rituximab, Cyclophosphamide and Plasma exchange his condition declined. Because of poor prognosis VV-ECMO was not admitted. He soon died in company of his family.

Conclusion: this patient did not respond to PJP therapy because of a rapid progressive interstitial lung disease associated with amyopathic dermatomyositis.

There is mold that meets the eye

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A 42-year old woman was admitted to the intensive care unit with respiratory insufficiency after a recent bilateral lung transplantation, complicated by hyperacute rejection for which she was treated with high dose methylprednisolon. On day 28 after transplantation the patient developed transient blurred vision of the right eye. The ophthalmologist's examination showed no abnormalities but 11 days later re-fundoscopy showed extensive vitreous opacities, suggestive for endophthalmitis of the right eye.

Serum galactomannan testing and aspergillus Polymerase Chain Reaction (PCR) assay in bronchoalveolar lavage were positive. PCR tests and culture of the vitreous biopsy were positive for *Aspergillus fumigatus*, establishing the diagnosis of Invasive Pulmonary Aspergillosis (IPA). Treatment with systemic intravenous voriconazole plus intravitreal amphotericin B was started and immunosuppressive therapy was reduced. Unfortunately, patient lost total vision of the right eye, potentially necessitating enucleation.

Endogenous *Aspergillus* Endophthalmitis (EAE) is a rare but catastrophic complication in immunocompromised patients with IPA. The diagnosis of EAE is usually made after enucleation or during autopsy which in any case is too late for the treatment of the patient. A prompt diagnosis and treatment of EAE may reduce the risk of vision loss. This case illustrates the severe consequences of EAE in an immunocompromised patient. Blurred vision in patients at risk for invasive aspergillosis should raise suspicion for EAE and requires close attention and diagnostic testing.

When MAO is not functioning well

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Case: A 60-year-old woman, with a medical history of severe depression was presented at our emergency department after committing a suicide attempt. Physical examination during primary survey showed signs of a sympathomimetic toxidrome including tachypnea, tachycardia and agitation. Secondary survey unveiled that she had taken 80 tablets of tranylcypromine 45 minutes before arrival at the hospital. The diagnosis of a severe monoamine oxidase (MAO) inhibitor intoxication was made. Gastric lavage was performed immediately and charcoal was administered.

With the passing of time symptoms increased. Continuous shivering and hypertension were first to be noticed. Midazolam and phentolamine infusion were started. The blood pressure was manageable but muscle tonus was accumulating. Lockjaw occurred resulting in total respiratory insufficiency making intubation and sedation inevitable. Generalized myoclonus persisted. Electroencephalography (EEG) was performed to exclude epilepsy. Rocoronium infusion was then started resulting in relaxation of the muscles and decrease of remaining symptoms. In the course of the following days medication could be tapered off. Patient was extubated and could be transferred to a psychiatric ward with a mild remaining delirium. After three weeks of psychiatric treatment she was discharged from the hospital.

Discussion: This case shows the dangers of MAO inhibitor intoxication. It shows that we should not be misled by mild or absent symptoms at the first hours after ingestion. Although the half-life of the plasma concentration is 2.5h average, biological half-life is much longer. Any physician providing care involving psychiatric patients should be able to assess the dangers involving MAO inhibitor use.

Hunting a deadly chameleon

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Since October 2015 there has been an outbreak of the so-called original UK strain of the hypervirulent sequence type 11 clonal complex (cc11) of meningococcal serogroup W disease in the The Netherlands. From the 137 cases, 17 patients died. (1)

In a timespan of four months, two immunocompetent patients, aged 18 and 45 years old, presented to the emergency room with complaints of progressive arthralgias, gastrointestinal symptoms, with fast proceeding septic shock and multi-organ failure. Upon immediate antibiotic treatment with ceftriaxone and dexamethasone, with prompt resuscitation, intubation and ECMO support, 1 patient died and the other survived with severe multi-organ damage.

The similarities between the outbreak in England and the The Netherlands were striking, where there was a distributed age with peaks below 5 years old, adolescents, and an increasing incidence above 45-years old (1). The clinical picture can be misleading because of an atypical presentation with gastrointestinal symptoms, pneumonia, arthralgia and sepsis with high fatal rates.

In response to the outbreak, the public health care organization in the The Netherlands decided to replace the current MenC vaccination in 2018 with the quadruplevalent MenACWY vaccination for babies aged 14 months and offer it to children aged 12-14 years old.

To this end, heightened awareness of the potential rapid emergence and atypical presentation of meningococcal serogroup W disease is essential also for other countries in Europe and beyond to ensure early detection and public health response.

Bronnen:

Efficacy and Safety of an Individualised Phosphate Replacement Strategy for Severe Hypophosphatemia in the ICU

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Background: Experience with individualized phosphate replacement is limited in patients with severe hypophosphatemia. This study compares the efficacy and safety of an individualised regimen in ICU patients with a serum phosphate <0.4 mmol/L to that observed in patients with moderate hypophosphatemia (0.4-0.6mmol/L).

Methods: This retrospective cohort study included 36 patients with severe- and 35 patients with moderate hypophosphatemia. Supplementation dose was calculated according to the equation: Phosphate Dose (in mmol) = $0.5 \times \text{Body Weight} \times (1.25 - [\text{serum Phosphate}])$. Sodium-potassium-phosphate was infused at a rate of 10 mmol/hour. Blood samples were taken at baseline and the next morning at 06.00 a.m.

Results: Serum phosphate rose to a level >0.40 mmol/L in all patients with severe hypophosphatemia. Serum phosphate increased to a level >0.60 mmol/L in 56% of patients with severe hypophosphatemia and in 86% of patients with moderate hypophosphatemia ($P=0.01$). Mild hyperphosphatemia was observed in one patient only (1.53mmol/L), hyperkalemia was observed in three patients (all patients had severe hypophosphatemia, average potassium after supplementation was 5.2 ± 0.2 mmol/L), serum calcium levels remained unchanged in both groups.

Conclusion: Individualised phosphate replacement was effective and safe for both moderate and severe hypophosphatemia, but was more accurate in moderate hypophosphatemia.

Sepsis of unknown source: history taking revisited

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Case: A 48-year-old male was hospitalized with possible urosepsis with symptoms of fever, chills and suprapubic pain for three days. Physical examination showed hypotension (100/55mmHg), signs of delirium and several non-suspicious scratches on both legs. He has a history of alcohol abuse.

Laboratory on admission showed leucocytosis ($10.9 \times 10^9/L$), thrombocytopenia ($28 \times 10^9/L$), acute kidney injury (creatinine 328 $\mu\text{mol/L}$), elevated liver enzymes (ASAT 481 U/L, ALAT 201 U/L, LD 547 U/L, gGT 145 U/L, Total bilirubin 66 U/L, Alkaline phosphatase 66 U/L) and elevated CRP (319 mg/L). Urinalysis showed pyuria (>50 leucocytes/high-power-field).

The elevated liver enzymes and thrombocytopenia were attributed to alcoholic hepatitis, with possible cirrhosis and sepsis, and delirium provoked by alcohol withdrawal syndrome and sepsis. He was treated with 3rd generation cephalosporin, fluid resuscitation and benzodiazepines. As sepsis progressed (qSOFA 3), the patient required ICU admission. Blood- and urine cultures were negative. A CT-Abdomen was normal.

Considering the severe sepsis combined with acute kidney injury and elevated liver enzymes without evidence of cholangio- or urosepsis, we considered leptospirosis as a possible cause despite a negative travel history. History-taking with his girlfriend revealed that he had fallen in a canal in The Hague while intoxicated, one week before presentation. Antibiotic treatment was switched to penicillin and he gradually recovered with normalization of all laboratory parameters. A quantitative PCR for leptospirosis was positive in urine.

Conclusion: Leptospirosis is a rare infectious disease which can be acquired in the urban Western world. Medical history remains essential in ascertaining the source of sepsis.

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The many faces of thrombotic microangiopathy

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Background: Thrombotic microangiopathy (TMA) is a disease entity characterized by obstruction of the (micro) circulation with intravascular hemolysis as a consequence. This results in anemia, thrombocytopenia, and in severe cases organ failure. In this article we describe three cases to emphasize the variable clinical presentation.

Cases: Case 1 is a 76-year-old male with a medical history of pulmonary embolism, myocardial infarction, and granulomatosis with polyangiitis. On a regular outpatient visit, progressive renal failure and proteinuria was found without new complaints. Immunosuppressants were started, but GFR still decreased and proteinuria worsened. Renal biopsy showed TMA and plasma exchange was initiated. Together with strict blood pressure regulation, renal function stabilized and proteinuria improved. Case 2 is a 74-year-old male with in his medical history an ischemic cerebrovascular accident, B-cell lymphoma, and myocardial infarction for which he used clopidogrel. He presented at the emergency department with confusion, tiredness and headaches. The presence of anti-ADAMTS13 antibodies confirmed the diagnosis of Drug Induced TMA (DITMA). Clopidogrel was discontinued, and full recovery was established with plasma exchange and steroid treatment. Case 3, a 25-year-old female presented at the emergency department with a hypertensive emergency with retinopathy and end-stage renal disease. Hemolytic anemia and thrombocytopenia were also present. Antihypertensive treatment and plasma exchange was started and hemolysis had disappeared in two days.

Discussion and conclusion: Patients who are diagnosed with TMA can not only have different causes but also different presentations of disease. Quick recognition of the disease and immediate start with treatment is of vital importance.

Impact of arterio-venous fistula flow on ventricular contractility in hemodialysis patients – a cardiac magnetic resonance study

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Background: The arterio-venous fistula (AVF) in hemodialysis patients often leads to a substantial increase in cardiac output. The resulting high-output state can have detrimental effects in the long term. In this study the relation between AVF flow and ventricular contractility parameters was investigated using cardiac magnetic resonance imaging (CMR).

Methods: CMR was performed in 11 hemodialysis patients and 5 age-matched controls. CMR acquisitions were obtained prior to and after dialysis to differentiate between the effects of AVF flow and volume status (fluid overload). AVF flow, measured using ultrasonography, was used to subdivide the patients in Group 1 (low flow, <1000ml/min) and Group 2 (high flow, >1000ml/min). Short- and long-axis cine images were used for calculating global longitudinal strain (GLS), global circumferential strain (GCS) and global radial strain (GRS) with the tissue-tracking module of Circle Cardiovascular Imaging.

Results: There were no significant differences in the contractility parameters between the three groups prior to dialysis. Following dialysis, no significant changes in contractility were observed between Group 1 (n=5) and the control group (n=5). In comparison to the control group, patients in group 2 (n=6) had a significantly lower GLS (-14.2±2.3% vs. -20.4±3.3%, P<0.05), GCS (-13.5±1.6% vs. -22.3±2.1%, P<0.05) and GRS (23.3±4.7% vs. 45.0±8.4%, P<0.05) after the dialysis session.

Conclusion: These findings suggest that patients with high AVF flow are at an increased risk for developing ventricular dysfunction. Tissue-tracking analysis can be used to detect subtle early changes in contractility and could improve the diagnosis and prognosis of this patient group.

Falsely positive anti-glomerular basement membrane antibodies in a patient with hantavirus induced acute kidney injury – a case report

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Background: Hantavirus infection is an uncommon cause of acute renal failure with massive proteinuria. Serology tests to support a presumptive diagnosis usually takes a few days. During the initial work-up, autoimmune causes including anti-glomerular basement membrane (GBM) glomerulonephritis need to be excluded, because these require urgent therapy. In this case the delay in serological testing caused a dilemma in treatment initiation.

Case presentation: An 18-year-old patient was admitted to the hospital with acute renal failure, erythrocyturia and massive proteinuria. Routine blood analysis showed leucocytosis ($40,5 \times 10^9/L$) and a serum creatinine of $233 \mu\text{mol/L}$.

Before hantavirus serology results were known, test results for anti-GBM antibodies were positive. Treatment for anti-GBM glomerulonephritis was withheld, because of the absence of other signs and symptoms of the disease and slight improvement of renal function.

The diagnosis of acute hantavirus infection was later on confirmed, by seroconversion of a follow-up serum sample. Without further intervention renal function recovered and anti-GBM antibodies disappeared. Anti-GBM antibodies are supposed to be 100% specific. No earlier reports of false positive anti-GBM titers were reported. Nevertheless, the anti-GBM antibodies in this case was seen as an innocent bystander effect.

Conclusion: This is the first case in which positive anti-GBM antibodies are found in the course of an acute hantavirus infection. This finding falsely suggested an anti-GBM glomerulonephritis. Considering the need of urgent initiation of plasmapheresis and administration of immunosuppressants this may lead to therapeutic dilemmas with crucial consequences. Knowledge of this pitfall in diagnosing acute renal failure is therefore important.

Effects of the high flow arterio-venous fistula on right ventricular contractility in hemodialysis patients

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Background: The inability of the right ventricle (RV) to adapt to volume overload in the presence of an arterio-venous fistula (AVF) in hemodialysis patients leaves it susceptible to dysfunction. Early recognition of RV failure can contribute towards improved and personalized therapeutic strategies. This study utilizes cardiac magnetic resonance tissue-tracking (CMR-TT) to describe the relation between AVF flow and RV contractility.

Methods: Patients and age-matched controls underwent CMR prior to and after dialysis to distinguish between the effects of AVF flow and fluid overload. The patients were divided in Group 1 (low flow, <1000ml/min) and Group 2 (high flow, >1000ml/min) based on AVF flow. Global longitudinal (GLS), global circumferential (GCS) and global radial strain (GRS) of the RV were calculated with the tissue-tracking module of Circle Cardiovascular Imaging.

Results: The contractility parameters between the groups were similar prior to dialysis. After dialysis, there were no significant changes observed between Group 1 (n=5) and the control group (n=5). In comparison to the control group, patients in Group 2 (n=6) had a significantly lower GLS (-16.5±3.0% vs. -28.1±4.4%, P<0.05) and GRS (31.0±8.5% vs. 71.7±23.7%, P<0.05) after the dialysis session. No significant change was observed for the GCS between the control group and group 2 (-3.6±10.6% vs. -15.6±3.5%, P=0.06).

Conclusion: These findings suggest that patients with high AVF flow have significantly lower contractile parameters and thereby have an increased risk for developing right ventricular dysfunction. CMR-TT offers the possibility to detect subtle early changes in right ventricular contractility and could have significant therapeutic consequences.

Oral versus intravenous hydration in prevention of contrast induced nephropathy. A review of current evidence

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Background: Contrast induced nephropathy (CIN) is associated with adverse outcome, contributing to overall harm to patients' health and generating costs. In current guidelines intravenous hydration is prescribed to decrease this risk in high-risk patients, necessitating a longer admission time especially in outpatients.

Objective: To determine whether, based on current literature, oral hydration is non-inferior to intravenous hydration in the prevention of CIN.

Methods: A literature search was conducted in Pubmed and Embase. Studies were selected according to predefined inclusion and exclusion criteria. Selected articles were critically appraised with respect to relevance and validity to obtain the best available evidence.

Results: The search yielded 190 articles. After screening, 8 articles remained for critical appraisal. Between studies, there was a high variation in study population, study protocol and endpoint definition. In 7 out of the 8 identified studies, no significant difference in CIN incidence between oral and intravenous hydration was reported. One study found a significant difference in favour of intravenous hydration.

Conclusion: Based on the current evidence, oral pre- and posthydration is non inferior to intravenous pre-and posthydration. However, due to heterogeneity evidence grade is low. Furthermore, because of lack of evidence in patients with pre-existent renal impairment, this result might not be extendable to this group.

PTA of the renal artery: sometimes still indicated

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Case: A 73-year old male was referred because of persistent hypertension for which he was previously treated with an ACE-inhibitor. His medical history included peripheral arterial vascular disease and a unilateral contracted kidney due to left renal artery stenosis. On examination, a blood pressure of 211/117 mmHg was seen. Laboratory tests showed a creatinine rise from 91 umol to 157 umol/L and urine sodium of 21 mmol. Urine sediment showed proteinuria, indicating a renal problem. The ACE-inhibitor was replaced by a calcium-antagonist. Ultrasound and duplex imaging showed a normal sized right kidney with a high resistant signal of the renal artery. Urine output diminished and creatinine level increased to 403 umol/L. Saline infusion resulted in decompensatio cordis after which the patient was transferred for emergency dialysis. An acute occlusion of the right renal artery was suspected. Invasive angiography revealed stenosis of the right renal artery of more than 90%. A stent was placed and re-angiography showed sufficient patency. As soon as one day after intervention, renal function improved and blood pressure normalized. After 1 week, renal function recovered to previous level.

Conclusion: Several studies show no significant improvement of renal function or hypertension after stenting of renal artery stenosis. Therefore, the general advice is to treat conservatively. This case report shows that in case of a solitary functioning kidney, emergency stenting of renal artery stenosis may still be indicated to improve renal function and hypertension in case of an observed acute event. Early recognition of the clinical picture is imperative.

Case report: acute kidney injury at the campsite, need for renal biopsy?

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A 67-year old male without relevant medical history was admitted to the gastroenterology ward with sudden onset fatigue, nausea and loss of appetite over the last 6 days, superimposed on longer-existing difficulty with swallowing. At admission he had fever (38.5°C) and chills, and an increase in serum creatinine from 158 to 340 µmol/L overnight (baseline 98 µmol/L) for which Internal Medicine was consulted. Physical examination was unremarkable, without edema. Laboratory results included CRP 178 mg/L, hyperphosphatemia 1.99 mmol/L, thrombocytes $120 \times 10^9/L$, normal leukocyte count and liver enzymes. Urine analysis demonstrated albuminuria (+++), erythrocyturia (+), and a protein creatinine ratio of 5.2 grams/10mmol. Light microscopy did not demonstrate acanthocytes or red blood cell casts. Ultrasonography excluded post-renal causes, although both kidneys had a somewhat hyperechogenic appearance. Autoimmune serology was negative. Despite 4L/24h i.v. saline, creatinine concentration increased to 447 µmol/L overnight and renal biopsy was considered. Upon questioning, the patient mentioned he spent the previous six weeks on a campsite in the eastern The Netherlands, with many mice in a hollow tree behind the caravan. We then considered Hanta virus infection as working diagnosis. We obtained serology, postponed the renal biopsy and ceased intravenous fluid therapy. Creatinine decreased the next seven days from 487 to 112 µmol/L and recovered completely the next month. Hanta puumala IgM and IgG titers were $\geq 1:1000$, confirming the diagnosis. Hantavirus' *nephropathia endemica* is a self-limiting illness with increased prevalence in the eastern The Netherlands. Increased clinical awareness can justify watchful waiting and avoid unnecessary renal biopsies.

Unusual presentation of a hantavirus infection

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A previously healthy 62-year-old man was admitted to the hospital because of headache, abdominal discomfort, sweating without fever, and muscle ache for which he used NSAIDs. He had not traveled to tropical countries and had no domestic pets. Blood pressure was 159/97mmHg, temperature was 36.8°C. Laboratory investigation showed a CRP of 147 mg/L, normal blood count and acute kidney failure (eGFR of 7 ml/min/1.72m²). Urine analysis showed proteinuria (1.2 g/24 h), high ratio of alfa-1-macroglobulin of 9.72 mg/mmolkr and hematuria without dysmorphic erythrocytes, and no leukocytes. Ultrasound showed normal kidneys. Additional analysis of creatinine kinase, M-protein, cryoglobulins and auto-immune serology were all normal. Blood cultures yielded no growth. Treatment with prednisone was started because we considered a tubulointerstitial nephritis likely due to NSAIDs. Although the thrombocyte count was normal (thrombocytes $245 \times 10^9/L$), we also considered hantavirus infection. Laboratory investigation revealed the presence of IgM and IgG antibodies against puumalavirus indicating acute hantavirus infection. Therefore, we concluded that the acute kidney failure was due to hantavirus infection and prednisone was discontinued. During the following months, the kidney function normalized completely. Later, the patient mentioned that he had regularly visited a friend who lived near a forest in the area of Brussels, where mice are known to be infected with puumalavirus.

Conclusion: Acute kidney failure due to puumalavirus infection is rare and always combined with thrombocytopenia. This case illustrates the importance of clinical awareness for hantavirus infection in patients with acute renal failure even in the absence of thrombocytopenia.

Healthcare costs of chronic kidney disease, dialysis and kidney transplant patients compared to matched controls

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Background: In this study we assessed healthcare costs for patients with CKD, dialysis or kidney transplantation in comparison with age, sex and social economic status (SES) matched controls, separately for three age groups.

Methods: Patients were identified using Dutch claims data and subdivided into three age categories (19-44 years, 45-64 years, ≥65 years). For each patient 2 matched controls were selected. As high treatment costs for RRT patients hampers the comparison with the control group, hospital costs were also analyzed with exclusion of treatment-related costs.

Results: *Average annual costs:* Young CKD patients (19-44) had 7 times higher costs than their controls (€9,416 vs. €1,425). This cost ratio decreased to 3 when aged ≥65 years (€11,627 vs. €4,221). Young dialysis patients had 77 times higher costs compared to controls (€92,686 vs. €1,201) which decreased to 21 (€90,808 vs. €4,292) in category ≥65 years. In transplant patients cost ratio declined from 14 (€18,176 vs. €1,277) to 6 (€20,743 vs. €3,774) in the youngest versus the oldest patients.

Hospital costs excluding treatment-related costs: In dialysis patients the cost ratio decreased from 13 (€7,368 vs. €587) to 3 (€8,476 vs €2,591) and in transplant patients from 7 (€4,058 vs. €591) to 3 (€7,085 vs. €2,382) in the youngest versus the oldest age group.

Conclusion: Although annual healthcare costs of CKD, dialysis and transplant patients were much higher than their controls, these cost differences decreased remarkably with age. When excluding treatment costs, cost differences decreased but the decline with increasing age persists.

Acute Kidney Injury in Amphia, is it avoidable ?

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Background: Acute kidney injury (AKI) is characterized by a rapid reduction in kidney function with accumulation of waste products, oliguria and a failure of fluid, electrolyte and acid-base homeostasis. AKI is associated with increased length of hospital stay, chronic kidney damage, and a higher mortality rate. We defined AKI according to KDIGO criteria, and investigated if AKI is avoidable.

Method: In a retrospective, case-record study, admissions over a one week period were included. Incidence, severity, cause, and avoidance of AKI were analyzed.

Results: 345 adult patients were hospitalized for at least one day (53% men). AKI incidence was 16.5%, of which 46% was present on admission, whereas 54% occurred during the hospital stay. The patients with AKI were older (median age 75y vs 68y, $p < 0.002$), stayed longer (median hospital stay 7 vs 4 days, $p < 0.001$), had more comorbidities such as hypertension, chronic renal failure, diabetes mellitus or heart failure ($p < 0.002$), had a higher mortality rate (12% vs 3%, $p < 0.002$) and had a decrease of their kidney function, 6-12 months after admission (median eGFR from 64 to 53 ml/min/1.73m², $p < 0.05$). None of the patients required dialysis. AKI was primarily caused by prerenal factors (91%), which may be considered as potentially avoidable in 66.6%, because haemodynamically acting medication (RAS-blockers, diuretics, NSAIDs) were dosed too high or continued during hypovolemia.

Conclusion: AKI is common and often potentially avoidable. More awareness for AKI is needed. Avoidance of RAS-blockers and nephrotoxic drugs and correcting volume depletion during acute illness are recommended to avoid AKI.

Worldwide health insurance claims databases in kidney research and a new initiative: The Dutch Kidney Atlas

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Background: Health insurance claims data are a valuable source of medical information and give rise to new research opportunities. We present an overview of claims databases across the world and their publications in renal medicine. We will introduce the Dutch claims database and a new initiative to use this database for the development of a Dutch Kidney Atlas.

Methods: Claims databases and their published papers were identified by internet and literature search. Only papers using claims data as their primary data source were selected and were classified into four study categories: validation, descriptive epidemiological, cost and outcome studies.

Results: We identified 7 claims databases in 6 different countries using their data for publications in renal research (Canada, France, Japan, South Korea, Taiwan, USA). We identified 8 studies testing the validity of claims data in identifying renal patients. Few studies were descriptive epidemiological studies or costs studies. Published studies on outcomes research were mainly focusing on survival differences or risk of cardiovascular disease.

The Vektis database contains all health insurance claims of Dutch inhabitants and makes it possible to study patients with renal diseases and to observe regional differences for incorporation in the Dutch Kidney Atlas.

Conclusion: Health insurance claims databases offer important opportunities for studies on large populations of patients with (kidney) diseases and health outcomes in a non-experimental setting. The Dutch claims database offers a unique opportunity to design the Dutch Kidney Atlas on (regional differences in) risk factors, diagnoses, treatment, outcomes and costs of patients with renal diseases.

A Tropical Storm With Eosinophilia

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Case: A 20-year-old woman with a history of asthma and nasal polyps fell ill 2 days after arriving in Indonesia where she suffered from recurrent periods of rash, increased activity of asthma, muscle ache, and night sweats for 6 months. She was treated there several times with prednisolone and antibiotics, which improved her symptoms. Complaints continued after returning home and initial laboratory testing revealed eosinophilia. Originally, parasitic and other infectious diseases were considered to be the most likely causes. However, she presented prematurely to the emergency department with fever (39.2°C), dyspnea, and skin rash. General laboratory testing showed severe eosinophilia (2,6E9/L) and chest X-ray was markedly abnormal. Together with the fact that she was ill so quickly after arrival in Asia, it made us doubt the thought of an infectious condition and auto-immune diseases were considered. Thorough examination revealed multi-organ involvement with multiple consolidations in the lungs, cardiomegaly with perimyocarditis with extremely elevated troponin (9.3ug/L) and NT-proBNP (2103ng/l), pseudo-urticaria, gastroenteritis, and painful asymmetric neuropathy with foot drop. The patient met all six criteria for the classification of Eosinophilic Granulomatosis with Polyangiitis (EGPA) as described by the American College of Rheumatology (asthma, >10% eosinophils on differential leukocyte count, mononeuropathy, pulmonary opacities, paranasal sinus abnormality, biopsy showing accumulation of eosinophils in extravascular areas) and was treated accordingly.

Conclusion: EGPA should be considered in patients presenting with a systemic disease in combination with eosinophilia. It may develop into a life-threatening disease and adequate care should be initiated immediately after the diagnosis is made.

PGNMID: a hematologic problem of renal significance

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A 41-year old woman with a history of hypertension presented with swelling of arms and legs and worsening of kidney function during the last month. She gained 9kg and had some dyspnea with exertion. Examination showed bilateral pitting edema of the lower extremity and to a lesser extent of the upper extremity. Vital signs and further examination were normal. Laboratory testing matched a nephrotic syndrome (serum creatinine 115 μ mol/l, albumin 19g/l, total cholesterol 6,6mmol/l). Urine analysis revealed protein loss of 5,8g/24h. Further urine analysis, auto immune testing, complement and cryoglobulins were normal. Serum protein electrophoresis was normal. However, the lambda free light chain (FLC) was 50 mg/l, with a ratio 0.36. Kidney biopsy showed a membranoproliferative pattern with endocapillary proliferation. Immunofluorescence showed glomerular basement membrane depositions of IgG, especially lambda FLC and C3. The combination of serum and biopsy results made the diagnosis of proliferative glomerulonephritis with monoclonal immunoglobulin deposit (PGNMID). This is a relative new entity of a monoclonal gammopathy of renal significance (MGRS), which can present as a nephrotic syndrome. Multiple Myeloma and a lymphoproliferative disorder were excluded. She is treated with 3 cycles Bortezomib/dexamethasone and will have an autologous stem cell transplantation. After 2 cycles urine protein is 0,6g/24h with normalization of FLC and a stable renal insufficiency stage IIIa. If kidney biopsy shows a membranoproliferative pattern with immunoglobulin deposit, think about PGNMID. When finding a new renal insufficiency or nephrotic syndrome, testing for M-protein and FLC can be helpful, because monoclonal gammopathy can be of renal significance.

Renal insufficiency and reduced C₃ levels: two uncommon cases with distinct pathophysiology and histopathology

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Case 1: A 25-year old male presented with hematuria since seven months. He had no other complaints. Physical examination was unremarkable. Serum creatinin level was 130 $\mu\text{mol/l}$. The C₃ level was reduced with abnormal alternative pathway activity. There were no signs of hemolysis. Urine analysis showed glomerular erythrocyturia and proteinuria. Renal biopsy revealed mild mesangial proliferation, 20% interstitial fibrosis and tubular atrophy and granular C₃ staining in the absence of IgA. No genetic abnormalities were detected in complement genes. There was no C₃-nephritic factor. Anti-FH antibodies were positive. A diagnosis of anti-FH antibody mediated C₃-glomerulonephritis was made. He was treated with rituximab.

Case 2: A 60-year old male with JAK2+ essential thrombocytosis and myelofibrosis developed progressive renal insufficiency directly after starting PEG-interferon. His symptoms included peripheral edema, pruritus, dry skin and fatigue. Physical examination was characterized by hypertension, pitting edema and splenomegaly. Laboratory results showed a serum creatinin of 194 $\mu\text{mol/L}$ and DAT negative hemolysis. C₃ levels were reduced with normal complement activity assays. Renal biopsy showed thrombotic micro-angiopathy (TMA). A diagnosis of PEG-interferon associated TMA was made. There were no complement mutations or auto-antibodies. Treatment consisted of PEG-interferon cessation and blood pressure control. The renal function is slowly recovering. Given the known effects of PEG-interferon it is suspected that the susceptibility is mediated by an endothelial factor.

The presented cases illustrate that renal insufficiency with low C₃ can be distinct in pathology and treatment. This underscores the relevance of complement pathway assessment, genetic mutation analysis and antibody screening.

Essential mixed cryoglobulinemia, a challenging disease

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Background: Cryoglobulinemia is a condition in which immunoglobulins precipitate at low temperatures. Different types can be distinguished, type 1 (monoclonal immunoglobulins) and type 2/3 (monoclonal and polyclonal immunoglobulins with rheumatoid factor activity), also called mixed cryoglobulinemia.

Case: A 62-year-old man presented with periods of subfebrile temperature, fatigue and weight loss without other complaints. Physical examination revealed a grade II systolic murmur and mild splenomegaly. Laboratory results showed anaemia, leukopenia and moderate renal insufficiency. Urinary tests showed dysmorphic erythrocytes and proteinuria (3.6g/24h). Hepatitis B, C and HIV tests were negative.

PET/CT scan showed splenomegaly, but no signs of malignancy. Bone marrow exam was normal. Kidney biopsy showed active local and focal intra- and extracapillary glomerulonephritis with deposits of IgM and C3 consistent with mixed cryoglobulinemia. Because no underlying disease was found the diagnosis of essential cryoglobulinemia type 2/3 was made.

Initial treatment consisted of high dose prednisolone followed by two courses of rituximab with a six month interval, resulting in clinical remission.

Conclusion: Cryoglobulinemia presents with a diverse clinical picture. In mixed cryoglobulinemia most patients have involvement of the skin (purpura, petechiae), joints, peripheral neuropathy and renal insufficiency. When patients only show a few symptoms, like our patient, diagnosing can be challenging, but is important for the choice of treatment. Mixed cryoglobulinemia is highly associated with hepatitis C infection (70-90% of the patients). Rituximab has been shown to be effective in inducing remission in those patients. Although our patient did not have hepatitis C, he had an excellent response to rituximab.

Renal thrombotic microangiopathy: an uncommon and unexpected cause of acute renal failure

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We present a 79-year-old woman, with a medical history of hypertension and a normal kidney function, who was admitted to our hospital with suspicion of septic arthritis of the left knee. Treatment was started with flucloxacillin, gentamycin and drainage of the knee, on which she recovered well. However, six days after admission, she suddenly became anuric. Biochemical examination showed acute renal failure (eGFR 19 ml/min/1.73m²). She remained anuric despite filling. An ultrasound of the kidneys did not show postrenal obstruction. Tubulointerstitial nephritis was suspected. Therefore, flucloxacillin was discontinued. The eGFR further deteriorated to 8 ml/min/1.73m² and dialysis was started. No hemolysis or thrombocytopenia were detected. A kidney biopsy was performed, which showed multiple microthrombi in the capillaries of the glomeruli, compatible with the diagnosis of renal thrombotic microangiopathy (TMA). We referred the patient for plasmapheresis, which was discontinued after systemic TMA was excluded. The patient and her kidney function fully recovered. Feces PCR showed a Shiga toxin-producing E. Coli toxin, but this variant was not known to be associated with TMA. Immunological examination did not show clues for a systemic disease, although C₃ and C₄ were low, but factor I and H were normal. Finally, the TMA might be secondary to MGUS, although unlikely (M-protein 2.6 g/L). This case illustrates the additional value of a kidney biopsy in case of acute renal failure with a broad differential diagnosis and the challenge in establishing the underlying cause of TMA.

Treatment of parathyroid hormone-related protein (PTH-rP) induced hypercalcemia in advanced endometrial cancer

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Introduction: In solid tumors without bone metastasis, hypercalcemia induced by PTH-rP is difficult to treat. In advanced endometrial cancer PTH-rP induced hypercalcemia is rare.

Case: A 68-year-old woman diagnosed with advanced clear cell endometrial cancer with hepatic and peritoneal metastases, was admitted to hospital with acute nausea, weakness of both legs and malaise in the evening after her first carboplatin paclitaxel chemotherapy. Laboratory results showed hypercalcemia (corrected for albumin): 3,36 mmol/l (normal 2,15-2,55 mmol/l), hypophosphatemia: 0,52 mmol/l and hypomagnesemia: 0,54 mmol/l; normal vitamin D and depressed PTH levels. Imaging revealed no bone metastasis. As suspected, PTH-rP was high: 2,7 pmol/l (normal < 0,6 pmol). After initial treatment, 4 re-admissions because of recurrent, symptomatic hypercalcemia were needed. Her hypercalcemia treatment required [cumulatively]: many inpatient days⁵², normal saline 0.9% iv [approx. 60 l], 5x zoledronic acid iv [20 mg], 1x denosumab sc [120 mg], 1 week calcitonin sc [2100 IE], 17 days iv phosphate supplementation [720 mmol], 15 days oral phosphate supplementation [615 mmol], 22 days oral cinacalcet [1230 mg] and tube feeding. Due to early progression after the 3rd cycle, 2nd line liposomal doxorubicin was given.

Fortunately, thereafter during oral maintenance with cinacalcet 60mg and phosphate 15 mmol twice daily, already after the first chemotherapy cycle, corrected calcium (2,40 mmol/l) and magnesium normalized, but phosphate (0,59 mmol/l) not yet.

Conclusion: Although rare in advanced clear cell endometrial cancer, our case illustrates that treatment of PTH-rP hypercalcemia is intensive. Only a causative, effective antitumor therapy, can bring long term success.

Influence of genes and lifestyle on hypertriglyceridemia

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Case: A 44-year old woman was admitted to the intensive care with pancreatitis caused by hypertriglyceridemia. The patient presented with epigastric pain, nausea and vomiting. Pancreatitis was suspected based on elevated amylase and lipase levels. Fasting triglycerides were 28 mmol/L. She had no relevant medical history, except two uncomplicated pregnancies and used oral contraceptives and ezetimibe 10mg. She was overweight with a BMI of 29.7 kg/m². Diabetes mellitus was ruled out, as were nephrotic syndrome, alcohol abuse and hypothyroidism. There were no signs of atherosclerosis or cardiovascular disease. The *APOE* genotype was $\epsilon 2\epsilon 3$, ruling out familial dysbetalipoproteinemia (the most frequent genetic cause of hypertriglyceridemia). Further genetic analysis revealed two compound heterozygote mutations in genes involved in triglyceride metabolism (*APOA5* and *LPL*). The lipoprotein lipase (LPL) activity was 45% compared to pooled healthy controls. The post-heparin triglyceride reduction was 6%, compared to a normal reduction of >20%. The patient was treated with gemfibrozil 600mg twice daily, but this was discontinued due to hair loss. With a triglyceride low diet and discontinuation of the oral contraceptives only, triglycerides were lowered to 2.4 mmol/L.

Conclusion: Hypertriglyceridemia is a risk factor for pancreatitis and cardiovascular disease, and has a broad differential diagnosis that should be evaluated in severe cases. When most common causes of hypertriglyceridemia are ruled out, genetic causes should be considered. The patient in the case report achieved near-normal TG values with a low-fat diet only, illustrating the importance of lifestyle measures. There are also several pharmacological options, including fibrates.

Subsegmental pulmonary embolism; an innocent bystander?

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Background: Little is known about the clinical characteristics of patients with subsegmental pulmonary embolism (SSPE). This study describes a population with SSPE and investigates whether patients with untreated SSPE differ from patients with treated SSPE.

Methods: All Computed Tomographic Pulmonary Angiography and chest CT radiology reports, made from January 2013 until December 2016, were retrospectively reviewed for SSPE diagnosis. Charts were reviewed for characteristics and outcomes, both were compared between treated and untreated patients with SSPE.

Results: SSPE was reported in 136 of 6387 scans (2.1%). Thirty-eight patients were excluded based on a priori set exclusion criteria. Of 98 patients with SSPE, 16 patients were left untreated (16%). In treated as well as untreated SSPE patients, conventional PE symptoms and clinical signs were seen in the majority of patients (70% and 65%, respectively). A Wells score >4 was found in 52% of both treated and untreated SSPE. SSPE as an incidental finding was rarely described ($n=5$, 5%). Regarding outcomes, one of 16 untreated patients (7%, 95% CI 0-24%) and two of 82 treated patients (2%, 95% CI 0.2-8%) showed a recurrent VTE in three months of follow-up. No mortality 'likely due to PE' was reported.

Conclusion: Based on our findings, SSPE does not seem to be an innocent finding. Treated SSPE patients do not have more comorbidities, neither more VTE risk factors or a more serious presentation than untreated patients. Management of SSPE seems to be based on clinical assessment of the likelihood of PE rather than CTPA/chest CT results.

Large-vessel vasculitis often overlooked as a cause of vascular occlusion

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A 64-year-old woman presented with pain in her arms and shoulders since one month and chronic pain in her pelvic girdle. Laboratory results showed increased inflammatory markers, other results were unremarkable. Polymyalgia rheumatica was considered the most likely diagnosis and the woman was treated with low-dose prednisone.

After a week, she presented with an increasing pain in her left arm and absent radial pulse. Percutaneous transluminal angioplasty (PTA) was performed to treat severe stenosis of the axillary arteries and occlusion of the left brachial artery. Two weeks later, pulses of the right hand were absent and PTA of a severe stenosis of the right axillary artery was performed.

A month later, she presented at the emergency department with an extreme headache and increased inflammatory markers. PET-CT showed increased activity throughout the subclavian, brachial, brachiocephalic and carotid arteries and thoracic and abdominal aorta. She was treated for a large-vessel giant-cell arteritis with high dose prednisone.

Discussion: diagnosing large-vessel vasculitis is often delayed, since it has few or aspecific symptoms at the onset of disease. Vascular symptoms at a later stage can include absent pulsation of the brachial arteries, difference in systolic blood pressure between arms and claudication of extremities caused by dilatation, narrowing or occlusion of arteries.

Differentiating vasculitis from atherosclerosis can be difficult, especially since some degree of inflammation can be seen in atherosclerosis. The length, localisation and non-calcification of the occlusion, combined with absence of risk factors for atherosclerosis, should make us aware of other causes of vascular occlusions.

Renin blues: the importance of renin and aldosterone measurement in hypertensive patients

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Background: We present two hypertensive patients who were referred for hypokalaemia-analysis in whom aldosterone/renin-ratio results were unexpected.

Case 1: A 41-year-old man was referred because of hypokalaemia and unexplained dyspnoea. He used nifedipine 100 mg, acetylsalicylic acid and potassium supplementation. He did not use glycyrrhizic acid containing products. Blood pressure was repeatedly >180/110 mmHg and potassium level 2.9 mmol/l. We suspected primary hyperaldosteronism; surprisingly the aldosterone/renin-ratio revealed a secondary hyperaldosteronism (renin 1300 mE/l; aldosterone 3.51 nmol/l, ratio 2.7 pmol/mE). With this extremely high renin level, a reninoma was suspected and a CT-angiography was performed. This showed an occlusion of the abdominal aorta with an occluded renal artery on the left side and significant stenosis right. Soon after, patient was admitted decompensatio cordis due to hypertension. We performed a percutaneous angioplasty of the right renal artery, after which potassium requirement decreased and blood pressure could be lowered to 140/85 mmHg with RAAS inhibitors.

Case 2: A 68-year old female with schizophrenia was referred because of hypokalaemia (3.3 mmol/l) and hypertension (180/102 mmHg), without antihypertensive medication. She denied liquorice usage. We suspected primary hyperaldosteronism and performed a renin/aldosterone-ratio after correction of potassium. This showed a pseudohyperaldosteronism (renin 3.4 mE/l; aldosterone <0.07 nmol/l; ratio <20.6 pmol/mE). Repeated anamnesis revealed she drank 1 liter of star mix tea daily, notorious for its glycyrrhizic acid. After abolishing, blood pressure and potassium returned to normal.

Conclusion: Although primary hyperaldosteronism is the most common cause of hypertension and hypokalaemia, careful evaluation with aldosterone/renin-ratios can lead to surprising results with important consequences.

Dual anticoagulation therapy in cancer-associated thrombosis: lifeline or pain in the neck?

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Case: A previously healthy, 51-year-old male presented with swelling of the neck. CT scan showed extensive thrombosis of both jugular veins extending to the subclavian veins. Other findings were a pulmonary embolism and cervical and mediastinal lymphadenopathy. No primary tumor was detected. Rivaroxaban 15 mg td was started. The patient developed fever and antibiotics were started for suspected Lemierre's syndrome. Serologic tests for autoimmune disorders associated with thrombosis were negative. Then, the patient developed progressive shortness of breath. CT scan showed progression of jugular thrombosis and pericardial effusion. Because of suspected malignancy, rivaroxaban was switched to therapeutic-dose nadroparine. After drainage of pericardial effusion, shortness of breath improved. Pericardial fluid showed malignant cells and PET-CT showed increased uptake in the esophagus, lymph nodes, pleurae, pericardium and vertebrae. A lymph node biopsy showed large cell neuroendocrine carcinoma of pulmonary or pancreatic origin (TTF-1 and Ca19.9 positive). Treatment with carboplatin and etoposide was initiated. The patient however experienced progressive swelling of the neck, for which edoxaban 60 mg qd was started in addition to nadroparine. With dual anticoagulation therapy, jugular thrombosis decreased and no bleeding occurred. Despite chemotherapy malignancy progressed. Eventually, a new thrombus arose in the azygos vein.

Conclusion: Progression of thrombosis despite anticoagulation in patients with cancer is clinically challenging. Data regarding the management of persistent or recurrent VTE during treatment with LMWHs are scarce. We present a case of aggressive malignancy and extensive thrombosis, in which a combination of LMWH and DOAC temporarily halted the progression of thrombosis.

Migration problems

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Introduction: patients with pulmonary emboli are admitted to the Intensive Care Unit when there are signs of right-ventricular dysfunction. This can be identified by elevated brain natriuretic peptide (NT-proBNP) or elevated Troponin (TnT) accompanied by typical findings on echocardiography or CT. It is still debated when giving thrombolytic therapy in intermediate risk patients. We present a case in which we pronounce the value of echocardiography when considering thrombolytic therapy.

Case: a 67-year-old woman was admitted with shortness of breath and thoracic pain. She was immobilized after a fall. There was no collapse.

Physical examination: A: no obstruction. B: Respiratory Rate 30/min Saturation 90% while on ambient air. C: RR 90/60 mmHg Pulse 90/min regular, distended jugular veins. D: E4M6V5. E: no signs of deep venous thrombosis. Arterial blood sample: pH 7.47 pCO₂ 27mmHg pO₂ 78mmHg Lactate 4.2 mmol/L. Venous blood sample: D-dimer 6.8 mg/L (reference < 0.50mg/L) NT-proBNP 1900 pmol/L (reference <12 pmol/L) hs-TnT 55 ng/l (reference 0-14ng/L) ECG: sinus rhythm, right bundle branch block. CTA: bilateral emboli, dilated truncus pulmonalis.

Follow-up: This patient was admitted to the Intensive Care Unit (PESI III, intermediate risk), because of hemodynamic stability we renounced thrombolytic therapy. An echocardiography showed a large thrombus migrating between right atrium and ventricle. We decided to treat her with thrombolytic therapy. After 24 hours the thrombus was disappeared, there were no complications.

Discussion: Although intra cardiac thrombus localization seems relatively rare we think that echocardiography will be valuable when considering thrombolytic therapy in intermediate risk patients.

Inflammation in disguise

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A 53-year-old caucasian woman with a history of pulmonary embolism, pneumonia, irritable bowel syndrome and smoking, was referred with abdominal pain since one week. The pain was constant, cramping, in epigastrio, which radiated to her back. There were no other complaints. She was afebrile with tenderness in epigastrio on abdominal palpation. There was no skin, mucosal, or joint pathology. An abdominal ultrasound showed a cuff around the truncus coeliacus. Her blood count and urinalysis were within normal limits. Auto-immune antibodies and complement were negative. A computed tomography (CT) revealed a cuff surrounding the a. lienalis and truncus coeliacus. Furthermore, a saccular aneurysma of the a. gastrica sinistra and a. hepatica propria just after they branched, was found. A PET-scan showed no FDG uptake in the cuff, but an infarction of the spleen. There were no signs of lymphadenopathy with FDG uptake or atherosclerotic plaques. Most likely diagnoses at this time were retroperitoneal fibrosis and vasculitis. The abdominal pain became more severe. Treatment with high-dose prednisone was initiated, together with clopidogrel. After a few days, the pain resolved and the vascular abnormalities normalised. The prednisone dose was tapered and finally stopped.

Discussion: This case shows that patients with abdominal pain and signs of severe vascular inflammation due to either vasculitis or retroperitoneal fibrosis, may have completely normal blood and urine results, and no signs of FDG uptake with PET-scan. In these difficult cases, prednisone may be very effective.

Edema of the lower limbs caused by an aortic aneurysm

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A 68-year-old man was referred because of bilateral lower limb edema that existed for six weeks. He was previously diagnosed with a macroprolactinoma with hypogonadism for which he was treated with cabergoline and testosterone. On physical examination he had bilateral edema with a more affected right limb without other signs of heart failure. Laboratory results revealed no signs of inflammation (CRP <6mg/l (reference range <10mg/l)) and no proteinuria. Right lower limb ultrasound showed no deep venous thrombosis. Because of inguinal lymphadenopathy on physical examination, obstructive lymphedema due to a malignancy was suspected. Computed Tomography of the thorax and abdomen showed no tumor masses, but it did show an infrarenal aortic aneurysm with a diameter of 83mm. The edema disappeared within three days after an Endovascular Aneurysm Repair (EVAR). Reasons for edema related to an AAA, which are described in literature, are vena cava thrombosis, periaortitis with compression of the vena cava inferior (VCI) or a fistula between the aorta and the VCI with hyperdynamic heart failure. All these were excluded. Compression of the VCI by the aneurysm was only to a limited extent on CT, but in upright position this may be more pronounced. The aneurysmal sac depressurization by EVAR could explain the edema resolution.

In conclusion, compression of the VCI by the aortic aneurysm seems to be the most likely cause of the bilateral lower limb edema. Because of the risk of an AAA, it is important to keep this diagnosis in mind with bilateral limb edema.

Marfan syndrome presenting with hydronephrosis and 18F-FDG-PET-CT avid bilateral iliac artery aneurysms

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Case: A 41-year-old male presented with abdominal pain, erythrocyturia and impaired renal function. Systemic examination was normal. Initial blood monitoring revealed mild elevated ESR (17 mm/h) and normal CRP (4mg/L).

Abdominal ultrasound showed left-sided hydronephrosis, whereas additional CT scanning revealed aneurysms of both common iliac arteries (4.3 and 3.8 cm) with peri-vascular infiltration, causing left-sided ureter obstruction. A double-J catheter was placed, fully recovering renal clearance.

Additional analysis was performed in order to screen for underlying systemic disease with negative laboratory results for ANCA, MPO and PR₃ values. However, a PET CT scan showed FDG avid lesions at locations of the aneurysms, assuming vasculitis. Based on this finding treatment with high dose prednisolone was initiated. After 6 weeks of prednisolone treatment, a PET CT scan was repeated with negative FDG-avidity and an aortic bi-iliac prosthesis and left urethrolysis was performed. Pathologic images of the iliac artery showed extensive atherosclerosis and a chronic, non-necrotic inflammation, without signs of vasculitis. However, the procedure was performed months after starting prednisolone treatment and therefore this could have influenced the results.

Since family history was positive for artery disease (father underwent a Bentall procedure, brother suffered from an ischemic stroke) our patient was referred to the clinical geneticist. This resulted in a genetically proven diagnosis of Marfan's syndrome with underlying SMAD3 mutation; a relatively new mutation found to cause Marfan syndrome without typical phenotype.

Conclusion: Marfan syndrome should be considered even without phenotypic symptoms and with PET-CT avid arterial aneurysms mimicking large artery vasculitis.

Floating aortic arch thrombus

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Case: A 64-year old woman with a medical history of COPD gold IV was referred to our hospital with fever and abdominal pain. Physical examination showed a hemodynamic stable patient with a temperature of 39°C and upper abdominal pain. Laboratory results showed a strongly raised WBC count 34.9×10^9 , CRP 134 mg/l, creatinine 130 $\mu\text{mol/l}$, LDH 903 IU/l. CT-abdomen revealed multiple bilateral kidney infarctions and a splenic infarction. Transthoracic echography, performed with contrast agent, showed neither cardiac thromboembolism, nor a patent foramen ovale, ventricular septal defect or valvular vegetations. We performed a CT-aorta which revealed a thrombus in the aortic arch. We treated the patient with acenocoumarol and a statin. The elevated levels of WBC count and LDH are probably caused by cell necrosis due to the infarctions. After 3-months, a control CT-aorta was performed showing complete resolution of the thrombus in the aortic arch. We continued anticoagulation therapy for six months.

Background: The pathophysiology of a so-called floating aortic thrombus, is not yet completely understood. It is suggested that it originates from an atherosclerotic plaque rupture or underlying hypercoagulability. Treatment options are (endo)vascular surgery or anticoagulant therapy with a minimum duration of six months. Afterwards is often switched to antiplatelet therapy. There are no studies published regarding the use of NOACs in patients with a floating aortic thrombus. Furthermore, patients should be treated with a statin.

Conclusion: In patients with arterial thromboembolism apparently not originating from the heart, a search for a floating aortic thrombus could be considered.

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Evolution of eHealth – a survey among medical specialists and residents

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Background: The implementation of eHealth in the Dutch healthcare sector is still limited. Data concerning the actual needs of patients and clinicians to facilitate eHealth implementation is currently lacking.

The aim of this study was to assess the perception of eHealth by physicians and identify factors restricting its wide-spread implementation.

Methods: All consultants and residents of the Internal Medicine department in a teaching hospital were invited to fill in a pre-structured questionnaire. The questionnaire was divided in perception and expectations.

Results: The questionnaire was completed by 39 participants (78% response, 46% consultants and 54% residents).

Of the participants, 87% used one or more eHealth solutions (apps, n=24 (62%); screening instruments, n=16 (41%). Websites (n=24, 62%) and apps (n=18, 46%) are frequently recommended during the consultation. The majority expected that eHealth solutions could improve the quality and efficiency of care as well as increase patient empowerment (n=35, 90%). The largest constraints for eHealth were considered to be lack of knowledge amongst physicians (n=21, 54%) and shortage of resources (n=16, 41%). Physicians pointed out that it is important that they must be actively involved during the creation and implementation process (n=22, 56%).

Conclusion: These results demonstrate that there is a widespread use of eHealth applications amongst physicians. Physicians expect that eHealth can enable patient empowerment. The majority finds it important and are willing to actively participate in expanding the eHealth evolution (co-creation). The major stakeholders should realize that proper resources need to be allocated in order to enable and encourage this evolution.

