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Background: Gentamicin is frequently used as part of empirical treatment of sepsis in the emergency department (ED). To achieve an optimal effect, the gentamicin peak-concentration should be sufficiently high (i.e. ratio peak-concentration/MIC =8-10). Patients with severe sepsis in the ICU often need higher gentamicin doses to achieve sufficiently high peak-concentrations. We have investigated which dose is needed in patients presenting with sepsis in the ED.

Methods: Patients with sepsis in the ED were included from August 2015 until December 2016. Peak-concentrations were measured in blood 30 minutes after the first gentamicin dose with a validated fluorescence polarization immunoassay (Roche Cobas-Integra ®800). The study consisted of three phases. In the first phase, peak-concentrations were measured after a dose of 5mg/kg. In the second phase a simulation ((peak-concentration/actual dose) x simulated dose) was performed to determine which dose was needed to reach adequate gentamicin peak-concentrations of 16-20mg/L. In the third phase, peak-concentrations were measured for the best simulated dose.

Results: In phase one, 88 patients received a dose of 5mg/kg, 40.9% did not reach the target peak-concentration of =16mg/L, and 85.2% =20mg/L, respectively. In phase two, the simulation showed that with a dose of 7mg/kg 96.6% would reach peak-concentrations =16mg/L, and 77.3% =20mg/L, respectively. In phase three, 33 patients received a dose of 7mg/kg, 85.3% reached peak-concentrations of =16mg/L, and 64.7% =20mg/L, respectively.

Conclusion: Patients with sepsis at the ED need higher doses of gentamicin. A dose of at least 7mg/kg is needed to achieve adequate peak-concentrations in the majority of these patients.
Impact of diagnostic criteria on the prevalence of gestational diabetes in The Netherlands

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Background: Recently, many international guidelines (e.g. ADA, IADSPG, ES) have adapted their diagnostic criteria for gestational diabetes to those determined in the HAPO study (fasting plasma glucose (FPG) = 5.1 mmol/l and the 2-hour post load glucose (PLG) = 8.5 mmol/l). The recently update of the Dutch guideline (NIV/NVOG 2016) doesn’t make a statement on the introduction of these new criteria and, thus, current national criteria remain based on the 1999 WHO guideline (FPG = 7.0 mmol/l and PLG = 7.8 mmol/l), referentie).

Methods: We conducted a retrospective analysis of 1500 75 gram OGTT’s conducted over 2014 and 2015 in a single center to investigated the impact of switching from the current criteria to the HAPO criteria on frequency and etiology of gestational diabetes.

Results: Using current Dutch criteria, less than 1% of the women screened were diagnosed with gestational diabetes based on FPG alone. This is in stark contrast to findings when applying the criteria from the HAPO study, where 12% (2014) and 17% (2015) of patients had gestational diabetes based on FPG. The opposite was true for PLG, where 18% (2014) and 12% (2015) of women classified as diabetic using the current Dutch criteria, versus 5% (2014) and 2% (2015) when using the HAPO criteria.

Conclusion: These data show that by introducing the HAPO criteria, gestational diabetes will be diagnosed based on glucose impairment rather than glucose intolerance. However what should we do with 20% of patient who developed type 2 diabetes based on the old criteria?
The Portuguese disease of the feet

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Case: A 34-year old Armenian male was referred with various complaints. He had suffered from diarrhoea for 2 years. Although extensive research including endoscopy with biopsies was performed, no diagnosis was established. He also experienced numbness of the feet, erectile dysfunction and developed urinary retention. At physical examination, there was a decreased sensation of the lower extremities. Laboratory, - and liquor investigations were unremarkable. The brain MRI showed no pathology. Revision of the colon biopsies including Congo red staining revealed the presence of amyloid. Evaluation of cardiac amyloidosis was negative. Because of the neurological symptoms and the absence of hematological or inflammatory abnormalities, the diagnosis transthyretin familial amyloid polyneuropathy (TTR-FAP) was considered. Genetic testing showed the 148G>A (p.Val50Met) mutation which confirmed this diagnosis. Treatment with Tafamidis, an oral drug which kinetically stabilizes transthyretine, was initiated.

Discussion: TTR-FAP is an autosomal dominant disorder caused by deposition of amyloid fibrils, and is a result of mutations that destabilize the transthyretin protein. The disease is endemic in Sweden, Japan and Portugal, where it is popularly known as the Portuguese disease of the feet. In The Netherlands, an estimated 80 cases have been described. If untreated, the disease is often fatal within 12 years after the onset of symptoms, mostly because of cardiac arrhythmias. Current treatment options are pharmalogical transthyretin stabilization, or a liver transplantation as transthyretin is predominantly produced by the liver. Establishing the diagnosis in an early stage is challenging, but important as this may improve the prognosis.
The presence of elevated C-reactive protein (CRP) and fever during PET(/CT) increase diagnostic yield in patients with fever of unknown origin

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Background: FDG-PET-CT is one of the most important diagnostic techniques in patients with fever of unknown origin (FUO). Diagnostic yield depends on the presence of inflammation, but it is unknown what parameter can best be used to optimize diagnostic yield of FDG-PET-CT in FUO.

Methods: All patients with FUO referred to the Radboudumc university medical center between January 2005 and June 2014 in whom PET(/CT) was performed were included in this retrospective study. Data on outcome of PET(/CT), body temperature at the day of the procedure and CRP value within two weeks before PET(/CT) were extracted from medical records. CRP >10mg/dL was considered elevated.

Results: 260 PET(/CT)s were performed in 177 patients. Median duration of fever at PET(/CT) was 263 days (range 14-15749 days). Overall, 87 PET(/CT)s (33.5%) contributed to the final diagnosis. CRP was available in 92 and elevated in 80 cases (87%). Fever was present on the day of PET(/CT) in 38 cases (14.6%). Diagnostic yields when elevated CRP or fever were present were not significantly different (50% vs. 65.8%, p=.118), but both were significantly higher than the overall diagnostic yield (p=.008 and p<.001, respectively). Combination of both fever and elevated CRP did not further increase diagnostic yield (p=.181 and 1.0, respectively).

Conclusion: In patients with FUO the presence of elevated CRP within 14 days before PET(/CT) increases the diagnostic yield to the same extend as the presence of fever during PET(/CT) and thus can be used as a parameter guiding the planning of PET(/CT) in these patients.
Nudging diminishes contamination of stethoscopes and phones in a hospital environment

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Background: Stethoscopes and phones are usually not subject to hospital hygiene rules. They are however frequently used and a potential source of pathogen transfer between patients. We investigated whether disinfection behavior could be ameliorated by increasing the awareness on this issue without imposing new rules (‘nudging’), and whether this influenced the amount of biological material and pathogens on stethoscopes and phones.

Methods: Surfaces of stethoscopes and phones of 65 health care providers were sampled unannounced at days 0 and 35 to measure the amount of pathogens and biological material, represented by ATP-values. On day 14 the results were shared with part of the participants (intervention group, N=31) but not with those in the control group (N=22). A questionnaire was used to monitor the change in disinfection behavior in both groups.

Results: The percentage of stethoscopes and DECT phones with low ATP values was significantly higher on day 35 in the intervention group (p<0.04), but not in the control group (p=0.48). The amount of pathogens was small in both groups and did not significantly change. The most isolated pathogen was S. aureus. At day 35 the disinfection frequency was improved in the intervention group, but not in the control group (stethoscopes: 45.8% vs. 0.0%, p=0.03; phones 50.0% vs. 12.5%, p=0.09).

Conclusion: The amount of biological material on stethoscopes and phones of in-hospital health care providers, and their disinfection behavior, can be improved by increasing the awareness of this contamination, so-called nudging, thereby probably diminishing pathogen transfer between patients.
Intravenous Flucloxacillin Treatment is Associated with Hypokalemia in Hospitalized Patients


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Background: Intravenous flucloxacillin is one of the most frequently used high-dose penicillin therapies in hospitalized patients, forming the cornerstone treatment of invasive Staphylococcus aureus infection. Being a non-reabsorbable anion, flucloxacillin has been suggested to cause hypokalemia, although the exact frequency and magnitude of this unwanted effect is unknown. We investigated the incidence and extent of hypokalemia after initiation of intravenous flucloxacillin compared to ceftriaxone therapy.

Methods: All adult patients admitted to our hospital from 2010-2015 receiving intravenous flucloxacillin or ceftriaxone (control) were retrospectively screened. Patients were included when they were normokalemic at start of antibiotic treatment, were treated for at least 48 hours and had a follow-up potassium level obtained at 48-120 hours after start of therapy. In addition, information on kidney function, diuretic use and in-hospital mortality was documented.

Results: In total, 77 patients receiving flucloxacillin (62% male, mean age 70.5 years (range 32-96 years)) and 84 patients receiving ceftriaxone (46% male, mean age 70.8 years (range 28-96 years)) were included; both groups had similar potassium levels at baseline (mean 3.9 mmol/l, range 3.3-4.7 mmol/l). Hypokalemia occurred significantly more often in patients receiving flucloxacillin than ceftriaxone (40% vs. 14%, respectively, \( p<0.001 \)). Follow-up potassium levels were significantly lower during flucloxacillin therapy than during ceftriaxone therapy (3.4 mmol/l (range 2.3-4.7) vs. 3.6 mmol/l (range 2.6-5.4), \( p=0.01 \)). This was not dependent on differences in mortality rate, diuretic use or kidney function.

Conclusion: Intravenous flucloxacillin use is associated with a striking incidence of hypokalemia after treatment onset. Therefore, standardized potassium measurements are necessary.
Islet autotransplantation after total pancreatectomy for chronic pancreatitis

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Total pancreatectomy for chronic pancreatitis is performed when conservative treatment options fail. After pancreatectomy, the absence of insulin and glucagon secretion combined with malabsorption may lead to labile glucose regulation. In islet autotransplantation, islets are purified from the removed pancreas and retransplanted into the patient, thereby retaining endogenous insulin production. We report on the first two patients in The Netherlands who have undergone this procedure.

Methods: Two female patients, aged 57 and 60 years, required pancreatectomy due to chronic pancreatitis with intractable pain. Both patients had received extensive treatment, including opioids, TENS, and celiac nerve blockade. After surgical removal, the chronically inflamed pancreases were immediately flushed and offered for islet isolation. Islets were isolated successfully from both pancreases. Islet autotransplantation was performed the same day through an infusion in the portal vein.

Results: Patient A received 180,000 islet equivalents. Patient B received 306,500 islet equivalents. Both recovered uneventfully. No severe hypoglycaemic events took place during follow up. After one year, patient A had a stimulated C-peptide after mixed meal test (MMT) of 0.56 nmol/L. Glycaemic control was difficult due to inadequate self-management (HbA1c 70.6 mmol/mol Hb). Patient B had a stimulated C-peptide after MMT of 1.42 nmol/L after one year. Her HbA1c was 43.7 mmol/mol Hb without the use of exogenous insulin. Pain symptoms improved substantially.

Conclusion: Islet autotransplantation after pancreatectomy for a benign disease is now performed in The Netherlands, with satisfying results. Through this procedure the patient retains endogenous insulin and glucagon production, with all its associated benefits.
Auto-immune pancreatitis, a radiological diagnosis?

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We present a 55-year old female patient with left abdominal pain. The dull pain radiated to her back and epigastric region. Laboratory results show an elevated lipase of 137 U/L which decreased spontaneously over time. The inflammatory parameters were normal. Abdominal ultrasound showed a slightly dilated pancreatic duct. A CT scan showed some widening of the common bile duct. An additional MRI pancreas/MRCP showed a ‘sausage-like pancreas’ and a diffusely decreased T1 signal, which can be seen in auto-immune pancreatitis. Additional tests showed normal serum IgG4 levels. In order to rule out malignancy endoscopic ultrasound with fine needle aspiration was performed. The pathology report reported no signs of malignancy. Based on these results serum IgG4-negative auto-immune pancreatitis (SIgG4-negative AIP) was the most likely diagnosis. Treatment with prednisone 40mg once daily was started and resolved the complaints immediately, confirming this diagnosis. An additional MRI after 4 weeks of treatment showed a normal pancreas.

Clinicopathological features of SIgG4-negative AIP differ from those of SIgG4-positive AIP. SIgG4-positive AIP is characterised by infiltration of IgG4-positive plasma cells and T-lymphocytes. It can be considered to be a pancreatic lesion of IgG4-related systemic disease. SIgG4-negative AIP is associated with a distinct characteristic histological pattern and is usually not accompanied by extrapancreatic manifestations. Moreover SIgG4-negative AIP patients are more likely to be female, present with abdominal pain or acute pancreatitis, and demonstrate segmental pancreatic body and/or tail enlargement. AIP is difficult to diagnose, it can sometimes be a radiological diagnosis rather than a serological diagnosis.
Tongue necrosis

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Case: A 73-year old woman with no medical history was admitted to the emergency room with sudden blindness of the left eye. The previous days she has had complaints of a painfull and swollen neck, jaw claudication, mild temporal headache and numbness of the tongue. Physical examination showed no tenderness of the temporal artery or decreased pulses. Examination by an ophthalmologist showed a pale optic disc in the left eye. Blood results showed a raised ESR (114 mm/h), WBC (17.8/nL) and CRP (300 mg/L). The diagnosis temporal arteritis was made. Because loss of vision, patient was immediately treated with 1000mg methylprednisolone for three days.

Two days after admission to the hospital, patient complained of a painful and swollen tongue causing difficulties with eating and talking. Her tongue showed a blue discoloration at the left side with a white/grey discoloration in the middle, suggestive of necrosis. This necrotic aspect increased during the next 12 hours. In an attempt to reduce permanent damage to the tongue, treatment with methylprednisolone 500mg was prolonged for three more days. Furthermore, acetylsalicylic acid and methotrexate were added. Because the necrosis was superficial a debridement was not necessary.

After three days of treatment there was a decrease in ESR, WBC and CRP. The pain and swelling of the tongue decreased after two weeks and the necrotic part of the tongue disappeared without intervention.

Conclusion: Tongue necrosis is a rare but severe complication of temporal arteritis. Awareness of ischemic events as a result of temporal arteritis is necessary.
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Hyperphosphatemia, not always what it seems

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Case: A 67-year old Caucasian female, with a medical history of MGUS developed increasing hyperphosphatemia. She had no symptoms and physical examination showed no abnormalities. Laboratory tests showed a serum phosphate of 6.01 mmol/l (0.9-1.5), which was 2.13 mmol/l seven months before. A phosphate limited diet with calcium carbonate as phosphate binder was initiated pending diagnostics. Renal function was slightly decreased (CKD-EPI 51 ml/min/1.73 m²), but stable. Total protein and M-protein (34g/l) were also stable. Serum calcium and parathormone were normal and vitamin D was low. There was no evidence of exogenous phosphate load, increased tubular reabsorption or cellular shifting. Our working diagnosis was pseudohyperphosphatemia by hyperglobulinemia, as described in literature before. There were no other causes of pseudohyperphosphatemia. Normally phosphate is measured using ammonium phosphomolybdate and electromagnetic light. Paraprotein reacts with ammonium phosphomolybdate, which causes cloudy serum and results in falsely elevated phosphate because of disturbed absorption. We found a normal serum phosphate (1.07 mmol/l) after diluting the plasma thrice. This finding proves pseudohyperphosphatemia. Unjustly phosphate lowering treatment in pseudohyperphosphatemia can result in hypophosphatemia. It is unclear why serum phosphate increased with stable renal function and M-protein in our patient. It is also unclear why only some patients with paraproteinemia develop pseudohyperphosphatemia.

Conclusion: hyperphosphatemia in patients with elevated M-protein or total protein should be re-measured after diluting the plasma to diagnose pseudohyperphosphatemia. This will prevent unnecessary treatment of hyperphosphatemia. Vitamin D, calcium and parathormone should always be determined in these patients to rule out other causes.
Surgery during influenza season is a risk factor for Acute Respiratory Distress Syndrome

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Background: Acute Respiratory Distress Syndrome (ARDS) is a multifactorial life-threatening complication of cardiac surgery. Asymptomatic respiratory viral infection at the time of surgery could be an extra risk factor for developing ARDS postoperatively.

Methods: In a single-center cohort study we compared incidence of ARDS in cardiac surgery patients during the three influenza seasons in 2009, 2010 and 2011, versus periods with low influenza burden. The influenza season was identified from data from The Netherlands Institute for Health Services Research on the incidence of influenza-like illness. ARDS was defined according the Berlin criteria.

Results: Among 2013 cardiac surgery patients, 119 developed ARDS postoperatively. The odds ratio of developing ARDS after cardiac surgery during the influenza seasons was 1.94 (95% CI: 1.11-3.39) compared to surgery during periods with low influenza burden. Also, time on mechanical ventilation was increased during the influenza season.

Conclusion: For development of ARDS following cardiac surgery, performing the intervention during the influenza season constitutes an extra risk. We hypothesize that the additional risk is caused by asymptomatic viral infection in the respiratory tract that may prime the lungs to be more susceptible to ARDS. If causal relation is confirmed in a prospective study, the risk on postoperative ARDS can be attenuated by diagnostic testing for respiratory virus infections preoperatively.
Evaluation of actual management of hypertensive crises in a Dutch Emergency Department: results from a clinical audit

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Background: Hypertension and suspected hypertensive disorders are common reasons for referral to the emergency department (ED). Current hypertensive crises guideline recommendations are difficult to apply. We aimed to evaluate the management of hypertensive crises in a university ED compared to the current Dutch hypertensive crisis guideline, and explore expert opinions on discrepant management through a clinical audit.

Methods: Records from 128 consecutive ED referrals for hypertension or suspected hypertensive crisis with blood pressure >180/100 mmHg from January 2012 until August 2013 were analyzed. Data extracted included anthropometrics, laboratory and imaging diagnostics, and physician prescribed diagnostics and treatment. Each file was assessed by three independent clinicians and compared to guideline recommendations. Expert opinions on discrepancies between guideline recommendations and actual management were evaluated.

Results: Guideline recommended tests were performed in approximately 95% for blood count, ECG, creatinin, and LDH; 65% for urinalysis and bilirubin; less frequently for chest X-ray (31%), fundoscopy (22%), fragmentocytes (13%), and haptoglobin (9%). ED diagnosis was hypertensive emergency (n=17), urgency (n=95), and severe hypertension (n=16). Treatment was consistent with the guideline in 54%. At least 1 out of 3 observers raised some concern on management in 80% of the cases; 2 out of 3 in 47%, and 3 out of 3 in 22%. Measure of agreement was moderate at best (intraclass correlation coefficient=0.487).

Conclusion: Management of hypertensive crises differed considerably from guideline recommendations, leading to expert concern in many cases. A manageable summary of the hypertensive crisis guideline is needed to improve adherence and possibly safety.
Unique homozygous snrpn point mutation as a new cause of prader-willi (like) syndrome

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Introduction: Prader-Willi syndrome (PWS) is a rare condition characterized by hypothalamic dysfunction and cognitive impairment. PWS is usually caused by loss of expression of an entire cluster of paternally expressed genes located in the PWS region on chromosome 15q11.2-q13. We describe a unique patient with the complete spectrum of PWS features, in whom these common causes were ruled out. Additional genetic testing revealed a homozygous point mutation in SNRPN (one of the genes located in the PWS region). This patient is unique, because point mutations have never been described before in patients with PWS.

Patients, materials and methods: In the index patient, we performed automated sequencing, methylation testing, Multiplex Ligation-dependent Probe Amplification (MLPA) analysis and SNP array.

Results: In the 46-years old index patient, genetic diagnose of PWS was initially rejected after regular genetic tests for PWS showed normal results. Since the patient had virtually all phenotypic features corresponding to PWS, we performed additional genetic testing which revealed a homozygous mutation in SNRPN, located in a large homozygous region on chromosome 15. The parents of the patient turned out to be first-degree relatives.

Conclusion: Until now, it is generally accepted that Prader-Willi syndrome can only be caused by functional loss of a cluster of genes within the PWS region on chromosome 15q11.2-q13. The unique finding of a homozygous point mutation in a single gene of this region (SNRPN) in a patient with virtually all features, means a revolutionary change in our knowledge of the pathophysiology of Prader-Willi syndrome.
Hypophosphatemic osteomalacia:
a diagnosis often overlooked

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We present two patients (females aged 39 and 45), previously diagnosed with fibromyalgia and chronic back pain and treated by a psychiatrist, who were referred to our departments for a second opinion. Both women suffered from progressive muscle and bone pain and weakness leading to wheelchair dependency. Physical examination showed proximal muscle weakness and abnormal reflexes of the lower extremities.

Biochemical analysis showed a low phosphate (0.5 and 0.2 mmol/L, ref 0.9-1.5 mmol/L), high alkaline phosphatase activity (377 and 200 U/L) and normal calcium and parathyroid hormone concentrations. Urinary collection showed excessive renal phosphate wasting. Radiological examination showed multiple fractures at the painful locations. These findings were consistent with a diagnosis of hypophosphatemic osteomalacia. Since in both cases there were no signs of underlying tubular disease, interfering drugs or congenital disease, tumor-induced osteomalacia was considered the most likely diagnosis. Indeed fibroblast growth factor-23 (FGF-23) concentrations were inappropriately elevated confirming FGF-23 overproduction. Both patients were treated with phosphate and 1,25 (OH) vitamin D suppletion which improved their symptoms.

FGF-23 producing tumors are of mesenchymal origin and express the somatostatin receptor and therefore a gallium-68-dotatate PET/CT scan was performed to localize the tumor. A gallium-68-dotatate positive lesion was identified in the left vastus medialis in patient A and in the sixth rib in patient B. After surgical resection of the tumors, phosphate concentrations normalized, providing curative treatment.

These cases illustrate the challenge in establishing the diagnosis tumor induced osteomalacia and underline the importance of phosphate measurements in chronic bone pain.
Is nitrous oxide really that joyful?


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Nitrous oxide as a ‘party drug’ is increasingly popular mostly because of the low costs, wide and legal availability and the quick effect. Many people consider the use of nitrous oxide as safe, but is it really innocent?

A 23-year old women from Yemeni origin with a previous history of iron deficiency and recurrent venous thromboembolism came to the emergency room with severe muscle weakness and tingling of her limbs. She mentioned recreational use of nitrous oxide. Laboratory work-up showed a non-immune hemolytic anemia, a deep vitamin B₁₂ deficiency and leukopenia. Electromyography showed an axonal polyneuropathy with demyelination. Lumbar puncture and additional magnetic resonance imaging of the cerebrum, and spine showed no abnormalities. Our patient was diagnosed with non-immune hemolytic anemia, leukopenia and severe neurological impairments as a result of a deep vitamin B₁₂ deficiency due to regular use of nitrous oxide. We started treatment with vitamin B₁₂ supplements, folic acid and intensive physiotherapy. After the start of supplements all laboratory abnormalities gradually normalized but the paraparesis persisted, although slight improvement was seen, requiring admission into a rehabilitation center.

One of the more unknown causes of vitamin B₁₂ deficiency is N₂O and recreational use of it is rapidly increasing. When N₂O is used in high daily doses within a short period or for a prolonged duration, it will irreversibly bind, oxidise, inactivate and eventually deplete vitamin B₁₂.

Conclusion: This case emphasises the serious adverse effects of nitrous oxide abuse with long-term neurological symptoms as a result of vitamin B₁₂ depletion.
A 35-year-old Moroccan man presented with pain in the upper left abdomen since one day. He had a 13-year history of high-dose albendazole treatment for inoperable cardiac cystic echinococcosis and dilated, but stable cardiomyopathy. Physical examination demonstrated a visible and palpable mass pulsating synchronous with every heartbeat in the left upper abdomen. Both cardiac MRI with contrast enhancement and CT demonstrated progression of pericardial *Echinococcus granulosis* cysts over a trajectory of 18 cm suggestive of breakthrough into the abdominal cavity. Infection with the tapeworm *E. granulosis* is common in Mediterranean countries. Cysts are commonly found in the liver and lung, however cardiac involvement is rare (prevalence 0.5-2% of all cases). Moreover, pericardial invasion and/or isolated cardiac involvement are uncommon features, and to our knowledge secondary involvement of the abdominal cavity has not been described yet. As surgery offers the only definitive treatment, this was reconsidered. However, in our patient, cyst evacuation and obliteration were considered too high-risk risk for spillage, and due to coronary and left ventricular wall invasion severe bleeding risk and tissue loss, respectively, are to be expected. Alternatively, heart transplantation was considered non-feasible due to the multilocularity and size of the echinococcosis, an expected lengthy transplantation time and vascular connection difficulties, with cyst localization around both atria and large vessels. After consultations with colleagues from other medical institutions in Europe, a conservative approach was followed. Albendazole treatment was continued and cimetidine and praziquantel were added. Our patient remained clinically stable, although radiological follow-up demonstrated slow disease progression.
Anti-Xa activity after a reduced therapeutic dose of nadroparin in patients with impaired renal function using a dosage guideline of the Dutch federation of nephrology

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Background: Low-molecular-weight heparins (LMWHs) are mainly excreted by the kidneys and may accumulate in patients with impaired renal function, leading to increased anti-Xa activity (aXa) associated with a 2-3 fold increased bleeding risk. Therefore, in patients with renal impairment the Dutch federation of Nephrology (NfN) recommend a dosage reduction.

Methods: In this prospective, observational, multicentre, cohort study patients were included between July 2014 and April 2016 if they met inclusion criteria: age > 18 years, therapeutic dose of nadroparin, subcutaneous administration = three days and written informed consent. Exclusion criteria were: dialysis, participation in another study and use of anti-Xa inhibitors other than nadroparin or four-factor prothrombin complex concentrate within seven days before the start of the study or during the study. After at least three adjusted doses on the third day of therapy a blood sample was drawn four hours after the administration of nadroparin (therapeutic range: 0.6-1.0 IU/ml).

Results: 97 respectively 100 patients with eGFR < 60 ml/min and > 60 ml/min were included. The mean aXa was 0.63 IU/ml respectively 0.62 IU/ml (p for equivalence = 0.015). In the group with renal impairment 51.6%, 11.6% respectively 36.8% of the patients achieved sub-, supra- and therapeutic aXa compared with 46.5%, 7.1% respectively 46.5% in the normal renal function group (p = 0.30).

Conclusion: In patients with impaired renal function a dosage reduction of therapeutic nadroparin using the dosage guideline of the NfN results in equivalent treatment compared to patients with normal renal function treated with a standard dose.
The mimic of vasculitis, segmental arterial mediolysis

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Case: A 45 year old woman was referred because of remitting abdominal pain. Her medical history included an abdominal uterus extirpation, cholecystectomy, hypertension and MGUS with slightly elevated IgG lambda levels (24.4 mg/L). Previous ultrasonography had shown a dissection of the hepatic artery, but was normal otherwise. Emergency CT-angiography showed dissections of the hepatic, superior mesenteric, right external iliac and left internal iliac arteries, and caliber jumps in the superior mesenteric and both renal arteries. Initial laboratory testing showed elevated ESR (42 mm/h) and CRP (43 mg/L), normal renal and liver panels. Blood cultures, lues-serology, hepatitis A/B/C serology, cryoglobulines, ANA and ANCA were negative. PET-CT furthermore showed slightly elevated uptake among abdominal arteries. Absence of systemic inflammation and the characteristic CT-findings led us to a rare diagnosis, segmental arterial mediolysis (SAM). Subsequently the inflammatory markers normalized spontaneously. Follow-up CT-angiography, whilst the patient remained asymptomatic, showed new dissections and stenoses in the superior mesenteric and left hepatic artery, with persistently normal inflammation markers.

Discussion: We present a case with a subacute a non-arteriosclerotic, non-inflammatory vasculopathy leading to impaired perfusion of liver and kidneys. It is caused by lysis of the media of the arterial wall of which the etiology is unknown. Most common presentation is spontaneous abdominal hemorrhage with high mortality. Treatment with immunosuppressants are likely counterproductive. Follow-up with CT-angiography and endovascular treatment of aneurysms are advised. The differential diagnosis of SAM includes fibromuscular dysplasia and various vasculitis and is based on radiological findings and exclusion of other causes of vasculopathy.
Quantification of non-osmotic sodium storage capacity following acute hypertonic saline infusion in healthy subjects

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Background: The assumption that sodium accumulation in the human body is always accompanied by water retention has been challenged by data showing that sodium can be stored non-osmotically by negatively-charged glycosaminoglycans in the skin or endothelial surface layer.

Methods: We investigated the contribution of non-osmotic sodium storage to short-term sodium homeostasis after hypertonic NaCl infusion (540 mL, 2.4%) in healthy individuals on a low sodium diet. During four hours after infusion we compared the observed changes in plasma sodium concentration and urinary cation excretion with changes that were calculated with the Adrogue-Madias and Nguyen-Kurtz formulas; formulas that are widely applied to guide dysnatremia treatment.

Results: We included 12 healthy non-smoking male individuals with normal blood pressure, body mass index and kidney function. Right after infusion, the average observed plasma sodium change from baseline (3.5 mmol/L) was similar to the predicted changes by the Adrogue-Madias (3.3 mmol/L) and Nguyen-Kurtz formulas (3.1 mmol/L). However, the observed plasma sodium concentration change after four hours (-1.8 mmol/L) was very different from the changes as predicted by the Adrogue-Madias (0.4 mmol/L) and Nguyen-Kurtz formulas (-0.9 mmol/L). Moreover, only 47 and 55%, respectively, of the expected principal cations (sodium and potassium) were excreted in the urine. We observed no changes in hemodynamics.

Conclusion: Healthy individuals are able to osmotically inactivate significant amounts of sodium after hypertonic saline infusion. This phenomenon complicates the use of the Adrogue-Madias and Nguyen-Kurtz formulas in dysnatremia treatment. Frequent laboratory follow-up of dysnatremic patients after initiation of treatment is therefore essential.
Medication adherence in patients with apparent resistant hypertension: findings from the SYMPATHY trial


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**Background:** Resistant hypertension is defined as hypertension despite the use of three or more antihypertensive drugs. It is important to objectively assess adherence to antihypertensive drugs to understand the condition of resistant hypertension. Our aim was to explore the degree of adherence in apparent resistant hypertensive patients, potential determinants of non-adherence, relation with blood pressure (BP) and change in adherence overtime.

**Methods:** This project was a sub-study (n=98) of SYMPATHY (n=139), an open-label randomized-controlled trial to assess the effect of renal denervation on BP six months after treatment compared to usual care in patients with resistant hypertension. Stored serum samples were used to qualitatively assess adherence at baseline and six months. Office and 24-hour BP were measured on the same day that blood was sampled. Patients and physicians were unaware of adherence measurements.

**Results:** At baseline 74% were either poorly or non-adherent (<80% detected). Of the average of 3.6 prescribed BP lowering pills, 1.8 were detected in blood (P<0.001). The higher the number of prescribed antihypertensive pills or the higher office systolic BP, the lower was the adherence. A decrease of 1 pill in adherence between baseline and six months was related to a significant increase in BP of 4/2 mmHg (P=0.042 and 0.045, respectively).

**Conclusion:** Poor adherence was highly prevalent in patients with apparent resistant hypertension and was associated with higher BP. It represents a relevant medical but also societal problem, since these patients consume healthcare unnecessarily. Strategies to address poor adherence should be developed.
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Agonist-induced platelet reactivity correlates with bleeding in hemato-oncological patients

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Background: Prophylactic platelet transfusions are administered to prevent bleeding in hemato-oncological patients. However, bleeding still occurs, despite these transfusions. This practice is costly and not without risk. Better predictors of bleeding are needed and flow cytometric evaluation of platelet function might aid the clinician in identifying patients at risk of bleeding. This evaluation can be performed within the hour and is not hampered by low platelet count. Our objective was to assess a possible correlation between bleeding and platelet function in thrombocytopenic hemato-oncological patients.

Methods: Inclusion was possible for admitted hemato-oncology patients aged 18 years and above. Furthermore, an expected need for platelet transfusions was necessary. Bleeding was graded according to the WHO bleeding scale. Platelet reactivity to stimulation by either adenosine diphosphate (ADP), crosslinked collagen-related peptide (CRP-xL), PAR1- or PAR4-activating peptide (AP) was measured using flow cytometry.

Results: A total of 114 evaluations were available from 21 consecutive patients. Platelet reactivity in response to stimulation by all four studied agonists was inversely correlated with significant bleeding. Odds Ratio’s (OR) for bleeding were 0.28 for every unit increase in median fluorescence intensity (MFI) [95% Confidence interval (CI) 0.11-0.73] for ADP; 0.59 [0.40-0.87] for CRP-xL; 0.59 [0.37-0.94] for PAR1-AP and 0.43 [0.23-0.79] for PAR4-AP. The platelet count was not correlated with bleeding (OR 0.99 [0.96-1.02]).

Conclusion: Agonist-induced platelet reactivity was significantly correlated to bleeding. Platelet function testing could provide a basis for a personalized transfusion regimen, in which platelet transfusions are limited to those at risk of bleeding.
Background: Metastatic infection is an important complication of *Staphylococcus aureus* bacteremia (SAB). Early diagnosis of metastatic infection is crucial, as specific treatment is required. $^{18}$F-fluorodeoxyglucose positron emission tomography combined with computed tomography ($^{18}$F-FDG-PET/CT) has been described to improve the detection of these silent metastatic foci. In this study, we investigated the role of $^{18}$F-FDG-PET/CT in patients with SAB for detection of metastatic infection and its consequences for treatment and outcome.

Material/methods: All patients with SAB at the Radboud university medical center were included between January 2013 and April 2016. Clinical data and results of $^{18}$F-FDG-PET/CT and other imaging techniques including echocardiography were collected. Primary outcomes were newly diagnosed metastatic infection by $^{18}$F-FDG-PET/CT, subsequent treatment modifications, and outcome.

Results: 184 patients were included, and $^{18}$F-FDG-PET/CT scans were performed in 105 patients. $^{18}$F-FDG-PET/CT detected metastatic infectious foci in 71.4% of patients. Three-months' mortality was higher in high risk bacteremia patients without $^{18}$F-FDG-PET/CT performed compared to those in whom $^{18}$F-FDG-PET/CT was performed (32.7% versus 12.4%, p<0.05). In a multivariate analysis, $^{18}$F-FDG-PET/CT was the only factor independently associated with reduced mortality. $^{18}$F-FDG-PET/CT led to a total of 106 treatment modifications in 75 patients: shorter treatment duration in 25 patients, surgical or radiological intervention in 19 patients, prolonged intravenous antibiotic therapy in 16 patients, addition of a second drug in 10 patients, and extension of treatment duration in 36 patients.

Conclusions: $^{18}$F-FDG-PET/CT is a valuable technique for early detection of metastatic infectious foci, treatment optimization, and associated with significantly reduced three-month mortality.
The impact of the introduction of bortezomib on dialysis independence in multiple myeloma patients with renal failure: a nationwide population-based study

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Background: Studies have shown that bortezomib has a positive effect on renal function in multiple myeloma (MM) patients with renal impairment, which encouraged the Dutch HOVON Myeloma Working Group to publish a guideline recommending bortezomib as first line therapy in patients with renal insufficiency in 2010. The aim of this study is to determine the effect of the introduction of bortezomib on dialysis independence.

Methods: Patients on renal replacement therapy are registered in the Dutch registry ‘Renine’. We selected all patients with MM registered between January 2002 and January 2016. As the guideline was published in The Netherlands on March 29, 2010, we divided the cohort in two periods, pre-guideline (January 1, 2002 till March 29, 2010) and post-guideline (March 29, 2010 till January 1, 2016).

Results: A total of 700 patients were included in the study (422 patients pre-guideline and 278 post-guideline). In the post-guideline period, 15% of patients reached dialysis independence compared to 8% in the pre-guideline period (HR_adj = 2.1 (95%CI 1.3 - 3.3)). In addition, patients who started dialysis in the post-guideline period became dialysis independent more rapidly than in the pre-guideline period (1.2 compared to 1.7 years; p <0.001).

Conclusions: In this nationwide population-based study, covering all patients with MM and concomitant renal failure, we found almost a doubling of patients becoming dialysis independent in the post-guideline period compared to the period where bortezomib was not used as first line treatment. Furthermore, patients reached dialysis independence more rapidly in the post-guideline period.
Panniculitis and polyarthritis as the presenting feature of pancreatic cancer

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Case: A 64-year-old man presented at the dermatologist with painful erythematous nodules on both legs, resembling erythema nodosum. Histological examination showed a panniculitis. Within 6 weeks some lesions started secreting a yellow-brown purulent-appearing material and a severe oligoarthritis developed. The physical condition deteriorated and the patient had to be hospitalized. An abdominal CT-scan showed an extensive retroperitoneal tumor mass. A paraneoplastic syndrome was suspected but not exactly declared. The patient died 2 weeks later. Autopsy revealed metastasized pancreatic acinar cell carcinoma (ACC). The skin lesions could be interpreted as lobular panniculitis with fat necrosis, matching pancreatic panniculitis. Afterwards, a premortal serum lipase was found to be extremely increased.

Discussion: Pancreatic panniculitis with (poly)arthritis is a rare manifestation of pancreatic disease. Hypersecretion of lipolytic pancreatic enzymes causes fat lipolysis, leading to focal necrosis and secondary inflammation of periarticular and subcutaneous fat. The skin lesions can ulcerate and extrude an oily material due to liquefaction fat necrosis. Although the phenomena usually includes pancreatitis, sometimes it occurs in the presence of pancreatic cancer, mostly ACC. Up to 10% of pancreatic ACCs present with pancreatic panniculitis, often (45-60%) preceding the signs of abdominal disease. The skin lesions and articular manifestations, as in our patient, are often initially misdiagnosed as erythema nodosum, leading to inappropriate or delayed treatment.

Conclusion: Panniculitis with (poly)arthritis is a recognizable clinical and histological entity that may serve as a clue to underlying pancreatic disease, especially in the presence of abdominal symptoms. Serum lipase should be measured to determine pancreatic panniculitis.
ICARES: A real-time automated detection tool for clusters of infectious diseases in The Netherlands

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Background: Clusters of infectious diseases are frequently detected late. Real-time, detailed information about an evolving cluster and associated conditions is essential for healthcare professionals, local policy makers and the population. This is currently illustrated in the Zika virus outbreak.

Methods: In the Leiden-The Hague region, ICARES (Integrated Crisis Alert and Response System) has been developed and tested on three syndromes as an automated, real-time tool for early detection of clusters of infectious diseases. From a hospital, local general practices and General Practice Out-of-Hours services, the numbers of routinely used syndrome codes for three piloted tracts i.e. respiratory tract infection, hepatitis and encephalitis/meningitis, are sent on a daily basis to a central unit of infectious disease control. Historic data combined with information about patients’ syndromes, age cohort, gender and postal code area have been used to detect clusters of cases.

Results: During the first two years, two out of eight alerts appeared to be a real cluster. The first was part of the seasonal increase in Enterovirus encephalitis and the second was a remarkably long lasting influenza season with high peak incidence.

Conclusions: ICARES is able to detect and follow small regional clusters in real time and can handle any disease entity that is regularly registered by clinicians. In the near future we hope to add more hospitals to ICARES thus improving further the signal-to-noise ratio, expanding coverage and to evaluate diagnostic protocols for possible outbreaks. Instant information about an outbreak is essential for individual patient care and public health care.
Changes in Pathogens and Pneumococcal Serotypes Causing Community-Acquired Pneumonia in The Netherlands

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Background: In 2006 a 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in the immunisation programme for infants in The Netherlands for infants and replaced by PCV10 in 2011. Limited data exist about the impact of PCV on the aetiology of CAP as a whole. The aim of the present study is to describe the overall changes in microbial aetiology, pneumococcal burden (including non-bacteraemic pneumococcal pneumonia) and its serotypes in adult community-acquired pneumonia (CAP) after the introduction of these PCVs.

Methods: Hospitalised adult CAP patients who participated in three consecutive trials were studied (2004-2006 (n=201), 2007-2009 (n=304) and 2012-2016 (n=300) and considered as pre-PCV7, PCV7 and PCV10 period). Extensive conventional microbiological testing was applied for all patients. In addition patients with a serotype-specific pneumococcal antibody response were diagnosed with pneumococcal CAP. Changes in proportions of causative pathogens and distributions of pneumococcal serotypes were calculated.

Results: The proportion of pneumococcal CAP decreased from 37 to 26% comparing the pre-PCV7 period with the PCV10 period (p=0.01). For other pathogens, including Legionella spp., Mycoplasma pneumoniae, S.aureus, H.influenzae, and respiratory viruses, no sustained shifts were observed in their relative contribution to the aetiology of CAP. Within the pneumococcal CAP patients, we observed a decrease in PCV7 and an increase in non-PCV10 serotype disease. Notably, PCV7 type disease decreased both in bacteraemic and non-bacteraemic patients.

Conclusion: Our findings confirm that PCV introduction in infants impact the microbial aetiology of adult CAP and suggest herd effects in adults with CAP after introduction of PCVs in children.
Corticosteroids in patients hospitalised with community-acquired pneumonia: systematic review and individual patient data meta-analysis

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Background: Benefits and harms of adjunctive systemic corticosteroids for community-acquired pneumonia (CAP) are inconclusive. We aimed to evaluate the effects of adjunctive corticosteroids in adults hospitalised with CAP, on patient-important outcomes using individual patients’ data of randomised placebo-controlled trials.

Methods: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and trial registers (all through 9 June 2016) were systematically searched for eligible trials. Data from 1,506 individual patients in six trials were analysed using uniform outcome definitions. We investigated pre-specified effect modifiers using multivariable hierarchical regression adjusting for pneumonia severity, age, and clustering effects.

Results: Within 30 days of randomisation, 37 of 748 patients (5.0%) assigned to corticosteroids and 45 of 758 patients (5.9%) assigned to placebo died (adjusted OR 0.75; 95% CI 0.46-1.21, p:0.24). Time to clinical stability and length of hospital stay were reduced by approximately one day with corticosteroids (adjusted difference, -1.03 days, 95% CI -1.62-(-0.43), p<0.001; and -1.15 days, 95% CI -1.75-(-0.55), p<0.001, respectively). Patients who received corticosteroids had a higher incidence of hyperglycaemia requiring insulin treatment (adjusted OR 2.15, 95% CI 1.60-2.90, p<0.001; number needed to harm [NNH] 9) and CAP-related re-hospitalisation (adjusted OR, 1.85; 95% CI 1.03-3.32, p<0.04; NNH, 45). No significant differences for other CAP-related or corticosteroid-related adverse effects between groups were found.

Conclusion: Adjunct corticosteroids for patients hospitalised with CAP reduce time to clinical stability and length of hospital stay by approximately one day without a significant effect on overall mortality but with an increased risk for CAP-related rehospitalisation and hyperglycaemia.
A sacred purge induced coma

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A 68-year-old male was brought to our emergency room with coma (EtMiVi) after visiting a healing ceremony where he had drunk an herbal potion. The patient was intubated. The blood pressure was 140/60 mm Hg and with a regular pulse of 62 bpm. Based on his medical history of severe hemophilia A, an intracerebral hemorrhage was excluded by computed tomography of the brain, however, edema of the temporal lobes and pons was present. Laboratory data showed a severe hyponatremia (110 mmol/L) and an antidiuretic hormone effect was suspected (urine osmolality 385 mOsmol/kg, urinary sodium was inappropriately high, 53 mmol/L). The healing ritual consists of drinking ayahuasca (a psychoactive potion) repeatedly combined with one liter water to clean body, mind and soul by its purgative effects. In the Amazon, ayahuasca is brewed from the vine Banisteriopsis caapi and the leafs Psychotria viridis, and is to be regarded as a sacred plant medicine. The compounds are MAO inhibitors and are notorious for their antidiuretic effects. Hypertonic saline was administered and fluid restriction was enforced. A few hours later, the patient experienced a massive upper gastrointestinal tract bleeding due to a Dieulafoy lesion and was clipped after co-administration of Advate (recombinant FVIII). When stimulus for inappropriate vasopressin release slowly weakened, serum sodium became within the normal range and the patient fully recovered. To our knowledge this is the first case report of severe hyponatremia after ingesting ayahuasca due to its MAO inhibitory effects in combination with excessive fluid intake.
An extremely high ferritin under ANCA therapy

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Introduction: Leucopenia is common in patients treated with cyclophosphamide for ANCA associated vasculitis (AAV). Bone marrow suppression and viral infections are well-known complications. However, extremely high ferritin in AAV has not been described before. Case: A 71-year-old man was diagnosed with acute renal failure with erythrocyturia and proteinuria. ANCA appeared positive (MPO 80E/ml). Kidney biopsy showed a necrotizing crescentic glomerulonephritis with acute tubular necrosis. Patient was treated with prednisone, cyclophosphamide, plasmapheresis and hemodialysis. Two weeks later, he presented with pulmonary embolism. He had fever, leucopenia ($3.3 \times 10^6$), elevated liver enzymes, and serum ferritin of 18.569 ug/L. Cyclophosphamide was stopped. The persistent leucopenia, fever and elevated liver enzymes made us diagnose CMV re-activation (CMV titer $3 \times 10^6$ copies/ml). The highly elevated ferritin was suggestive for a hemophagocytic lymphohistiocytosis (HLH) which was confirmed by bone marrow aspirate. Ganciclovir was started for the CMV reactivation. Anakinra (interleukin 1 receptor antagonist) was administered for 10 days in order to limit the excessive inflammation cascade and inhibit phagocytosis. The patient recovered but stayed on dialysis. Discussion: HLH is a life threatening overstimulation of the immune system causing inflammation and multi-organ failure. Activation of macrophages and histiocytes cause phagocytosis of the blood elements. Autoimmune diseases and immunodeficiency are predisposing conditions for HLH and viral infections including CMV reactivation are well-known triggers. Conclusion: Although leucopenia is a common complication of cyclophosphamide, one should consider alternative diagnosis as CMV. Elevated ferritin is suggestive for HLH. Mortality of HLH is over 38% and immediate treatment is indicated.
**Management and short-term prognosis of recurrent venous thromboembolism in anticoagulated patients**

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**Background:** ACCP guideline recommendations for the treatment of recurrent venous thromboembolism (VTE) during anticoagulant therapy are based on low quality evidence. We aimed to describe the management of VTE during treatment with anticoagulants and investigated the clinical course of these treatment regimens.

**Methods:** This prospective multi-center observational cohort study included patients with objectively confirmed VTE during anticoagulant treatment (breakthrough event) for any indication.

**Results:** We registered 121 patients with a breakthrough event with a mean age of 56 (range 19 to 90) years; 61 (50%) were male. Active malignancy was the provoking factor in 58 patients (48%). At the time of the breakthrough event, 57 patients (47%) were treated with a vitamin K antagonist (VKA), 53 patients (44%) with low-molecular-weight heparin (LMWH) and 11 patients (9%) with other types of anticoagulants. Twenty-one patients (17%) had a sub-therapeutic dose of anticoagulant. The main regimens to treat the recurrence in patients on VKA were: switch to LMWH (33%), LMWH added to VKA temporarily (23%) and VKA with a higher target INR (19%). In patients with a breakthrough on LMWH the most frequently chosen regimen was to increase the dose permanently (74%). During 3-month follow-up 5-7% of patients had a second breakthrough event and 8% had major or clinically relevant non-major bleeding.

**Conclusion:** There is a wide practice variation in the management of breakthrough events, reflecting the heterogeneous and complex nature of this clinical situation. Breakthrough events often develop in patients with cancer or in patients receiving subtherapeutic anticoagulation. The risk of a second breakthrough event in this high-risk population is 5-7%.
A 30-year-old male was presented with trismus and inspiritional stridor at the emergency room. His medical history included hyperventilation. Medical examination revealed an endangered airway due to trismus, no signs of cyanosis, a saturation of 97% and normal breathing sounds. Further examination revealed rigor of all muscles and was otherwise indifferent. Inspection with the fiberscope showed no obstruction of the airway. Laboratory results yielded a severe respiratory alkalosis with a pH of 7.71, pCO2 2.1, pO2 15.5, bicarbonate 20.2, lactate 3.2 and phosphor <0.22, other electrolytes were normal and inflammatory parameters were low. The diagnosis was trismus and rigor caused by hypophosphatemia due to hyperventilation as a result of a panic attack. Hypophosphatemia due to hyperventilation is caused by alkalosis, in this case as a result of a low carbon dioxide. As a consequence of the intracellular alkalosis phosphofructokinase is stimulated, which is the rate limiting enzyme in glycolysis. This reaction causes the consumption of intracellular phosphate. As a result, phosphate is redistributed into the intracellular space, reducing extracellular phosphate concentration. As well, glycolysis produces lactate, which was also elevated in this patient.

The patient was admitted to the intensive care and observed for 24 hours after which the patients symptoms, hypophosphatemia and arterial blood gas abnormalities spontaneously recovered. Patient was referred to centre 40–45 for his panic attacks to deal with a past war trauma.

Conclusion: Trismus is a life threatening symptom which can be caused by a hypophosphatemia.
‘Ecstasy-light’, not as light as its name suggests?

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Background: In recent years, the use of 4-fluoroamphetamine (4-FA or ‘ecstasy-light’), has shown a marked increase. Although many users perceive the risk of using 4-FA as low, it can result in serious medical problems, as illustrated below.

Cases: Case 1 is a 21-year-old male who used 200 mg 4-FA at a party. As a result, he developed a tonic-clonic seizure, bruxism, mydriasis, and rhabdomyolysis, which resolved after rehydration within several days. Case 2 is a 19-year-old female, without any psychiatric history, who was brought to the hospital by the police because of confusion and a suicide attempt. This started shortly after the ingestion of 5 tablets 4-FA at a party and spontaneously resolved within several hours of observation. The last patient is a 22-year-old man who developed tachycardia of 170 bpm, hypertension (190/130 mmHg), and hyperthermia (38.7°C), after a suicide attempt with 14 tablets of 4-FA. Intubation, sedation, and cooling was necessary. He recovered completely within 24 hours.

Discussion and Conclusion: These 3 cases illustrate that 4-FA can result in serious medical problems. Over the last years, the use of 4-FA has shown a marked increase, because its relative mild toxic effects. However, this also resulted in an increased need for medical assistance from 0 reports in 2011 to 184 reports in 2015. Next to the abovementioned symptoms, severe headaches, cardiac problems, and cerebral bleeding can occur. Therefore, 4-FA will be prohibited in April 2017. Treatment is supportive and based on its pharmacologic resemblance with amphetamine and ecstasy.
Predicting Mortality in Patients at the Emergency Department with Sepsis using qSOFA, SIRS and National Early Warning Score

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Background: Sepsis is a serious condition with high mortality rates. In 2016, Systemic Inflammatory Response Syndrome (SIRS) was discarded as part of the sepsis definition. Currently, sepsis-related mortality is assessed using the qSOFA. However, early warning scores can possibly also predict mortality in patients with sepsis. We aimed to compare qSOFA to SIRS criteria, and National Early Warning Score (NEWS) in predicting mortality in patients at the Emergency Department (ED).

Methods: Patients visiting the ED between 2012-2015 with suspected infection (defined as initiation of intravenous antibiotics and/or collection of any culture at the ED) were included. Outcome was specified as 10-day and 30-day mortality after ED presentation. Parameters required for qSOFA, SIRS and NEWS and mortality data were collected. Predictive performance was expressed as discrimination using logistic regression and sensitivity, and specificity were calculated.

Results: 7,334 patients met inclusion criteria. In total 258 (3.5%) and 459 (6.3%) patients died within 10- and 30-day mortality, respectively. NEWS performed best in predicting 10- and 30-day mortality, followed by qSOFA and SIRS (10-day AUC: 0.814, 0.776, 0.713, 30-day AUC: 0.784, 0.747, 0.688). Furthermore, qSOFA lacked a high sensitivity vs. SIRS and NEWS (27.9%, 74.8%, 57.8%).

Conclusion: This is the first European study that showed that qSOFA is a better performing prompt in predicting mortality of sepsis than SIRS. However, NEWS performed superior in predicting mortality. Additionally, due to the low sensitivity in qSOFA, the value of qSOFA as a prompt at the ED will be challenged.
An autointoxication with aluminium phosphide

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Case: a 61-year old man alerted the emergency services because he had deliberately ingested aluminium phosphide tablets; a rodenticide to eliminate moles. Upon arrival of the ambulance the patient was vomiting and a garlic smell filled the room. At the emergency department the patient had a saturation of 91% despite maximal oxygen supply and a blood pressure of 84/41 mmHg. Furthermore, his abdomen was distended and hypertympanic. Lab results demonstrated a metabolic acidosis (pH 7.14) and acute kidney failure. The national poison centre was consulted and since the patient was a potential danger to his surroundings he was moved outside the hospital into a ventilated tent to receive further care. The patient was treated with inotropes, vasopressors and non-invasive ventilation in the ventilated tent during 6 hours after which he was transferred to the ICU. After four days of supportive care in the ICU the patient was transferred to the internal medicine ward and he was discharged without any residual symptoms.

Discussion: aluminium phosphide is converted to phosphine (PH₃) upon contact with water or acids. Phosphine is an extremely toxic gas because of its direct corrosive effects on mucosa and its disruption of mitochondrial metabolism, which leads to multi-organ failure. Ingestion of metal phosphides is a well-known suicide route, especially in Asia, with mortality rates around 70%. There are no known antidotes and curative interventions are limited to supportive care. Upon encounter with metal phosphide intoxication, health care workers should be aware of the threat to their own safety.
Thoracocervicofacial purpura: Seizures under my skin?

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Introduction: Purpura have been reported in patients with normal platelet counts and platelet function. In this case, thoracocervicofacial purpura developed after a syncope. The typical location as well as an elevated prolactin level, led to the diagnosis of seizure-induced purpura.

Case: A 44-year old male, with a history of depression and obstructive sleep apnea syndrome, was admitted for observation after a syncope. He was found collapsed on the couch after an unwatched event. Physical examination showed petechial thoracocervicofacial purpura, bilateral tongue hematoma and a small conjunctival hemorrhage. Except for retrograde amnesia for the episode neurological examination was normal. Vital signs, platelet count, coagulation profile and brain MRI were normal. Radiological imaging showed normal cervical and thoracic vasculature without signs of obstruction or malformation. Biopsy of a purpuric lesion revealed extravasation of erythrocytes. Despite a normal electroencephalography after sleep deprivation, we concluded that the collapse was attributable to a tonic-clonic seizure. Supportive of this conclusion are the typical site of the purpura, the retrograde amnesia and tongue hematoma after a syncope, and an elevated serum prolactin level (0.66 U/L) in a sample that was obtained at the emergency department. Alternative causes of the episode were excluded. The purpura completely resolved within three weeks.

Conclusion: We report a case of thoracocervicofacial purpura as the pivotal manifestation of an epileptic seizure due to increased thoracic pressure and intense contractions of chest musculature. Seizure-induced purpura are a rare finding that might be the diagnostic clue in the absence of other objective signs.
Is multimorbidity associated with increased length of stay at the emergency department?

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Background: Overcrowding in the emergency department (ED), a frequently accounted problem, is associated with higher patient morbidity, mortality and medical errors. It is presumed that overcrowding is caused by a longer length of stay (LOS) of patients with multimorbidity. This study investigates whether LOS differs between multimorbid and non-multimorbid patients. Furthermore, other factors influencing LOS are sought for.

Methods: From 9-30 September 2016, all 280 patients admitted to the ED for internal medicine specialties and their attending physicians were asked to complete time registration forms. LOS, door-to-doctor-time, triage time, type and number of procedures and discharge diagnoses were collected. Multimorbidity was defined as the presence of two or more chronic diseases requiring on-going therapy or monitoring. Mann Whitney U-test was used to evaluate whether ED LOS was longer in multimorbid patients. Other potential factors associated with LOS were examined by linear regression.

Results: 162 patients (mean age 55 years, 40% male, 57% multimorbid), whom had at least one time registration form filled out, were included. The median LOS was 206 (interquartile range 261-170) minutes. Multimorbidity was not associated with LOS (p = 0.166). A higher amount of diagnostic imaging studies, discharge diagnoses, and electrocardiography, were associated with increased LOS. In elderly (aged >70 years), discharge home was associated with increased LOS.

Conclusion: Multimorbidity appears not to be associated with increased ED LOS, whereas an increase in diagnostic tests and discharge diagnoses is. To improve LOS, measures should be taken to improve the diagnostic process for patients with multiple discharge diagnoses.
A 68-year old woman presented to the emergency department with an attempted suicide with antipsychotics, selective serotonin reuptake inhibitors and benzodiazepines. Her medical history included long-term depression and multiple self-poisonings. On physical examination the patient was lethargic, but hemodynamically stable with no abnormalities on ECG. She was admitted for observation with cardiac monitoring, again without abnormalities. The next day at discharge, the patient suddenly suffered from nausea, dyspnea and chest pain. She developed hypotension, increased heart rate, and low peripheral oxygen saturations that did not resolve despite fluid and oxygen administration. Moreover, increased central venous pressure and dorsobasal crepitations were found. Laboratory diagnostics yielded increased cardiac biomarkers. CT-angiography ruled out pulmonary embolism. Echocardiography demonstrated an extensive akinetic apical left ventricular wall with an overall poor left ventricular function. These findings led to the diagnosis takotsubo cardiomyopathy. The patient was transferred to the ICU for mechanical ventilation. Treatment with clopidogrel, simvastatin, beta blockers and diuretics was initiated. Coronary angiography showed no coronary artery disease. Follow-up echocardiography demonstrated markedly improved left ventricular function. As the patient improved clinically, drug treatment could be tapered. Takotsubo cardiomyopathy is a rare condition that should be taken into consideration, especially when a patient has endured severe emotional or physical stress. Takotsubo cardiomyopathy predominantly affects menopausal women. Notwithstanding life-threatening initial presentation, most patients recover completely and long term prognosis is good.
Direct Oral AntiCoagulant (DOAC’s); is recognition as an anticoagulant by different specialists a problem?

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Background: Since 2016 the Dutch guidelines prefer direct oral anticoagulants (DOAC’s) over vitamin K antagonists for the treatment of venous thrombosis and DOAC’s are more and more prescribed by internists and other specialists. The fear has been pronounced that not all physicians do recognize these medicine as anticoagulant drugs and this could be potentially harmful. We investigated whether this fear is indeed true.

Methods: A questionnaire was taken by phone in the UMC Utrecht among 60 doctors in training for 7 different specialties. The doctors were randomly selected from prespecified specialties. The questionnaire existed of two cases in which doctors had to recognize Acenocoumarol and Rivaroxaban as anticoagulants, direct questions about Rivaroxaban, Apixaban and Dabigatran asking the respondents to explain what kind of drugs these are.

Results: All 60 respondents (100%) recognized Acenocoumarol and Rivaroxaban was recognized by 90%. 97% said to know what kind of drug Rivaroxaban is, 95% thought to know Apixaban and 97% Dabigatran. 95% (57) gave the right description of Rivaroxban, 93% (56) of Apixaban and all 97% described Dabigatran correctly.

Conclusion: DOAC’s are well recognized as anticoagulant drugs among physicians in training of our prespecified specialties. Although DOAC’s were well recognized as anticoagulants, many physicians were not certain and indicated that they would contact the thrombosis expert for advice.
A 29-year old, 28 weeks pregnant woman presented at our emergency department with hyperglycemia. She complained of polyuria, polydipsia, weight loss and malaise since the past week. Medical history revealed no diabetes mellitus and first trimester glucose was 4.6 mmol/l. Her first pregnancy was prematurely aborted due to spina bifida. At physical examination she had signs of dehydration with tachycardia. Arterial blood gas showed a respiratory compensated metabolic acidosis (pH 7.36, bic 15 mmol/l, pCO₂ 3.5 kPa) with a high anion gap (15.9 mmol/l) and lactate 3.1 mmol/l Additional laboratory tests showed: glucose 54 mmol/l, sodium 126 mmol/l, potassium 5.5 mmol/l, calcium 3.16 mmol/l and urine analyses showed ketonuria. We concluded that the woman had a de novo diabetes during pregnancy with a hyperglycemic hyperosmolar state, dehydration, and mild ketoacidosis. She was treated with aggressive volume replacement, intravenous insulin and correction of electrolytes. Maternal and fetal response to therapy were closely monitored. Despite good maternal response to therapy, fetal distress arose requiring an emergency cesarean. Unfortunately the fetus died before arriving at the operation room. After delivery, insulin requirements of the woman gradually decreased, and could be stopped after four weeks. Anti-GAD antibodies were negative. Hyperglycemic hyperosmolar syndromes and diabetic ketoacidosis are very rare presenting signs of diabetes in pregnancy, especially in gestational diabetes. Clinical presentation of polydipsia and polyuria in pregnancy requires immediate glucose measurement. Diabetic ketoacidosis in pregnancy can be insidious, usually at lower glucose levels and often progress more rapidly as in nonpregnancy, with all the risks that entails.
Genetic susceptibility, obesity, and lifetime risk of type 2 diabetes: a prospective cohort study

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Background: We aimed to study the value of genetic information in lifetime risk prediction of type 2 diabetes, and whether a healthy weight may counterbalance high genetic risks.

Methods: We used data from 7,428 participants aged 45 years and older from a prospective population-based cohort study in Rotterdam, who were free of diabetes at baseline. Incident type 2 diabetes was defined as serum fasting glucose ≥7.0 mmol/L or the use of diabetic medication. We quantified the lifetime risk of diabetes, and estimated the risk reduction of a healthy weight within categories of a genetic score composed of common DNA sequence variants so far identified for type 2 diabetes.

Results: Among participants at high genetic risk, the relative risk of type 2 diabetes was 112% higher compared to those at low genetic risk (hazard ratio [HR] 2.12, 95% confidence interval [CI] 1.66-2.71). Participants aged 45 at low, intermediate, and high genetic risk had a remaining lifetime diabetes risk of 24.5%, 29.4%, and 37.7%, respectively. The risk of type 2 diabetes was lower among lean participants compared to obese participants, irrespective of the genetic risk category. In participants with a high genetic risk of type 2 diabetes, adherence to a normal weight was associated with a 61% lower risk compared to obesity (HR 0.39, 95%CI 0.25-0.62).

Conclusion: Genetic information adds to the lifetime risk prediction of type 2 diabetes, and a healthy lifestyle with regard to weight was associated with a reduced risk of diabetes in genetically high risk participants.
Pheochromocytoma induced cardiomyopathy

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Case: A 47-year old male presented to the emergency department with typical angina pectoris complaints. The arterial blood pressure was elevated at 141/100 mmHg with a heart rate of 91 beats/min. The ECG showed ST-depression over the precordial leads. Blood tests showed an elevated Troponine-T of 0.519 ug/l (ref <0.014 ug/l). Treatment was started with intravenous nitrate. Angiography showed no signs of coronary artery disease.

Cardiac MR (CMR): CMR showed a mild reduction of the LVF (ejection fraction 50%) and striking regional wall motion abnormalities (WMA), with akinesia of the basal segments and hyper-dynamic contraction of the mid-ventricular and apical segments. The segments with WMA demonstrated hyper-enhancement on the T2 weighted images (Figure 1 left panel, global relative enhancement ratio of 2.5) and epicardial enhancement on the late gadolinium enhancement images (Figure 1 center panel, scar burden 19.2%). These findings were suggestive for myocarditis.

In addition, an incidental finding on the CMR scout images was bilateral enlargement of the adrenal glands (Figure 1, right panel). Suspecting a neuroendocrine tumor 24-hour urinary fractionated metanephrines was performed which was positive for a pheochromocytoma with an absolute metanephrine of > 36.8 umol/mol (normal <1.52), absolute normetanephrine of > 54.2 umol/mol (normal <2.84) and 3-methoxytyramine of 4.94 (normal <2.75).
An Endocrine Cause of Tetraparesis

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A twenty-six year old Asian male patient with otherwise unremarkable history presented to the emergency department with paralysis of the extremities. Tetraparesis was observed with reduced reflexes mostly affecting lower extremities. His ECG showed a prolonged QTc interval and marked U-waves, which corresponded to an extremely low serum potassium level (1.5 mmol/L). Other electrolytes and acid-base values were normal. Urinary potassium excretion was similarly low (11 mmol/L), which excluded renal potassium loss. Although there were no clinical signs of hyperthyroidism, our work-up included high free T4 (55.8 pmol/L) and suppressed TSH (0.01 mU/L) confirming the diagnosis of thyrotoxic periodic paralysis (TPP). Graves’ disease was diagnosed based on increased anti-TSH receptor antibodies (13.6 IU/L) and diffuse uptake of radioactive iodine. He was treated with IV potassium and propranolol, correcting potassium levels but also rebound into hyperkalemia during treatment. After discharge, he was treated with propranolol and thiamazole and showed no signs of recurrence. TPP is a rare, and potentially lethal complication of hyperthyroidism, affecting mostly Asian males, but has also been described in Caucasians. It is frequently overlooked because many affected patients have no signs of hyperthyroidism, as was the case in our patient. Similarities exist between TPP and hypokalemic periodic paralysis, with common nucleotide polymorphisms only recently discovered regulating the potassium voltage-gated channel Kir2.6. Adequate treatment should be initiated promptly to avoid cardiopulmonary complications and includes IV potassium, propranolol and treatment of the underlying hyperthyroidism. In conclusion, TPP should be considered in all patients with tetraparesis and hypokalemia.
Central diabetic insipidus as presentation of nivolumab associated hypophysitis

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**Case:** A 58-year-old woman presented with nausea, vomiting and hypernatremia (sodium 160mmol/l) after the first cycle of third-line palliative chemotherapy docetaxel for cT3N3M1b lung carcinoma. Polyuria of almost 6 litres per 24 hours with an urine sodium of 13mmol/l and osmolality of 103mOsmol/kg was seen. Detailed history showed increased thirst, polydipsia and polyuria after starting nivolumab 6 months earlier. Due to disease progression, nivolumab was stopped a few weeks before chemotherapy. Oral intake was disrupted by side-effects of the chemotherapy leading to dehydration. Nivolumab induced hypophysitis was suspected. Anterior pituitary hormones were tested and no insufficiency was seen except the gonadal axis failed (TSH 1.5mU/L, FT4 12pmol/l, cortisol 681nmol/l, FSH 1.0U/l). MRI-cerebrum showed a swollen pituitary stalk of 3.5mm, compatible with hypophysitis. Desmopressin nasal spray was started and plasma sodium concentration normalised. No corticosteroids were given due to mild nature of hypophysitis and nivolumab was already discontinued.

**Discussion:** Two months later, pituitary function increased (FT4 15pmol/l; FSH 50U/l; cortisol 295nmol/l; ACTH 27.6ng/l) but she still needed desmopressin. Nivolumab, a PD-1 monoclonal antibody, prevents inhibition of cytotoxic Tcells and thereby stimulating Tcell anti-tumour response. Auto-immunity, including auto-immune hypophysitis, is a known side-effect of nivolumab. However, hypophysitis of the pituitary stalk and thereby causing central diabetic insipidus is uncommon. Treatment with corticosteroids does not alter recovery of pituitary function, it is only necessary with grade 3-4 toxicity or if treatment with nivolumab is continued. Treating oncologist should be aware of diabetic insipidus as side-effect of nivolumab and inform patients about it.
Hyperandrogenism in a postmenopausal woman

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Case: A 61-year-old postmenopausal Caucasian woman was referred to our outpatient clinic because of new onset hyperandrogenism. She reported progressive lowering of her voice and a male body hair distribution with balding. Furthermore, anamnesis revealed an increase in shoe size without other signs of growth hormone excess. Clinically, we suspected hypercortisolism on basis of increasing central obesity, elevated fasting glucose levels, hypertension accompanied by hypokalaemia, osteoporotic fractures and early-onset cataract. Biochemical testing revealed increased circulating levels of testosterone (5.24 nMol/L; normal: 0.5-2.8) and FSH (34 U/L; normal: 2.5-25), with normal LH levels (19.6 U/L; normal: 0.5-2.8). DHEA-S was suppressed (0.6; normal: 1.0 to 7.0 µmol/L). Levels of androstenedione, 17-OH progesterone and IGF-1 were normal. We did not detect (cyclic) hypercortisolism. A CT-scan showed normal adrenal glands and ovaries and a vaginal ultrasound was unremarkable. We diagnosed her with ovarian hyperthecosis and she was scheduled for a bilateral adnex extirpation.

Discussion: New onset hyperandrogenism is rare in postmenopausal women. The differential diagnosis includes ovarian or adrenal tumor, Cushing’s syndrome, congenital adrenal hyperplasia, premenopausal-onset polycystic ovary syndrome (PCOS) and hyperthecosis. Clinical features of hyperthecosis resemble those of PCOS in premenopausal women, however, with more markedly elevated levels of testosterone. The hyperandrogenism results from differentiation of the ovarian interstitial cells into steroidogenically active luteinized stromal cells. The primary pathology is severe insulin resistance. Treatment consists of GnRH agonist therapy or bilateral adnex extirpation, which can also improve insulin resistance (mechanism unknown).

Conclusion: Ovarian hyperthecosis is a rare cause of postmenopausal hyperandrogenism.
Systematic screening for environmental and behavioral determinants identifies factors detrimental to skeletal health

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Background: An increasing amount of biomedical data is becoming available, and methods are needed to tackle these ‘big data’.

Methods: We performed a systematic evaluation of 138 environmental and behavioral factors in relation to bone mineral density (BMD) in the National Health and Nutrition Examination Survey (NHANES). Dual energy X-ray absorptiometry (DXA) scans were available for total body, head, pelvis and lumbar spine for 27,259 participants from NHANES surveys 1999-2000 (A), 2001-2002 (B), 2003-2004 (C) and 2005-2006 (D).

Results: Higher serum levels of a-tocopherol and of g-tocopherol, forms of vitamin E, were associated with decreased BMD (per SD $\beta=-36.9\%$ and $\beta=-15.0\%$ for lumbar spine). In contrast, retinol serum levels were related to higher BMD (per SD $\beta=+11.6\%$ for total body). Serum lead levels had a negative relationship to BMD of the lumbar spine (per SD $\beta=-1.2\%$) and head (per SD $\beta=-2.2\%$). Higher levels of physical activity were associated with higher BMD (total body: per MET +1.2%). Being a current or past smoker was associated with decreased BMD of the total body, pelvis and head.

Conclusion: In conclusion, our study demonstrates consistently that several behavioral traits and fat-soluble vitamins may have detrimental effects on BMD, while reinforcing the benefit of physical activity for skeletal health.
Ectopic Cushing’s syndrome by an adrenocorticotrophic hormone secreting large cell neuroendocrine lung cancer: a case report

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Ectopic adrenocorticotrophic hormone (ACTH) secretion leading to endogenous Cushing syndrome (ECS) has been reported in association with various solid tumours. An association with large-cell neuroendocrine carcinoma of the lung (LCNEC) is very rare and has only been reported in one previous case report.
We describe a rare presentation of ECS based on a metastasized LCNEC and stress the importance of recognizing this rapid-onset progressive syndrome. Due to this rapid onset patients do not typically show all the pathognomonic cushingoid features which means that diagnosis should also be based on laboratory results possibly resulting in a delay in treatment and high mortality. Even when treatment is initiated, prognosis is poor. In this case a 60-year old female patient presenting with severe hypokalemia, a perforated diverticulitis, edema and metabolic alkalosis is described. Biochemical evaluation showed suppressed plasma aldosterone activity with elevated ACTH and cortisol levels irrepressible by multiple dexamethasone overnight suppression tests suspicious for ACTH dependent Cushing’s due to ECS. The ECS appeared to be based on a metastasized LCNEC.
Treatment was complicated. Hypercortisolism was treated with metyrapone and mifepristone. Chemotherapy and/or bilateral adrenalectomy were considered. However, due to a concomitant abscess formation and poor clinical condition the patient finally decided to stop further treatment and palliative care was initiated.
Hypoparathyroidism and severe lactic acidosis: an unusual combination

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A 28-year old female of Moroccan descent presented with abdominal pain, vomiting and inability to take her alfalcaldido for her idiopathic hypoparathyroidism. Her medical history further reported an idiopathic gastoparesis, general muscle complaints and anorexia. At presentation, she had a decreased consciousness(E3M6V2), tachypnea(44/minute), tachycardia(110 bpm), blood pressure of 105/60 mmHg, and temperature of 36.5°C. Her BMI was 17.3 kg/cm². Laboratory investigation showed a severe lactic acidosis(pH 7.07, lactate 20.0 mmol/L), hyperglycemia(glucose 17.6 mmol/L), hypocalcemia(calcium 1.79 mmol/L) and increased creatin kinase(1233 U/L). She was admitted to the ICU and given mixed glucose-NaCl infusion with calcium suppletion. After correction of the lactic acidosis her clinical situation improved, glucose levels returned to normal without insulin therapy. No underlying cause for the lactic acidosis and rhabdomyolysis was found. Since her older brother was known with a limb girdle dystrophy, deafness, hypoparathyroidism and idiopathic cardiomyopathy, it was hypothesized that a mitochondrial defect could explain the clinical picture and testing for mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) and maternally inherited diabetes and deafness (MIDD) was performed. A m.3243A>G mutation (heteroplasmy 15%) was found, confirming a diagnosis of MELAS/MIDD. Due to the high heteroplasmy level and absence of diabetes and deafness, a diagnosis of MELAS is more compatible with the clinical presentation of our patient, including her previous unexplained complaints of anorexia, gastoparesis and muscle pains. It even explains the hypoparathyroidism since mitochondrial defects have been reported to be causative for hypoparathyroidism. This case illustrates the heterogeneity of symptoms due to mitochondrial diseases, including hypoparathyroidism.
ACTH-producing pheochromocytoma, initially presenting with hypokalemia

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A 59-year-old woman with type 2 diabetes mellitus was admitted to the hospital for analysis of a severe hypertension and hypokalemia. She suffered from fatigue and muscular weakness. On physical examination, hypertension, palsy of the legs and facial hair growth was found. Laboratory results confirmed hypokalemia. Ultrasonography of the abdomen showed an enlarged left adrenal gland. During the hospital stay, additional endocrine tests and imaging studies were ordered because of rapidly progressive and severe hypercortisolism. These led to a high clinical suspicion of an ACTH-producing pheochromocytoma of the left adrenal gland. A laparoscopic left adrenalectomy was performed after preoperative treatment with α- and β-adrenergic-blocking agents. The clinical diagnosis was histologically confirmed employing immunohistochemical markers. Postoperatively, hydrocortisone supplementation was administered and the patient recovered rapidly. During follow-up, the antidiabetic and antihypertensive treatment and, later on, the hydrocortisone therapy could be stopped. In hindsight, the diabetes mellitus was the first manifestation of hypercortisolism one year earlier. Ectopic ACTH-producing tumors are a rare cause of Cushing's syndrome. Ectopic ACTH production by a pheochromocytoma is even more rare. Recently, another case came to our attention, which we will present as well. In conclusion, ACTH-producing pheochromocytomas should be considered in patients with hypertension with hypokalaemia and rapidly progressive hypercortisolism.
An unusual treatment of primary hyperparathyroidism

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Case: A 51-year old women presented with severe progressive pain on the right chest. Her medical history included hypertension and nicotine abuse. CT scan showed a destructive mass in the right chest wall with also a right sided hilar mass, suspect for primary lung cancer. Histology however, showed metastatic melanoma. She was referred for immunotherapy with Pembrolizumab. Simultaneously, serum calcium was 3.43 mmol/L. Further laboratory results showed parathyroid hormone of 23.5 pmol/L, a low vitamin D 28 pmol/L, suggestive of primary hyperparathyroidism. Parathyroid scintigraphy confirmed a parathyroid adenoma. First, she was treated with hyperhydration and bisphosphonate infusion, without lowering of serum calcium. Despite high dose of Cinacalcet, hypercalcaemia persisted and Cinacalcet was not tolerated due to vomiting and nausea. While she had started treatment elsewhere with Pembrolizumab, she also developed severe hemoptysis, for which no bleeding source was found, despite bronchial artery angiography. Tranexamic acid was started but hemoptysis persisted. Because of the risk of recurrent hemoptysis, the tumor mass in the right lung was irradiated, after which hemoptysis stopped.

Because of severe symptoms of hypercalcaemia, she was frequently admitted to the hospital. In this situation, while waiting for response to Pembrolizumab therapy, surgical treatment, the preferred therapy, was not desirable. Therefore, in multidisciplinary consultation, it was decided to perform local super selective cryoablation therapy guided by ultrasound. Next day, parathyroid hormone was normalized and calcium value decreased to below 3 mmol/L.

Conclusion: Local cryoablation of parathyroid adenoma is a suitable option for selected patients with an increased surgical risk.
Case: A 51-year-old postmenopausal woman with a history of obesity and unsuccessful IVF was hospitalized at the department of gastroenterology because of post-prandial nausea and vomiting during the last 6 months, and she was diagnosed with acute pancreatitis. She lost 15 kg in weight. Physical examination, gastroscopy and abdominal ultrasound showed no abnormalities. A CT-scan was performed, which showed splenomegaly, generalised lymphadenopathy and pancreatic edema. A supraclavicular lymph node biopsy was performed. In addition, as requested by the patient the thyroid function was checked, showing a secondary hypothyroidism. During endocrine consultation, anamnesis revealed cold-intolerance and fatigue. There were no signs of visual field loss or nipple discharge. No other symptoms. Further analysis revealed a hypogonadotrophic hypogonadism, secondary adrenal insufficiency, a slightly elevated prolactin-level and normal IGF-1. There were no signs of insufficiency of the posterior pituitary. Hydrocortisone treatment was started, followed by levothyroxine. The symptoms of nausea, decreased appetite and fatigue disappeared immediately after hydrocortisone was started. Magnetic resonance imaging (MRI) of the pituitary showed an isolated, homogeneous, abnormal aspect of the pituitary and pituitary stalk. The lymph node biopsy showed notable fibrosis with granulomas and giant cells, possibly matching sarcoidosis. Additional laboratory results, as well as reassessment of the biopsy specimen, excluded possible causes as IgG4-mediated disease, tuberculosis or vasculitis. Pulmonary function test and electrocardiography revealed no abnormalities. Treatment with 60mg prednisone/day was started.

Conclusion: Neurosarcoidosis with adeno-hypopituitarism detected upon patients’ request to do a thyroid function test, in combination with splenomegaly and probably also pancreatitis.
Effects of thyroid stimulating hormone on
serum lipids are mediated via direct effects
on peripheral thyroid hormone metabolism

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Background: Subclinical hypothyroidism is associated with dyslipidaemia and atherosclerosis. Whether
part of these effects are mediated via direct effects of TSH on peripheral thyroid hormone (TH)
metabolism and/or concentrations of serum lipids is not clear.

Methods: To examine whether TSH has a direct effect on peripheral TH metabolism and serum
lipids we retrospectively analysed 82 patients with differentiated thyroid cancer. All patients had
undergone total thyroidectomy and 1-131 remnant ablation. During follow-up, TSH stimulated
thyroglobulin measurements using 2 successive injections of recombinant human TSH (rhTSH) were
performed in patients on a stable dose of levothyroxine. In all patients TSH, thyroxine (T4), free T4
(FT4), triiodothyronine (T3), reverse T3 (rT3), total cholesterol, apolipoprotein B (ApoB), high-density-
lipoprotein (HDL-C), low-density-lipoprotein, lipoprotein(a) (Lp(a)) and triglyceride levels were measured
immediately before administration of rhTSH and approximately 72 hours after the second injection of
rhTSH.

Results: After rhTSH stimulation, T3 values decreased significantly (from 1.91 to 1.81 nmol/l, p<0.001).
Median ApoB, Lp(a), triglyceride and non HDL-C levels increased significantly after rhTSH (from 0.90
to 0.92 g/l, p=0.03; from 0.21 to 0.24 g/l, p<0.001, from 1.98 to 2.5 mmol/l, p<0.001 and from 4.10
to 4.36 mmol/l, p<0.001 respectively). Serum HDL-C decreased from 0.98 to 0.81 mmol/l p<0.001.
Multiple regression analysis showed that the changes in lipids could be attributed to the change in
T3 levels.

Conclusion: rhTSH has direct effects on peripheral TH metabolism by decreasing T3 levels in
thyroidectomised patients. This decrease in T3 levels is accompanied by unfavourable changes in serum
lipids.
Hyponatremia: the only presenting symptom of Addison’s disease

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Case: A 70 year old woman with history of hypothyroidism and recently diagnosed Alzheimer dementia was seen at our policlinic because of hyponatremia in routine laboratory control. Laboratory diagnoses showed a hyponatremia of 120 mmol/l with an increased natrium excretion in the urine. With the exception of weight loss and low-tension without tachycardia, there were no other symptoms/signs of adrenal insufficiency. Synacthen test showed hypocortisolism and 21-hydroxylase antibodies were detected. Hyponatremia disappeared when started with hydrocortison suppletion therapy.

Discussion/conclusion: Primary adrenal insufficiency causes a combination of a low cortisol concentration with a increased ACTH-concentration. It is a rare disorder and nowadays 70- 90% of primary adrenal insufficiency is caused by autoimmune destruction of the adrenals. The clinical presentation of cortisol insufficiency is very nonspecific. Almost all the patients present with malaise, fatigue, weakness, anorexia, weight loss and hyperpigmentation. 88-94% Of the patients have signs of (orthostatic) hypotension. Elektrolyte abnormalities are seen in 92% of the patients. Hyponatremia is found in 85-90% of patients. Hyperkalemia occurs in 60-65% of patients due to mineralocorticoid deficiency. The most used test to diagnose adrenal insufficiency is the synacthen test. However an early morning low serum cortisol concentration (less than 80 nmol/L) is strongly suggestive of adrenal insufficiency. In 86% of patients, antibodies against 21-hydroxylase are detected. Adrenal crisis requires urgent intervention with glucocorticoid stress replacement therapy. After the acute phase there is started with a maintenance glucocorticoid and mineralocorticoid suppletion to mimic the endogenous production of these hormones.
Extremely metabolic alkalosis as presenting sign of ectopic ACTH production

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A 65-year-old woman, recently diagnosed with stage IV small-cell lung cancer (SCLC), was admitted to the Emergency Department with discomfort and abdominal pain. First survey showed hypertension (200/80 mmHg), hypokalemia (potassium 1.5 nmol/l, normal 3.5-5.0 nmol/l) and metabolic alkalosis (pH 7.71, bicarbonate 53 nmol/l (normal 22-29 nmol/l). Electrocardiography showed PVC's in bigeminy with ST-depression on inferolateral leads. She was admitted to the ICU for IV potassiam-suppletion. Secondary survey showed a restless patient, with a moonface and facial hair. The hypokalemia and hypertension were difficult to correct. Cushing's syndrome was suspected. Morning cortisol after 1mg-dexamethasone overnight was 2868 nmol/l (normal <50 nmol/l) and ACTH was 109.0 pmol/l (normal 1.6-13.9 pmol/l). These results fits the diagnosis Cushing's syndrome, likely caused by ectopic ACTH-production due to SCLC. Palliative chemotherapy for SCLC was declined by the patient consistently. Metyrapon and spironolactone were started to palliate her hypercortisolism-induced symptoms, and to aim for normokalemia on oral potassium suppletion. She could be discharged two days later. Follow-up, serum cortisol on metyrapon-therapy was decreased to 1410 nmol/l, however, she stopped active treatment and palliative sedation was started. She died five days after discharge. Metabolic alkalosis due to hypokalemia can be the first sign of ectopic ACTH-production and is caused by the mineralocorticoid effect of hypercortisolism. About 1% of SCLC-patients have ectopic ACTH-production. Preferably, the therapy for ectopic ACTH-production is resection of the tumour. In palliative care, hypercortisolism can be controlled with adrenal-enzyme-inhibitors like metyrapon, either as monotherapy or in a block-replacement strategy with hydrocortisone.
Introduction: Hypoglycemia is a common problem in elderly, but usually in patients with diabetes mellitus. An insulin-independent hypoglycemia is rare.

Case: A 84-year old male was referred to our outpatient department with recurrent hypoglycemias. He sets an alarm in the night to eat. His medical history reported a solitary fibrous tumor (SFT) since 2006 with three lobectomies (last in 2015), with currently his third relapse without treatment options, and metastatic prostate carcinoma. Physical examination showed a palpable mass in the right apical region of the chest. Patient was admitted for further analysis. On admission patient had a glucose level of 2.5 mmol/L. Insulin and c-peptide were measured during a hypoglycemia and were suppressed. The cortisol level was normal and this excludes hypocortisolism. IGF-1 was low (5.4 nmol/L; 6.8-26.1) and IGF-2 awaits to be measured, but pro-IGF 2 (also known as big IGF-2) was elevated (77 µg/L; 9-27). This suggests a non-islet cell tumor hypoglycemia. Awaiting the discussion for a possible treatment for his third relapse, patient was treated with overnight tube feeding resulting in stable glucose levels. This type of hypoglycemia is known as the ‘Doege-Potter Syndrome’, which is a paraneoplastic syndrome characterized by non-islet cell tumor hypoglycemia secondary to a solitary fibrous tumor. Hypoglycemias occur due to production of pro-IGF-2.

Conclusion: We present a case of severe hypoglycemia due to a pro-IGF-2 producing solitary fibrous tumor. Insulin-independent hypoglycemias are rare, but should be kept in mind. Paraneoplastic hypoglycemia could be a first presentation of a malignancy.
Two of a kind: Ochronosis in a 74 year old Turkish immigrant and a 47 year old Dutch man

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Background: Alkaptonuria (ochronosis) is a rare autosomal recessive disorder of tyrosine metabolism. The prevalence is 0.2 per 100,000 in the general population.

Results: The first case is a 74 year old Turkish woman referred to the cardiothoracic surgeon with symptomatic aorta valve stenosis and coronary artery disease. Her medical history noted bilateral total hip replacement. She underwent a CABG and aortic valve replacement. Perioperative findings included: black discoloration of the sternum, aorta ascendens and aortic valve. Urinalysis with homogentisinic acid (HGA) levels of 1116 mcg/mmol creatinine (normal range 0-2). After discharge, follow-up was in another hospital. The second case is a 47 year old Dutchman referred to our outpatient department with joint pain, blue discoloration of his ears and dark urine suspect for alkaptonuria. Urinalysis showed a HGA level of 900 mcg/mmol. He was referred to the orthopaedic surgeon for biological resurfacing of left shoulder joint which was severely arthrotic. Peri-operative observations revealed ochronotic discoloration. He was referred to ErasmusMC, Rotterdam for genetic testing and treatment with nitisinone. Alkaptonuria is a disorder of tyrosine metabolism resulting from a mutation of chromosome 3q21-q23. Homogentisic acid dioxygenase is deficient whereby HGA accumulates. This is deposited in the chondrocytes and osteoclasts resulting in ochronotic arthritis and complete ankylosis.

Management strategies are limited. These include: dietary restriction of tyrosine and phenalalanine; ascorbic acid and nitisinone are also used as treatment with limited evidence.

Conclusion: Although a rare disorder of tyrosine metabolism, alkaptonuria is a disorder still relevant in clinical practise. New treatments are currently being investigated.
Six months Results of Radiofrequency Ablation for Benign Solid Thyroid Nodules, and of modified Ethanol Ablation for Thyroid Cysts

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Background: Benign thyroid nodules and cysts are common. Symptomatic solid nodules are usually treated by surgery, cysts may be aspirated, but if they recur surgery is usually warranted. Recently, Radio Frequency Ablation (RFA) has been developed as an alternative to surgery, and modified Ethanol Ablation (EA) has been introduced to improve the results of cyst aspiration. In this study we present the first Dutch case series of RFA, and of modified EA.

Methods: Patients with thyroid nodules or cysts greater than 20 mm but less then 50 mm were included. Cysts had to be unilocular with benign cytology, solid nodules had to be benign based on clinical judgement, sonographic characteristics and cytology or histology. Toxic nodules were not included.

Results: Between January 2015 and March 2016 22 patients were referred for EA, and 34 for RFA. Nineteen were accepted for EA and 15 out of 34 were included for RFA. EA led to a sustained volume reduction of 87% at six months (p < 0.05). EA failed in 32% of patients. RFA reduced thyroid nodule volume by a median of 36% (p<0.05). Adverse events: one patient treated with EA developed a painful local inflammatory response. RFA was without clinically significant adverse events.

Conclusion: RFA and modified EA are promising alternatives to surgery in well-selected cases.
Psychiatric symptoms as a clinical presentation of hypocortisolism.

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Patient A, a 69-yr old woman curatively treated for breast cancer 10 years ago, was admitted with low appetite, weight loss and general body weakness. She was examined for possible underlying malignancy. Laboratory testing and CT-thorax-abdomen showed no evidence of this. She deteriorated within a few days displaying uncooperative behaviour progressing to somnolence and catatonia; while haemodynamics were preserved. Further testing showed a low morning cortisol (34 nmol/L). Patient A was subsequently treated with high dose of hydrocortisone with fast clinical response. Prior, the patient had experienced anxiety attacks for years, which disappeared after treatment. Patient B, a 58-yr old woman with chronic, persistent abdominal pain without apparent somatic origin, along with longstanding depression and an anxiety disorder; presented with lethargy, weight loss and low appetite. She was admitted after the GP discovered a low morning cortisol level (8nmol/L). Haemodynamics were stable. Patient B was treated with high dose hydrocortisone, and both her somatic and psychiatric condition improved slowly thereafter. In both cases central hypocortisolism was diagnosed with low cortisol, low ACTH levels and preserved other pituitary axes. Pituitary MRI was normal, in particular no evidence of an adenoma was found. Patient A had no history of corticosteroid use. Patient B had recently taken corticosteroid injections for pain control. It’s known that hypocortisolism can cause psychiatric symptoms, and diagnostic testing is often delayed when patients present with primarily psychiatric or nonspecific complaints. Early recognition of atypical psychiatric symptoms and screening for somatic causes including hypocortisolism can prevent severe somatic problems.
Losing appetite after an EBV infection.

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Case: Patient was an 80 year old woman who was presented with nausea and vomiting. Her medical history included aortic prosthesis and percutaneous catheterisation of her right coronary artery. Her complaints started two weeks after an episode with fever, enlarged glands in her neck and painful ears. Initial laboratory results showed normal inflammatory markers, glucose, liver and kidney panels. Gastroscopy showed only a mild bulbitis and pathology of the taken biopsies was normal. Abdominal CT revealed no signs of malignancy. A gastric emptying test was performed, which showed complete stasis of solid intake. In light of the viral episode she had two weeks before commencement of her nausea, viral serology was performed, with positive IgG levels for hepatitis E, Cytomegalovirus and Epstein Barr Virus (EBV), as well as positive IgM levels for EBV. The absence of other causes of delayed gastric emptying made EBV as the likely causative agent.

Discussion: Postinfectious gastroparesis (PIGP) is a known, but uncommon entity mostly affecting children and young adults. The underlying etiology is likely to be damage to the motor neurons in the gut, the cells of Cajal. A variety of viruses have been implicated in PIGP, like CMV, EBV, varicella virus, rotavirus. At the time of writing patient was still symptomatic without effect of anti-emetic medication, confined to small meals and afflicted with persistent nausea. Prognosis of chronic PIGP is mixed, with symptoms alleviating between weeks to up to a year.
Tertiary referral of patients with fever of unknown origin to an expertise center has high diagnostic and therapeutic value

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Background: Many patients with fever of unknown origin (FUO) are referred to expertise centers in university hospitals after being analyzed in other hospitals, but the yield of these tertiary referrals is unclear.

Methods: All patients referred to the Radboud university medical center because of FUO between January 2005 and June 2014 were included in this retrospective study. Data on diagnosis and treatment were extracted from medical records. Tertiary referral was defined as a patient being previously analyzed in another hospital because of FUO.

Results: Of a total of 236 FUO patients, 192 (81.4%) were tertiary referred. Mean age at first presentation to the Radboudumc in tertiary referred patients was 49.0 years. Tertiary referred patients had visited a median of one hospital (range 1-7 hospitals) and 3 consultants (range 1-15 consultants). During a median follow up of 23 months (range 0-116 months) a diagnosis was made in 57.3% of tertiary referred patients, compared to 59.3% in first opinions (p=.234). Another 42 tertiary referred patients (38.8%) were treated in absence of a diagnosis, which was effective in 21 of them (50%).

Conclusion: the diagnostic yield in tertiary referred patients with FUO is not significantly different from patients referred for first opinion. With total diagnostic and additional therapeutic yields of 57.3 and 10.9%, respectively, the total yield of referral to a university expertise center is 68.2%. Because of this, tertiary referral should be considered in patients with FUO in whom no diagnosis can be made in a non-expertise center.
Targeting the diagnosis and treatment of non-Langerhans cell histiocytosis

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Patient 1 is a 58-year old male with a 5-year history of bilateral, progressively worsening knee pain spreading to the upper legs. At presentation ESR was 50mm/h in the presence of elevated 1,25-dihydroxy-Vitamin D (up to 300nmol/l). Skeletal scintigraphy showed intense bilateral uptake of the long bones, especially around the knees. A CT-scan showed bilateral mesenteric and perirenal fat infiltration, so-called ‘hairy kidneys’. Patient 2 is a 47-year old female with a history of pituitary stalkitis resulting in diabetes insipidus, hypogonadotropic hypogonadism and growth hormone deficiency which resolved spontaneously. Eight years after, she presented with fever, fatigue and bone pain. She had eye-catching xanthelasmata and a normochromic anemia with elevated ESR. Radiologic examinations showed pericardial effusion, diffuse mediastinal, mesenteric and perirenal fat infiltration. Skeletal scintigraphy showed intense bilateral uptake of long bones, similar to patient 1. Bone biopsies taken at the sites of the uptake showed numerous clustered, foamy, vacuolated macrophages. Immunostaining was negative for S100, CD1a, positive for CD68 and RANKL, furthermore a BRAF mutation was identified, indicative of Erdheim Chester disease (ECD). ECD is a form of non-Langerhans’ cell histiocytosis with unknown etiology and is characterized by the presence of lipid-rich foamy macrophages in bone (>90%) and other organs. Peg-Interferon alpha is the standard treatment, however targeted therapy is an emerging option. Our first patient was started on PEG-interferon with additional denosumab for his bone pains. Due to the severity of the disease and comorbid KRAS mutation, the second patient received combined BRAF/MEK inhibition. Both patients responded extremely well.
A patient with gastric antral vascular ectasia (GAVE) syndrome and skin thickening

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Case: A 76-year old woman with presented with fatigue and a chronic iron-deficiency anaemia. She had a history of polymyalgia rheumatica for which she was treated with low dose prednisone. There was no overt blood loss. Upper gastrointestinal endoscopy revealed extensive vascular ectasias and patchy erythema in the distal antrum diagnostic of GAVE syndrome. There were no esophageal or gastric varices. No underlying condition was identified at the time. She was treated with multiple sessions of argon plasma coagulation therapy and blood transfusions.
A year after initial presentation, she developed skin thickening and nail fold capillaroscopy showed abnormalities consistent with systemic sclerosis. Cardial en pulmonary analysis showed no signs of pulmonary hypertension. She was treated with methotrexate and prednisone.

Discussion: Although GAVE syndrome is a rare medical condition, it should be considered in older patients with chronic iron-deficiency anaemia, especially in elderly females. It is associated with heart, liver, and kidney disease, diabetes, hypothyroidism, connective-tissue diseases and also bone marrow transplants. A prevalence of 6% in patients with scleroderma is reported.
Treatment consists of supportive measures (blood transfusions) and endoluminal therapy (mainly argon laser coagulation). Furthermore, corticosteroids may decrease blood loss. Antrectomy is the only reliable therapy with definitive and curative potential, especially for unresponsive or severe disease. Lastly, treatment of underlying medical conditions can lead to resolution of GAVE syndrome.
Conclusion: GAVE is a rare condition but should be considered as a cause of an iron deficiency anaemia. If present, the underlying condition should be treated.
Hyponatremia caused by abdominal large vessel compression

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A 61-year-old woman without prior medical history presented with hemodynamic and respiratory instability. From hetero-anamnesis we obtained the following information: Since approximately one week she had progressive complaints of fatigue, dyspnea and orthopnea, and a weight loss of five kilograms accompanying a decreased appetite. Also, she suffered from forgetfulness, dysarthria and bradyphrenia. Laboratory studies revealed abnormal liver tests, severe hyponatremia (105 mmol/L) with serum osmolality 246 mOsm/kg, a urine sodium of <20 mmol/L and a urine osmolality of 755 mOsm/kg. Computed tomography showed a 25-centimeter septated cyst causing severe compression of the inferior vena cava and large liver vessels, bile duct dilatation, and deviation of several organs including the heart, kidneys, pancreas and upper gastrointestinal tract. After drainage of 6.5 liters of cyst fluid, the patient's clinical condition improved and the hyponatremia resolved completely. Her symptomatic hyponatremia was caused by effective circulating arterial volume depletion due to the abdominal vessel compression, with a consequent auto-regulatory response of increased renal sodium and water reabsorption. As cytology of the cyst fluid did not show malignant cells, and chemistry and microbiology analyses revealed an infection with Escherichia coli, drainage was continued and antibiotics were administered, before sclerotherapy or surgery was to be considered for prevention of a recurrence.
An uncommon complication of pancreatic disease

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Case: A 84-year old patient is presented to the emergency department with an erythematous discoloration on the medial side of the ankle with a central ulcer. Medical history includes a kidney transplantation and three episodes of non-biliary pancreatitis in the months prior to the current presentation. The temperature is 36.6°C and laboratory investigation shows a C-reactive protein of 39 mg/l and white cell count of 12.2 x 10^9. Differential diagnosis comprises gout and cellulitis. The patient is treated for both with respectively colchicine and clindamycin. During treatment, painful erythematous lesions appear on both shins, and fluctuating nodules appear on several toes. Drainage of the nodules on the toes shows a pyoid substance. Microscopic examination does not demonstrate gout crystals or bacteria. A biopsy of the shin lesions is performed. Pathology shows a panniculitis, with extensive necrosis of adipous tissue with appearance of focal necrotic cells without a nucleus, called ‘ghost cells’. This fits the diagnosis of pancreatic panniculitis. Pancreatic panniculitis is a rare condition occurring in patients with pancreatic disease. The etiology is uncertain. Probably high serum levels of pancreatic enzymes cause necrosis of fat tissue, mainly in the lower extremities. The cell membrane of adipocytes is resistant to pancreatic enzymes causing anucleate cells called ‘ghost cells’. Treatment consists of treating the underlying pancreatic disease. The patient was treated with supportive measures for the pancreatitis. At first both the panniculitis and pancreatitis improved. However, unfortunately the patient was re-admitted with a severe pancreatitis and died.
Hypomagnesemia: a serious, but reversible side effect of proton pump inhibitors

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Case: A 57-year-old woman, with a history of essential tremor and gastro-oesophageal reflux treated with omeprazole 40 mg for years, presented with complaints of dizziness, headache and progression of tremors after nifedipine was started for hypertension. Quitting the calcium antagonist improved complaints except for increase in tremors. Laboratory investigation showed severe hypomagnesemia (0.14 mmol/L). She was admitted to the hospital for intravenous magnesium suppletion. Magnesium level was corrected in several days to 0.61 mmol/L with significant decrease in tremors. Omeprazole was replaced by ranitidine. Because of sustained serious gastro-oesophageal reflux omeprazole was reintroduced in half dose (20 mg). A few weeks later our patient reported progression of tremors. Laboratory research showed hypomagnesemia again (0.28 mmol/L). Omeprazole treatment was terminated and magnesium level improved without suppletion. Because of massive reflux symptoms despite H2-receptor antagonist, algeldrate and sucralfate our patient was referred to the surgery department for a laparoscopic fundoplication.

Discussion: Proton pump inhibitors (PPI) are frequently prescribed as a treatment for gastro-oesophageal reflux, mostly without serious adverse events. Nevertheless, PPI-induced hypomagnesemia should take into account. Research suggests that intestinal magnesium absorption is impaired. Hypomagnesemia affects the neuromuscular, central nervous and cardiovascular system, causing convulsions, tetany and bradycardia. Our case shows that PPI-induced hypomagnesemia can be serious, but is reversible: magnesium levels improved by interrupting omeprazole therapy and deteriorated by reintroducing omeprazole.

Clinical relevance: PPIs are frequently prescribed, but might cause serious symptomatic hypomagnesemia. Quitting the drug improves magnesium levels quickly. In case of drug resistant reflux symptoms, laparoscopic fundoplication can be considered.
Diagnostic and therapeutic strategies employed for anemia of chronic disease in general practice: a retrospective cohort study

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Background: Patients with anemia of chronic disease (ACD) are regularly referred to internal medicine outpatients clinics. Little is known regarding the handling of newly diagnosed ACD patients in general practice. We set out to clarify the diagnostic and therapeutic strategy of general practitioners (GPs) in patients diagnosed with ACD and the underlying causes established by GPs or internists.

Methods: A retrospective cohort of 267 patients with ACD, defined by ferritin above 100 µg/l combined with decreased iron and/or reduced transferrin and hemoglobin below 13.7 g/dl (male) or 12.1 g/dl (female), was studied, covering the period the first of February 2007 until the first of February 2013. Additional medical Information of these ACD patients was obtained from the electronic medical files of the participating GPs and the referral hospital.

Results: An underlying cause of ACD could be determined in 210 of 267 patients (79%). In 179 patients (77%) the cause was established through additional diagnostic investigations and in 31 patients (12%) the underlying cause was apparent at time of diagnosing the ACD. Most frequent causes were infection (32%), autoimmune disease (24%) and malignancy (23%). Thirty-Five patients (13%) received oral iron supplementation despite ACD and ferritin levels above 100 µg/l.

Conclusion: This unique study in patients with newly diagnosed ACD in general practice reveals that in the majority of patients the underlying cause could be determined sometimes in cooperation with internists. This cooperation should be the subject of future studies in order to improve the diagnostics and treatment in ACD patients.
The effectiveness of a standardized versus a personalized laboratory request in the diagnosis of anemia in general practice

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Background: Patients with anemia are regularly referred to internal medicine outpatient clinics in order to establish the underlying etiology. Therefore, it is important to clarify strategies general practitioners (GPs) employ to establish underlying causes of anemia. We investigated the effectiveness of a standardized versus personalized laboratory request in determining the underlying cause of anemia by general practitioners (GPs).

Methods: An extensive survey was spread among 836 GPs of whom 192 responded (23%). The survey consisted of 6 cases, selected from a large cohort of real world anemia patients, in whom 14 standardized laboratory parameters were performed. In 3 cases GPs were asked to chose laboratory tests from the list of 14 parameters (i.e. personalized approach) and in another 3 cases all results of the 14 parameters were directly presented (i.e. standardized approach) in order to determine the underlying cause of anemia. The answers of the GPs were compared with the answers of an expert panel.

Results: The correct underlying cause of anemia was established in 214 of 404 cases (53%) using a personalized approach and in 234 of 378 cases (62%) using a standardized approach (P = 0.01). A multivariate analysis demonstrated less correctly diagnosed underlying causes in patients with higher age (P = 0.005) and the influence of the underlying cause itself on the correct diagnosis, with ACD being hardest to diagnose (P = 0.004).

Conclusion: A standardized extensive laboratory analysis in general practice patients with newly diagnosed anemia is more effective than a personally ordered laboratory analysis.
Colonoscopy in the old: a geriatric dilemma

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**Background:** Colorectal cancer is the third most common cancer in The Netherlands. Seventy percent of the patients is aged 65 years or older. The gold standard to diagnose colorectal cancer is colonoscopy with histology. The aim of this study was to quantify the yield of colonoscopy in respect to the adverse events.

**Methods:** Retrospective cohort study of all patients aged 80 years or older that underwent colonoscopy between January 1st 2014 and December 31st 2015 at Jeroen Bosch Hospital, a non-academic teaching Hospital.

**Results:** 465 patients were included with an average age of 82.6 years. 78 patients (16.8%) were diagnosed with colorectal cancer. 70.5% of the performed colonoscopies had consequences, in 22.2% the colonoscopy was incomplete, in 4.5% a complication occurred and 13.5% had a bad or reasonable quality of preparation.

**Conclusion:** A high incidence of colorectal cancer is found with colonoscopy, with a low incidence of complications or bad preparation. However, in almost 1 out of 4 patients, the colonoscopy was incomplete.
Efficacy of a standardized oral vitamin D dosing regimen in somatic and psychogeriatric nursing home residents

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**Background:** The prevalence of vitamin D deficiency in nursing home residents (NHR) ranges from 79 to 98%. The aim of this cross-sectional observational study was to determine the efficacy of a standardized oral vitamin D dosing regimen (VDDR) consisting of a loading dose (LD) of 200,000 IU followed by a maintenance dose (MD) of 100,000 IU every 13 weeks in obtaining and maintaining an adequate and safe vitamin D trough level (VDTL) in somatic and psychogeriatric NHR.

**Methods:** Blood samples of NHR who had received the LD followed by at least one MD were analyzed for VDTL, calcium, PTH, and creatinine. Data on age, sex, race, body weight, length, co-morbidity, co-medication, number of MDs, calcium supplementation, smoking and use of alcohol were obtained from patient charts. The primary outcome for the efficacy of the VDDR was defined as the percentage of NHR with a VDTL 75-220 nmol/l. A percentage of 75.31% was considered to be non-inferior to the aimed percentage of 85% (α 0.05; β 0.0881). Secondary outcomes were analyzed as dichotomous variables using logistic regression.

**Results:** In 91 (58.3%) of 156 included NHR, a VDTL of 75-220 nmol/l was measured (average [SD] 81 [28], range 13-150). Data were abstracted from the charts of 138 (88%) NHR. The only variable found to be a significant predictor for obtaining a VDTL =75 nmol/l was a larger number of MDs (=4 vs 4; OR 2.69; 95%CI 1.357-5.328).

**Conclusion:** The VDDR was not efficacious in obtaining and maintaining an adequate VDTL in NHR.
A 63-years old woman presented at the Emergency Room with thoracic pain since 1 week. The pain continuously radiated from the upper spine and worsened with activities, but not with breathing. There were no risk factors for pulmonary embolism and Wells score was low. Physical examination was significant for pain at the thoracic spinal column. Both respiratory rate and oxygen saturation were normal. Laboratory findings showed normal blood counts, renal function (creatinin 83 umol/L) and calcium (2.53 umol/L). Pulmonary X-ray was unremarkable and computed tomography showed no pulmonary embolism. However, multiple laesions were seen in the spinal column. Beta-2 microglobulin was slightly increased (4.5 mg/L; normal <3.5 mg/L). Levels of IgG, IgA and IgM were decreased, however the light chain lambda was only slightly increased with 264 mg/L. Serum protein electrophoresis showed an abnormal paraprotein in the gamma-globulin region of 14 g/L. Bone marrow aspirate and biopsy showed a monoclonal population of plasma cells of plasma cells type IgD ? of 28%. Radiologic investigation of the skeleton revealed several bone laesions in the spinal column at different levels. Currently, patient is treated according to the HOVON protocol with standard VTD treatment (velcade, thalidomide and dexamethason).

Summarizing, this patient suffers from IgD multiple myeloma presenting with osteolytic laesions and decreased immune globulin levels. Less than 1% of the multiple myelomas is represented by IgD or IgE paraprotein. However, this type of multiple myeloma is usually aggressive.
A rare presentation of Anaplastic Lymphoma Kinase – Positive Diffuse Large B-Cell Lymphoma (ALK+DLBCL)

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A 67-year old man presented with pain in the right hemi-abdomen since two months. Radiologic examination showed mesenteric and para-aortic lymphadenopathy and splenomegaly. Histologic examination of a lymph node showed plasmablastic cells. These cells expressed CD38, CD138, CD4, MUM1 and weakly EMA. All B-cell markers (CD20, CD22, CD79a and PAX5) were negative. ALK staining was cytoplasmatic, so the tumor was classified as anaplastic lymphoma kinase positive diffuse large B-cell lymphoma (ALK+DLBCL). Bone marrow examination was negative and the patient was diagnosed with ALK+DLBCL stage III-S bulky disease, IPI low intermediate risk. Patient started first-line therapy including eight cycles of Rituximab-Cyclophosphamide-Hydroxydaunorubicin-Oncovin-Prednisone (R-CHOP). Response evaluation after four cycles showed partial response, but also partial thrombosis of the superior mesenteric and the portal vein. Therapeutic doses of LMWH were given. Treatment was continued, but unfortunately response evaluation after eight cycles showed extensive disease. Bone marrow examination now showed massive infiltration of lymphoma with a marker pattern corresponding to the previous lymph node biopsy. Second line therapy with Dexamethason-High-dose-Ara-C-Platinol (DHAP) was started. The first cycle was complicated by neutropenic fever as a result of catheter related sepsis, which was treated with vancomycin and removal of the central venous catheter. Given the clinical condition and the patient’s wish, no further treatment was given, after which the patient died soon. ALK-DLBCL is a rare subtype of DLBCL, which typically presents as lymph node-based disseminated disease and very rarely involves the bone marrow. The diagnostic work-up is challenging due to the non-distinctive clinicopathologic and immunophenotypical features.
Myelodysplastic syndrome associated with auto-immune disease

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**Case:** A 63-year old man presented with pancytopenia, episodic fever and a rash. His medical history included an idiopathic episode with pancytopenia and skin rash a few years earlier. Physical examination showed red skin discolorations on face, arms and legs. There were no palpable lymph nodes or signs of hepa-to-splenomegaly. Laboratory investigations showed a slightly increased ESR, pancytopenia (haemoglobin 6.9 mmol/L, leukocytes 2.0x10\(^9\)/L, thrombocytes 59x10\(^9\)/L). Renal function and liver tests were normal. The differential diagnosis included a systemic infection, lymphoma, auto-immune disease (SLE, vasculitis). Serology testing, auto-immune serology, blood and urine cultures were negative. Chest X-ray and abdominal ultrasound showed no abnormalities. Additional PET-CT scanning did not show signs of lymphoma. Bone marrow aspiration and biopsy showed a myelodysplastic syndrome. Deep tissue skin biopsy demonstrated a polyarteritis nodosa. The patient was diagnosed with cutaneous polyarteritis nodosa in combination with a myelodysplastic syndrome. He was treated with prednisone after which his rash resolved.

**Discussion:** Polyartritis nodosa is a rare ANCA negative vasculitis of small- or medium-sized arteries. Current literature suggests 10-20% of the patients with a myelodysplastic syndrome (MDS) also have a systemic auto-immune disease (AID). Only a few case reports describe patients with a polyartritis nodosa and MDS. The combination of AID and MDS has been associated with a higher AID relapse and mortality rate. Most patients are treated with corticosteroids of which no effect on MDS have been reported. The main question in this case remains: is there an association between MDS and auto-immune diseases?
Lenalidomide can cause toxic epidermal necrolysis (TEN): a case report

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A 67-year old male peritoneal dialysis patient was admitted to the hospital with fever, increasing rash, skin sloughing and a painful mouth developed within two days after start of flucloxacillin. He was also in the third week of his first cycle of lenalidomide and dexamethasone for multiple myeloma associated amyloidosis. Lenalidomide is an immunomodulatory derivative active against multiple myeloma. The clinical diagnosis TEN was made and supported by histology findings. The patient was treated with high dose dexamethasone, all non-essential medication was stopped and he was referred to a burn unit/ICU in another hospital. After four weeks, he returned to our hospital after extensive treatment for TEN, that had involved over 80% of the body surface and was complicated by several infections. Unfortunately, he eventually died of exhaustion and respiratory failure due to a pulmonary infection. TEN is a rare side effect which can mostly be seen in the first eight weeks following initiation of a new drug and has a mortality rate of more than 30%. It should be considered when a patient develops skin pain and sloughing, fever and mucositis. Discontinuation of the causative drug may improve prognosis. Although skin lesions developed soon after the start of flucloxacillin, lenalidomide was identified as the most likely culprit drug in this case based on the time frame and known capability to induce TEN or Stevens Johnson Syndrome.
Nephrotic syndrome as possible adverse drug reaction in patients using dasatinib

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A boy between 10 and 18 years with Ph+ common acute lymphoid leukemia, developed nephrotic syndrome (edema, proteinuria with protein creatinine ratio 126.7 mg/mmol, blood albumin 12 g/L and), 27 days after starting dasatinib, once daily 60 mg/m². Dasatinib was withdrawn and fluid intake restricted. One week after withdrawal of dasatinib the patient had recovered from the nephrotic syndrome. Previous treatment included cytarabine and mercaptopurine. Scientific literature describes at least another four patients with nephrotic syndrome associated with dasatinib. These patients concern two children and two adults, three females and one male. Daily doses were 60 mg/m² (child), 100 mg (adult), 140 mg (adult) and not reported in one case. Latencies were 26 days, two weeks after dose increase and not reported in two cases. All the patients recovered from the nephrotic syndrome after withdrawal or dose reduction (in one patient) of dasatinib, in two cases within a week. A possible mechanism is disruption of the vascular endothelial growth factor (VEGF) signaling pathway through inhibition of the SRC family kinases, one of the targets of dasatinib. VEGF expression occurs in human podocytes, and therapy targeting VEGF or inhibiting VEGF receptors is associated with proteinuria. Concerning other tyrosine kinase inhibitors sorafenib and sunitinib, both drugs with therapeutic targets that include VEGF receptors, nephrotic syndrome is described as adverse reaction in the Summary of Product Characteristics (SmPC). It is important to realize when a patient develops nephrotic syndrome while on therapy with dasatinib, this might concern an adverse drug reaction of dasatinib.
A 57-year old previously healthy man visits the internal medicine clinic because of aspecific, temporary complaints of his left hand. Blood tests show normocytic anemia (Hb 6.2 mmol/l) and renal insufficiency (creatinine 148 mmol/l; eGFR 45 ml/min/1.73 m²). The patient feels well and physical examination is unremarkable including a normal blood pressure. A serum monoclonal IgM paraprotein of 25.1 g/l is found with high serum free lambda light chains of 1090 mg/l. Bone marrow biopsy shows a lymphoplasmacytic lymphoma (positive for monoclonal lambda; Congo red-negative), consistent with a diagnosis of Waldenström’s Macroglobulinaemia (WM). The renal insufficiency remains unexplained. There is no proteinuria and renal ultrasonography is normal. Renal biopsy shows light chain depositions (lambda positive). Light chain deposition disease is a disorder in which free light chains are deposited in organs such as the heart and kidneys, comparable to other deposition diseases such as AL amyloidosis. In our patient, cardiac evaluation was normal. Treatment was initiated with 4 cycles of R-VCD (rituximab, bortezomib, cyclophosphamide, dexamethasone), followed by an autologous stem cell transplantation. This resulted in a very-good-partial response and an improved renal function. This case is an example of Waldenström’s Macroglobulinaemia-associated nephropathy. While renal insufficiency is a well-known complication of multiple myeloma (incidence to 40%), it is rare in WM patients. The incidence is up to 5% and there is wide variation in underlying kidney pathology. WM-related nephropathy is an established indication for initiation of treatment. We recommend to perform renal biopsy in WM-patients with unexplained renal insufficiency or nephrotic syndrome.
Localized AL-amyloidosis in a young woman

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Case: A 29-year-old Moroccan woman with an unremarkable medical history presented at the outpatient clinic with progressive hoarseness. Stroboscopy showed a process of the left vocal cord with no lymphadenopathy on additional imaging. Biopsy showed extensive nodular amyloidosis without light chain restriction of the sparsely present plasma cells. Systemic involvement was ruled out with absence of serum and urine monoclonal immunoglobulin/light chains and a negative congo red stained abdominal fat aspirate. A bone marrow biopsy and serum amyloid P (SAP)-scan were not performed because of the low a-priori probability of systemic involvement in nodular laryngeal amyloidosis with a negative abdominal fat aspirate. She experienced non-specific abdominal and musculoskeletal complaints without suspicion of underlying chronic inflammation/auto-immunity. Her family history was negative for amyloidosis. An amyloidosis expert centre confirmed the diagnosis of localised submucosal AL-amyloidosis. Her hoarseness improved after surgical amyloid removal.

Discussion: Localized AL amyloidosis is the term used for local amyloid deposits that are derived from locally produced monoclonal light chains, but are not due to an underlying systemic clonal plasma cell disorder. Hence, systemic disease should be actively ruled out. Localized AL-amyloidosis can be found in the skin, upper respiratory tract, genital and urinary tract, and eyes. Amyloid in the larynx is more frequently seen in elderly persons but occasionally affects young adults. The clinical course is usually benign and surgical excision is the preferred treatment.

Conclusion: Localized AL-amyloidosis is a distinct disease entity with a typically benign course.
Blue cures blue

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Case: A 31-year old woman presented with dyspnea which had progressed during the past week. Her medical history included asthma and non-bullous pemphigoid. During physical examination she appeared centrally cyanotic and tachypnoeic. Breath sounds were normal and her oxygen saturation was 89% by pulse oximetry and 98% by blood gas analysis. The chest X-ray was normal, Hb was 8.7 mmol/L and D-dimer was low. The discrepancy between oxygen saturation measured via pulse oximetry and calculated by blood gas analysis, prompted us to consider a methemoglobinemia. Co-oximetry demonstrated a methemoglobin fraction of 9.8% which was caused by the use of Dapsone for the treatment of pemphigoid. The patient was admitted to the ICU where she was treated with multiple methylene blue infusions. Methemoglobin levels normalized in four days.

Discussion: Methemoglobin is an abnormal hemoglobin in which the iron moiety is in the ferric state (Fe³⁺) rather than the ferrous state (Fe²⁺). Methemoglobin is unable to carry oxygen and is characterized by a brownish color which leads to the observed central cyanosis. The condition may arise as a result of a genetic defect, or it may be acquired following exposure to various oxidant drugs or toxins. Methylene blue functions as an exogenous electron acceptor of NADPH which subsequently reduces methemoglobin to hemoglobin. Given the technical limitations of the pulse oximeter there is a difference between the oxygen saturation measured at the bedside and calculated in the blood gas. This saturation gap provides a pivotal clue in the diagnosis of methemoglobinemia.
Atypical bone-pain in a patient with sickle cell anemia

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Case: A 31-year old man presented with a progressive tender swelling on the right upper leg that had developed over two months. He had been diagnosed with homozygous sickle cell disease (HbSS) at the age of nine and there was a history of repeated admissions due to sickle cell crises. Current physical examination showed a subcutaneous density below the right buttock that was painful on palpation. The patient reported no fever. He did mention having had bone pain in the same location a year earlier for which he had received some injection in a Portuguese hospital. More recently he had suffered from gastroenteritis. Current laboratory analysis showed: Hb 4.8 mmol/l, MCV 85 fl, Leukocytes 12x10^9/l (neutrophils 8.55 x10^9/l), CRP 22 mg/l, no other abnormalities. Ultrasound showed a subcutaneous echopenic disk-type lesion that extended to the femur. Subsequent MRI-findings revealed diffuse osteomyelitis of the femur with a fistula to the skin and a subcutaneous infiltrate or Brodie abscess. Cultures showed growth of Salmonella (group B). The patient coincidentally developed a sickle cell crisis and was admitted to our hospital. Antibiotic treatment was started and continued for 6 weeks (Ceftriaxon followed by ciprofloxacin). Symptoms and MRI findings normalised. Because of this, there was no indication for surgical debridement of the femur.

Conclusion: Patients with sickle cell disease are prone to infections because of functional asplenia. We describe a HbSS patient with a salmonella osteomyelitis probably caused by bacteremia following gastroenteritis. Long term treatment with antibiotics followed and surgical intervention eventually appeared not be necessary.
A 56-year-old man was brought to our emergency room because of circulatory arrest preceded by subacute dyspnoea, chest- and back pain. There were no signs of blood loss. Upon arrival, circulation was restored, but he was in severe distress, requiring 15 litres of oxygen via a non-rebreathing mask. He was clammy, had a sinus tachycardia of 100 beats per minute with a blood pressure of 120/70 mmHg. Electrocardiography showed anterolateral ST-depressions compatible with ischaemia. Laboratory evaluation showed a haemoglobin level of 1.7 mmol/l with an MCV of 66 fl and deep iron-deficiency. The manual blood count demonstrated remarkable neutrophil hypersegmentation. Folate and cobalamin levels were normal. CT-scan and extensive gastrointestinal evaluation did not show blood loss or mucosal abnormalities. With normal haemoglobin levels one year before, thalassaemia was unlikely. The patient later told he had not been eating well for months due to self-neglect. The chest pain and electrocardiographic abnormalities disappeared after blood transfusion, indicating secondary ischaemia. The patient was discharged with iron supplementation. In the months thereafter he regained weight and his haemoglobin rose to 10 mmol/l, even after discontinuing supplementation.

Neutrophil hypersegmentation is a well-known finding in folate or cobalamin deficiency. However, hypersegmentation can also occur in iron-deficiency through low concentrations of the heavy chain subunit of ferritin. This compromises DNA synthesis by inhibiting folate metabolism, but does not affect generation of nuclear components, resulting in hypersegmentation in neutrophils. We here present a case of extreme iron deficiency anaemia due to alimentary shortage and subsequent neutrophil hypersegmentation.
Non-immune hemolytic anemia, symptom of bone marrow infiltration of a solid tumor

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Introduction: The work-up of hemolytic anemia can be challenging. With this case we demonstrate that a structured approach revealed an unexpected diagnosis.

Case: A 68-year-old man was evaluated for progressive fatigue since several weeks. His history reported an T3NiM adenocarcinoma of the oesophagus, for which he received chemo-radiation and surgery in 2012. Physical examination was unremarkable. A recent CT-scan performed for periodic follow-up showed no sign of relapsing disease. Laboratory testing was revealed severe hemolysis with a hemoglobin level of 4.7mmol/L, LDH of 615U/L with increased reticulocyte index and normal platelet count. To differentiate between an immune mediated or non-immune mediated cause a direct antiglobulin test was performed, which was negative. An eluate was also negative, confirming a non-immune cause of haemolytic anaemia. He used to have normal hemoglobin levels, excluding hereditable diseases like hemoglobinopathies. During the work-up a gastroscopy, colonoscopy and PET-scan revealed no abnormalities. PNH, G6PD- and PK-deficiency were also negative. The peripheral blood smear showed fragmentocytes. A bone marrow biopsy was performed, revealing a localisation of metastasis of oesophagus carcinoma, which confirmed the diagnosis of confirmed the diagnosis of a microangiopathic hemolytic anemia (MAHA). He refused chemotherapy and died several weeks after the diagnosis.

Conclusion: MAHA is a mechanical hemolysis caused by diffuse intravascular coagulation, infection, malignancies, HELLP, severe hypertension, systemic rheumatic diseases or organ transplantations. In this case bone marrow invasion was the only localisation of the malignancy. MAHA caused by a malignancy has a poor prognosis and treatment is based on treatment of the tumor.
Hematomas in pregnancy: a case report

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A 27-year-old pregnant woman (G2P1, 31 weeks + 2 days) with an unremarkable medical history presented with an increasing number of non-traumatic bruises. She did not experience any other symptoms and did not use medication. On physical examination, we saw several purpura on her extremities, petechiae on her abdomen, and normal vital signs. Initial laboratory findings included severe thrombocytopenia 7x10^9/L, normocytic anaemia (hemoglobin level of 4.8 mmol/L), elevated levels of lactate dehydrogenase (LDH) 872 U/L, and proteinuria with normal complement levels, coagulation, kidney, and liver tests. Further laboratory testing showed coombs negative hemolysis with 7% schistocytes in the peripheral blood smear. Because the incidence of hemolysis elevated liver enzymes and low platelets (HELLP) is higher than of thrombotic thrombocytopenic purpura (TTP) she underwent an emergency cesarean section, even though two letters of the acronym HELLP were missing. She delivered a healthy baby boy, but her laboratory findings did not improve in the following days. ADAMTS13 activity came back as 5% in the presence of an inhibitor. The diagnosis of acquired TTP was made, and plasmapheresis and corticosteroid treatment initiated immediately, leading to a swift recovery. TTP is a rare life threatening disorder with an incidence of less than 1 per 100000 in pregnancy, but is still responsible for 5% of all cases of severe thrombocytopenia in pregnancy. Retrospectively, the high percentage of schistocytes (generally < 1% in HELLP), the absence of hypertension and abdominal pain, and normal liver enzymes in this case were more consistent with TTP than with HELLP.
Case report: An unexpected cause of a prolonged activated partial thromboplastin time

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Introduction: prothrombin time (PT) and activated partial thromboplastin time (aPTT) are the most commonly ordered coagulation tests for the screening of coagulation disorders. An isolated prolonged aPTT needs further evaluation, even in asymptomatic patients, because a coagulation factor deficiency or inhibitor might be present.

Case: A 27 year old male was referred to the outpatient clinic after a coagulation screening test showed an isolated prolonged aPTT of >100 seconds. The patient once experienced a prolonged bleeding of the skin after the removal of cutaneous warts, but did not have a history of inappropriate bruising, bleeding after minor trauma, surgery or dental works. He did not use any medication. There is no known family history of hemorrhagic diathesis or thromboembolic complications. Physical examination showed a healthy male without bruises or teleangiectasia. Further laboratory evaluation showed a normal prothrombin time (1.06 sec), thrombocyte count (221 x 10^9/L) and function. A mixing study was performed and showed normalization of aPTT. Factor VIII (126%) and factor IX (112%) activity was normal. On further examination a factor XII deficiency (2%) was found, explaining the prolonged aPTT.

Discussion: Factor XII deficiency is a rare congenital disorder, usually transmitted as an autosomal recessive trait. Affected patients have marked prolongation in the aPTT but do not exhibit a bleeding diathesis and thus do not require specific treatment. On the contrary, venous thromboembolism has been reported in a number of factor XII deficient patients, the reported incidence of serious thromboembolic disease in different studies varies from 1-8%.
A simple measurement for a rare disease

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A 55-year old male patient presented at the outpatient internal medicine with long existing high hemoglobin levels. At the age of 42 he was diagnosed with a myocardial infarct, and in the last months he suffered from headaches and itching after taking a hot shower. His brother and sister had also been found to have high hemoglobin levels, but the patient did not know their diagnoses. Once every three months his brother was undergoing phlebotomy. Laboratory results showed a high hemoglobin concentration of 12.6 mmol/L and hematocrit of 61%. Phlebotomy treatment was started to lower the hematocrit and reduce the symptoms. After three sessions, the hematocrit was decreased to 54% and all symptoms were gone. A normal erythropoietin concentration of 11 IU/L (4-29 IU/L) was measured, and the JAK-2 mutation was absent. A bone marrow aspiration was performed, but biopsy was unsuccessful. Taking together these results, the diagnosis of polycythemia vera could not be made. During a discussion about the case, a clinical chemist recognized the family name of the patient and started sequencing analysis. The patient appeared to be positive for beta 36 (C2)Pro>Thr characteristic for Hb Linköping. This disease is a type of high-affinity hemoglobinopathy, which is characterized by a ‘left-shifted’ hemoglobin oxygen dissociation curve and as such can be diagnosed by measuring a reduced P50 (pO2 at 50% oxygen saturation). Concluding, this case showed that, although high-affinity hemoglobinopathy is a rare disease, a simple P50 measurement can be used for diagnosis, avoiding inappropriate diagnostic investigations and (over-)treatment.
The value of Rituximab addition to chemotherapy treatment in real-world CLL patients: a 15 year single center experience

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Background: Chemoimmunotherapy has shown an effect on overall survival in prospective trials in CLL patients. The evidence in real world patients, however is scarce. We set out to confirm the efficacy of Rituximab (R) chemotherapy in a real-world CLL population.

Methods: All patients from a large teaching hospital diagnosed with CLL from 2000 to 2015 were enrolled. Treatment with chemotherapy (CTX) was compared with R-chemotherapy (R-CTX) with respect to treatment-free interval (TFI). Overall survival was studied for patients ever treated with R-CTX compared with patients treated with CTX only.

Results: In the observational period 124 of 375 CLL patients (33%) required first-line treatment. 68 patients (55%) received CTX and 56(45%) received R-CTX. In addition, 97(47%) of these patients required a subsequent line of (R-)CTX. In total 221 treatment periods were studied. The median TFI for patients treated with CTX was 31 months (range 20 - 42) in relation to not reached for R-CTX (range 49 - not reached), hazard ratio was 0.40 (95%CI 0.22 - 0.73) in first line; median TFI for CTX was 27 months (range 18 - 52) vs. 56 months for R-CTX (range 41 - not reached), hazard ratio was 0.47 (95%CI 0.26 - 0.84) for subsequent lines. Overall survival for patients receiving R-CTX was 83 vs. 52 months for patients treated with CTX alone (p=0.01).

Conclusion: In a real-world CLL population the benefit of adding Rituximab to chemotherapy is confirmed with respect to improved treatment free interval in first- and subsequent lines and prolonged overall survival.
A rare presentation of a B-cell lymphoma

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A 75 year old men was admitted to the internal medicine ward with progressive dyspnoe, fatigue and spiking fever. Furthermore, he had lost three kilograms of weight during the last month. At presentation, physical examination showed no fever, however this reoccurred during hospitalization, when he was severely ill and complained of night sweats. Laboratory test revealed anemia (hemoglobin 6.0 mmol/L), thrombocytopenia (144x10^9) and disturbed liver biochemistry. A viral infection was suspected. Extensive serologic testing including viral hepatitis (A,B,C,E), EBV, CMV and HIV were negative. Additional laboratory tests to specify the anemia, showed a highly elevated ferritin (2160 mmol/L). The diagnosis Still's disease was suspected and the patient was treated with ibuprofen. The next day’s, patients condition was deteriorating quickly and blood count declined. Prednisone was started and a bone marrow biopsy was performed, which revealed hemophagocytosis. Since treatment of the underlying condition is crucial in treating hemophagocytic syndrome, a PET-CT was performed. This showed abnormal cervical and iliac lymph nodes all below 2 cm, suggestive for lymphoma. Immunohistochemical panel on T-cell markers were all negative and further analysis revealed a diffuse large cell B-cell lymphoma. R-CHOP chemotherapy was directly started and complete remission was achieved. Today, ferritin levels remain elevated, but there are now clinical signs of relapse. This report demonstrates that, along with T-cell lymphoma’s, also B cell lymphoma can present with hemophagocytosis. This findings are in line with the literature. Accurate diagnosis and treatment is essential for a favorable outcome.
Kikuchi’s disease: an unusual cause of lymphadenopathy.

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Case: A 20-year-old woman, originally from Bhutan, was admitted with lymphadenopathy and prolonged fever. She was unresponsive to prior antibiotal treatment for a suspected tonsillitis. She had developed a clindamycin-induced anaphylactic reaction and a skin rash after treatment with amoxicillin. During admission, fever persisted and she developed hemorrhagic crusts on her lips and a papulovesicular skin rash around the eyes and ears. Vital parameters remained stable, however the patient was lethargic and food intake was minimal due to oral mucosal lesions and nausea. Physical examination revealed a palpable, tender lymph node located in the neck behind the sternocleidomastoid muscle. Laboratory analysis only showed mildly elevated liver enzymes and LDH. Tests for tuberculosis, EBV, CMV, HSV and HIV were all negative. Repeated blood cultures remained negative. CT-scans showed cervical, axillary and supraclavicular lymphadenopathy. Histopathology of a lymph node biopsy revealed no signs of malignancy but diffuse necrosis and histiocytic cells, typical for Kikuchi’s disease. Spontaneous resolution of signs and symptoms occurred within two months.

Conclusion: Kikuchi’s disease is a rare, benign cause of lymphadenopathy. The most common presentation is cervical lymphadenopathy and fever. Cutaneous involvement, including drug-induced eruptions, is seen in up to 40% of cases.

The disease is most frequent in young women from Asian heritage, but also occurs in men and patients from other ethnicities. The diagnosis is established by histopathology examination, showing a histiocytic necrotizing lymphadenitis. The disease is self-limiting and symptoms generally resolve within several months.
Paraneoplastic IgG4 related disease mimicking peritonitis carcinomatosa

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IgG4 related disease (IgG4-RD) is a rare auto-immune disease with a broad spectrum of symptomatology. We report a case of a 51 year old male, without any past medical history, presenting with fatigue, a cough and a mild anemia. An abdominal ultrasound showed a tumor in the right colon and histology confirmed the diagnosis of a colon carcinoma. During hemicolecotomy there was a strong suspicion of invasion of the abdominal wall and peritoneal metastases. Histological investigation of the resected tumor however showed only a T3 colon carcinoma surrounded by a large area of IgG4 positive plasma cells, raising the suspicion of IgG4-RD. No tumor invasion of the abdominal wall and no peritoneal metastases were seen. Two months after surgery the patient was referred to the outpatient clinic of the internal medicine department for analysis of IgG4-RD. At this time his constitutional symptoms of fatigue and his cough had vanished and there were no signs of IgG4-RD during examination. The serum IgG4 level was mildly elevated. We decided for watchful waiting for the IgG4-RD, since the diagnosis of a paraneoplastic phenomenon was suspected and our patient was asymptomatic. There have been 4 earlier case reports of paraneoplastic IgG4-RD in colorectal carcinoma. In one of these there was local IgG4 positive plasma cell infiltration in the tumor and in two cases the IgG4-RD went in complete remission after treatment of the primary tumor. The causal relation between malignant tumors and IgG4-RD remains unclear.
A 64 year old man with a history of urticaria not responding to antihistamine treatment presented with dyspnea on exertion and fatigue. The review of systems was entirely negative. CT of the chest revealed a right atrial mass suggestive of an atrial myxoma. One week after uncomplicated resection of the mass, ALAT (472 U/L), ASAT (60 U/L), and γGT (193 U/L) increased. Imaging studies of liver were normal, viral infections were not found, a toxic cause was considered unlikely. Subsequently, proteinuria of 2 grams per day and hematuria developed. Additional serological tests revealed ANA, anti-Sm, anti-RNP, and anti-C1q seropositivity with hypocomplementemia due to activation of both the classical and alternative complement pathway. Kidney biopsy revealed a mesangial proliferative glomerulonephritis with strong C3c staining but surprisingly without deposition of immunoglobulins, indicating C3 glomerulonephritis in the setting of a systemic lupus like disease. Treatment with high-dose corticosteroids and mycophenolate mofetil was initiated, after which the liver enzymes and proteinuria improved.

Conclusion: Cardiac myxoma is a benign but sometimes immunologically active tumor, producing proinflammatory cytokines such as interleukin 6. Although rare, it may mimic autoimmune disease, such as vasculitis and SLE. Usually signs and symptoms disappear after surgical resection. In our case however, patient deteriorated, developed specific autoantibodies, and immune-mediated liver and kidney disease. These findings suggest that cardiac myxoma may rather have been consequence, not cause of the immune dysregulation. C3 glomerulopathy, a new entity within the nomenclature of renal disease, has never been reported in association with cardiac myxoma.
Severe encephalopathy without liver failure in an immunocompromised patient

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Case: A 52-year-old man with a history of IL-12/23 receptor b1 (IL-12/23Rb1) deficiency, presented with severe encephalopathy. Electroencephalogram confirmed triphasic waves. Liquor puncture showed no evidence for infectious meningo-encephalitis. Brain MRI was unremarkable. Laboratory investigations revealed pancytopenia and elevated inflammatory parameters. Complementary liver- and renal function tests were normal. However, ammonia was highly elevated (131-216 mmol/L). Subsequently, abdominal ultrasound and CT-scan showed no liver cirrhosis, steatosis or porto-systemic shunts. Other causes of the metabolic encephalopathy like drug intoxication or urea cycle defects were excluded. An urease-producing infection was suspected in this immunocompromised patient. Blood, faeces, sputum, liquor and urine cultures remained negative. However, a PET-CT showed a remarkable, extensive FdG-uptake in the bone marrow. Bone marrow aspirate and biopsy were obtained and confirmed the presence of atypical mycobacteria. Cultures showed Mycobacterium Genavense. Lactulose, rifaximin and continuous veno-venous haemodialysis were initiated to lower ammonia levels. In order to restrict catabolism we maintained the patient on a low protein diet and added glucose infusions. Interferon gamma suppletion and triple therapy by rifabutin, isoniazid and clarithromycin were administered. Heteroanamnesis revealed patient had stopped his antimicrobial prophylactic medication.

Conclusion: An IL-12/23R b1 deficiency impairs the ability to produce interferon gamma, inducing a susceptibility for atypical mycobacterial infections. An urease-producing mycobacterial infection is an unusual but treatable cause of hyperammonemia. In immunocompromised patients without antimicrobial prophylaxis mycobacterial infection can cause a metabolic encephalopathy.
Prognosis of adult patients with fever of unknown origin

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Background: In half of patients with fever of unknown origin (FUO) no diagnosis can be made despite extensive evaluation in an expertise center. Little is known on the prognosis of these patients. The aim of this study was to gain insight in prognosis and effect of treatment.

Methods: Patients that remained undiagnosed after evaluation for FUO between December 2003 and June 2014 were included. Demographic data, data on survival and treatment were collected from medical records. Patients were contacted by phone or, when not reached by phone, received an e-mail or letter containing a standardized questionnaire on treatment and outcome.

Results: 94 of 116 eligible patients responded. Median age for responders was 45.0 years (range 18-81 years). Median duration of fever at the first visit to the Radboudumc was 554 days (range 5-17638 days). Median follow-up was 6.2 years (range 2.4-14.8 years). A total of 51 patients (54.3%) became fever-free during follow-up. In patients that became fever free, median duration of fever from the first visit was 16 months (range -2-47 months). Fifty-three patients (56.4%) received some form of treatment. Five patients (5.3%) died. None of these deaths were FUO related, all had a cardiac cause. Median age at death was 78 years (range 64-84 years) and 60% of deaths were >6 months from the first visit (median 13 months, range 3-42 months).

Conclusion: Prognosis of undiagnosed FUO patients is good. Half of them become fever-free and there was no fever-related mortality during a median follow up of 6.2 years.
A severe case of pulmonary leptospirosis contracted in The Netherlands

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Background: Leptospirosis is a relatively common zoonosis in the tropics, but rare in temperate climates. Most patients presenting in The Netherlands have contracted the disease abroad. Symptoms are often mild and nonspecific. Severe cases can present with renal dysfunction, jaundice, haemorrhage or alveolar haemorrhage. We present a case of severe leptospirosis after domestic fresh water submersion.

Case: A 34-year-old man presented with respiratory insufficiency, myalgia and haemoptysis two weeks after fresh water submersion related to a motor vehicle accident. There was no history of recent travel abroad. Laboratory results showed kidney dysfunction, elevated transaminases and prolonged coagulation times. Chest X-ray showed progressive bilateral infiltrates. The patient deteriorated quickly and was put on mechanical ventilation for hypoxic respiratory failure. Ceftriaxone was started. Blood, sputum and urine cultures remained negative, but a slide agglutination test (SAT) for leptospira was positive, as well as PCR for leptospira DNA. The antibiotic regimen was narrowed to penicillin G, resulting in a rapid and complete recovery.

Discussion: We describe a case of severe leptospirosis presenting with multi-organ dysfunction requiring ICU admission. The incidence of leptospirosis in The Netherlands has fallen below 0.2/100,000/year, and most cases result from exposure abroad, especially in Asia. ICU admission is required in a minority of cases. This case shows that, though severe leptospirosis after domestic exposure is rare, clinicians should suspect leptospirosis in all patients with a history of recent fresh water submersion.
STTD: a sexually transmitted tuberculous disease

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Case: A 29-year-old Eritrean woman presented with secondary amenorrhea, after she had been sexually assaulted in her homeland two years earlier. Hysteroscopy showed endometrial adhesions in the inner ostium of the cervix, which were relapsing despite several adhesiolyses. Histologic examination of the adhesive tissue revealed chronic inflammation with granulomas. Stains and cultures for bacterial (including Actinomyces) and fungal infections were negative, as well as stain and PCR for M. tuberculosis, and serology for syphilis and schistosomiasis. Finally, mycobacterial culture of the removed endometrium confirmed an infection with M. tuberculosis. There were no signs of other localizations of tuberculosis. The patient was treated with tuberculostatic therapy during six months. Six weeks after treatment initiation her regular menstrual cycle returned.

Discussion: We present a case of secondary amenorrhea caused by tuberculous endometritis. This is a common cause of secondary amenorrhea and female infertility in regions where tuberculosis is highly prevalent. Although this form of tuberculosis is rare in Western countries, it is more likely in immigrants from these regions. The exact pathogenesis varies. Mostly there is hematogenous spread from a pulmonary or other non-genital localization. Also direct contamination from peritoneal tuberculosis (via oviduct) and sexual transmission from a partner with tuberculous epididymitis are possible.

In this case the route of transmission is unclear; there were no signs of extragenital localization, pointing towards inoculation from a male sexual partner. In case of hematogenous spread, the injured genital tract might have acted as locus minoris, predisposing the uterus for bacterial seeding.
Fever, elevated ESR and arthralgia with culture negative endocarditis

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Case report: A 62-year-old Caucasian male was referred to our hospital for an aorta valve replacement because of valve insufficiency with decompensatio cordis. His medical history included unexplained periods of fever, elevated ESR and migratory arthritis during the last year. The last month, he suffered from progressive dyspnea. On examination, a systolic murmur was heard. Blood showed a CRP of 67 mg/l with a normal leukocyte count and ESR. A transoesophageal echocardiography confirmed a sclerotic bicupid aortic valve with insufficiency. He underwent successful replacement of the aortic valve. Peroperatively, the valve appeared inflamed macroscopically after which several blood cultures were taken and empirical antibiotic therapy was initiated with ceftriaxone and doxycycline. Histologic examination as well as a Gram stain of the valve did not reveal a micro-organism. As blood cultures showed no growth including for HACEK bacteria, a search for fastidious bacteria by serology, PCR and 16S analysis was performed. *Tropheryma whipplei* was detected by PCR and 16S rDNA-based PCR directly on the heart valve. No other micro-organisms were identified. The diagnosis Whipple endocarditis was made and the patient was treated with ceftriaxone for one month, followed by doxycycline and hydrochloroquine orally for 1.5 year. During his last follow-up 8 months after surgery CRP was normalized to 14 mg/l.

Conclusion: The diagnosis of T. whipplei endocarditis is typically not made until pathological or microbiological examination of tissue. Therefore, clinicians must have a high suspicion for it in the absence of identified organisms, especially among middle-aged white males with subacute symptoms.
A not so idiopathic granulomatous mastitis?

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Introduction: Granulomatous diseases have a broad differential diagnosis. We describe a case of granulomatous mastitis caused by *Corynebacterium kroppenstedtii*.

Case: A 40-year old woman with a history of recurrent mastitis, was admitted to our hospital with progression of mastitis. On physical examination we found severe mastitis, arthritis and erythema nodosum. Laboratory results showed an increased c-reactive protein. Ultrasound revealed an abscess, cultures and biopsies were taken. Cultures remained negative, as well as ANA and ANCA. sIL2r was slightly increased but ACE enzyme was low and high resolution CT showed no hilar lymphadenopathy. Biopsies showed granulomatous inflammation. We suspected idiopathic granulomatous mastitis (IGM) and started with prednisone 40mg/day, and later methotrexate, both with no effect. After two months new breast culture became positive for *Corynebacterium kroppenstedtii*.

Discussion: Granulomatous mastitis is a rare inflammatory condition that often mimics breast cancer. The differential diagnosis includes tuberculosis, sarcoidosis, granulomatosis with polyangiitis, infection, foreign body and IGM. The pathogenesis of IGM is unknown, but many case series describe supposed IGM in which *C. Kroppenstedtii*, a Gram-positive anaerobic bacteria, is isolated. The bacteria is often found deep in the breast tissue and is surrounded by granulomatous inflammation. Management, with antibiotics and surgery, is difficult as evidence for treatment is scarce and patient often have recurrences.

Conclusion: Granulomatous mastitis causes by *C. Kroppenstedtii* is a rare, complex disease, often mistaken for idiopathic granulomatous mastitis because of difficulties in identifying the causative pathogen.
Fever and a miliary interstitial pattern in a 62-year-old man

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Case: A 62-year-old male was transferred from the urology to the infectious diseases department, because of persistent fever while on ceftriaxone for 4 days because of initially presumed UTI. His medical history included stage pTaG3NoMo bladder carcinoma, for which he received treatment with intravesical live attenuated bacilli Calmette-Guérin (BCG) immunotherapy. At the night of his most recent instillation, he developed fever with chills, followed by dyspnoe a few days later. On physical examination, patient was not acutely ill, had a temperature of 38.6, an oxygen saturation of 95% on 2 liters of nasal cannula oxygen and bibasilar crackles. Laboratory results showed a CRP of 67 mg/l, leukocytes of 3.4 x10^9/l and an ESR of 49 mm/hr. Abdominal ultrasonography showed no radiological abnormalities of the kidneys/urinary tract. A HR-CT scan demonstrated bilateral fine diffuse nodules, suggestive of miliary disease. Bronchoscopy macroscopically revealed irregular mucosa in the right middle lobe. The diagnosis disseminated BCG-itis was made and therapy with rifampicin, ethambutol and moxifloxacin was started (6 months), simultaneously with glucocorticoids. PCR for M. tuberculosis complex on bronchoalveolar lavage was negative, as well were acid-fast stains and cultures for mycobacteria, so far. After 4 days of treatment, the fever and dyspnea disappeared.

Conclusion: BCG-itis is a rare complication of intravesical BCG treatment. As in most previously reported cases of infection, BCG was not recovered from cultures in our patient. Presumptive diagnosis was based on the temporal relation between intravesical instillation and the beginning of the symptoms as well as the patient’s clinical response.
A 56-year-old woman presented with slightly tender swelling on the right side of the neck accompanied by night sweats. She had no relevant medical history. On physical examination no abnormalities were found other than unilateral cervical lymphadenopathy. Laboratory tests showed an increased ESR of 46 mm/hr. CT of neck, chest and abdomen showed no abnormal findings other than two enlarged lymph nodes in the right cervical region. Examination of ear, throat and nose was unremarkable. Histopathological examination of a lymph node showed follicular hyperplasia and no signs of malignancy. Serological examination (non-treponemal and treponemal) for syphilis was positive and PCR testing for syphilis of the lymph node also appeared positive. Liquor studies showed no sign of neurosyphilis. The patient could not remember to have had any sexually transmitted disease. Treatment with intramuscular penicillin resulted in complete clinical improvement and normalization of the ESR. The differential diagnosis of lymphadenopathy is extensive and mainly consists of infectious and malignant diseases. Syphilis is a sexually transmitted disease caused by Treponema pallidum. Traditionally it is divided in three stages. The majority of patients in the second stage develops a typical exanthema which can be accompanied by several symptoms including generalized lymphadenopathy. Localized lymphadenopathy as the only sign of the second stage of syphilis is rare. Undiagnosed it will spontaneously heal but subsequently it can progress to the tertiary stage with major morbidity. Also is there the persisting risk of developing neurosyphilis. Therefore syphilis serology should be part of the work-up of lymphadenopathy.
A U.F.O. as a cause of F.U.O.

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Introduction: Amiodarone is an antiarrhythmic drug associated with pulmonary and extrapulmonary toxicity. Recognition of toxicity can be challenging because of atypical presentation.

Case: A 66 year old man was admitted because of fever, cervical myalgia and dysphagia not responding to antibiotic therapy. His medical history showed a curated NHL. Recently amiodarone was prescribed for an atrial flutter. Physical examination showed slight redness and profound tenderness of the neck. Blood tests demonstrated an elevated CRP (462mg/L) and leukocytosis (22.6*10^9/L). Chest x-ray was unremarkable. Broad-spectrum antibiotic therapy was initiated. High-grade fever (40°C) persisted and inflammatory parameters increased during and after discontinuation of antibiotic therapy. Microbiological cultures were sterile. Serology of a broad spectrum of viral and bacterial pathogens was negative, as was autoimmune serology. Imaging by CT of neck/thorax/abdomen showed mediastinal lymphadenopathy and pulmonary infiltration of the lower lobes. All abnormalities turned out to be negative on FDG-PET. A bronchial alveolar lavage was without any significant findings. Because of suspicion of drug-induced fever, the recently initiated amiodarone was halted and prednisone was started. Soon the fever and neck pain disappeared, inflammation parameters normalized and prednisone could be tapered off permanently. Follow-up pulmonary radiography was also normal.

Discussion: In this case we identified amiodarone as the cause of F.U.O. Immunomodulatory effects of amiodarone have been described extensively, often within the context of extended pulmonary toxicity. Here we describe an uncommon presentation of amiodarone as a cause of drug-induced fever without remarkable respiratory complaints, completely reversible after steroids and discontinuation of therapy.
Case: A 54-year-old woman with a history of polyarthritis presented with fever, shaking chills and dyspnea for 4 weeks. She was not taking any medication. She had several dogs and cats, but had not been bitten or scratched. On physical examination she had fever, poor dental health and a loud systolic heart murmur. Transthoracic echocardiogram revealed a large vegetation on the mitral valve. Because of heart failure, emergency surgery was performed. PET scan showed no other infective foci. All blood cultures remained negative. PCR analysis of 16S genes on the valve revealed Capnocytophaga canimorsus as causative microorganism of infective endocarditis. The patient fully recovered after 6 weeks of high dose intravenous benzylpenicillin. When revisiting the patient after diagnoses was made, she had splinter hemorrhage on two fingernails and admitted to omission of a dog bite roughly 6 weeks before admission, because she feared the consequences for her dog.

Discussion: Infective endocarditis caused by zoonotic microorganisms is rare and mostly due to Brucella or Coxiella species. Capnocytophaga canimorsus mostly causes sepsis but meningitis, cellulitis, arthritis, mycotic aneurysma formation and endocarditis have been described. Immune compromised or asplenic patients are mostly at risk. A history of dog or cat exposure, contact with contaminated milk or infected farm animals may be a clue in finding the causative pathogen in culture-negative endocarditis. Modern molecular techniques can help establishing the diagnoses.

Conclusion: Capnocytophaga canimorsus is known for causing fulminant sepsis following dog bites, however rare, infective endocarditis should also be kept in mind.
Complete remission of hepatitis C related acute lymphatic leukaemia and cryoglobulinemia with direct-acting antivirals and rituximab

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A 61-year-old man of African descent presented with unexplained fever and pain in both legs. His medical history included a longstanding well-controlled HIV infection with a CD4-count of 330 cells/ml blood and an undetectable HIV viral load, insulin-dependent diabetes mellitus type 2, and a chronic hepatitis C infection, genotype 4, for which he had been treated (unsuccessfully) with Pegylated interferon-alpha-2a and ribavirin in 2005. $^{18}$F-FDG-PET/CT, performed because of his unexplained fever, showed irregular uptake in the bone marrow. A crista biopsy revealed localization of B-lineage acute lymphatic leukaemia (B-ALL). Treatment with prednisolon, methotrexate and 6-mercaptopurin was started with biopsy-proven remission after 2 months. One year later HCV-associated cryoglobulinemia with glomerulonephritis was diagnosed. Treatment for active hepatitis C infection and concomitant cryoglobulinemia was initiated, despite the uncertain prognosis regarding B-ALL, with sofosbuvir (400 mg once daily), daclatasvir (60 mg once daily) and ribavirin (400 mg twice daily) for 12 weeks. Prednisolon (1mg/kg) daily and rituximab 1000mg (2 infusions over a 2 month period) were added because of the cryoglobulinemia. Plasma HCV RNA was undetectable four weeks after start of treatment and thereafter, and alanine aminotransferase levels remained normal throughout treatment. Two years after treatment, there was no activity of B-ALL in bone marrow, a normal renal function and no detectable cryoglobulins. This case illustrates the protean complications of chronic hepatitis C-infection. Our case suggests that direct anti-HCV treatment may obviate the need for chemotherapy for HIV-hepatitis C co-infected patients with lymphoproliferative disorders.
Progressive multifocal leukoencephalopathy in patients using dimethylfumarate

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A male patient between 70 and 80 years was hospitalized for lisping speech, left hanging mouth, mood swings and memory impairment. Dimethylfumarate used for psoriasis, was withdrawn. Laboratory evaluation showed leukocytes of 6.5 x 10⁹/L and lymphopenia grade 3 (0.42 x 10⁹/L). MRI-brain showed a contrast enhancing rightsided parietotemporal lesion. Differential diagnosis included glioma, lymphoma, or opportunistic infection after dimethylfumarate. Lumbular punction showed no lymphoma or infection. Subsequent brain biopsy was positive for JC virus, confirming the diagnosis progressive multifocal leukoencephalopathy (PML). Symptoms gradually improved over weeks. PML is a severe demyelinating central nervous system disease caused by a brain infection with JC virus. JC virus infections are common, but PML occurs almost exclusively in immunocompromised individuals. In The Netherlands dimethylfumarate Psorinovo® is used as self-compounded drug for psoriasis. Dimethylfumarate Tecfidera® received registration for multiple sclerosis in The Netherlands in 2014. Several cases of dimethylfumarate associated PML were published. The bioactive metabolite monomethyl fumarate is known to have immunomodulatory effects. Hypotheses of how dimethylfumarate may induce PML, include reduction of peripheral blood lymphocytes by anti-proliferative and pro-apoptotic effects or inhibition of integrin α₄ expression in circulating lymphocytes. In 2015 the European Medicines Agency (EMA) issued monitoring recommendations for dimethylfumarate Tecfidera®, including complete blood counts before and during treatment for timely detection of lymphocytopenia and a baseline MRI-brain. It is important to include PML in the differential diagnosis in patients with neurological deterioration while on therapy with dimethylfumarate, and to realize that a negative lumbar punction does not rule out PML.
Turkish delight – an unusual cause of epididymitis in a young man of Turkish descent

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A 25 year old male of Turkish descent was referred to the emergency department with progressive testicular pain and swelling. Symptoms had started 5 days before presentation and during the last days he had developed fever and night sweats. Medical history was unremarkable except for a recent tendinitis. He was examined by the urologist who noticed profound right sided testicular swelling with induration of the epididymis. Laboratory results showed a white blood cell count of $10.0 \times 10^9/L$ and C-reactive protein of 177 mg/L. The diagnosis of epididymitis was confirmed by ultrasound of the scrotum. The patient was initially treated with ciprofloxacin followed by doxycycline and metronidazole. Serology for sexually transmitted diseases was negative. Two days after admission blood cultures turned out to be positive for Brucella species. Additional history taking revealed that the patient had visited relatives on a farm in Turkey 5 months before, where he witnessed the birth of several lambs. Treatment was switched to doxycycline and rifampin for a total of 6 weeks. Fever and testicular pain resolved within a week, but symptoms of night sweats, malaise and arthralgia remained for another few weeks. Brucellosis, although uncommon in The Netherlands, is one of the most widespread zoonoses worldwide. Transmission occurs through contact with fluids from infected animals or consumption of unpasteurized milk products. Laboratory-acquired infections are frequently reported. Clinical manifestations include malaise, fever, night sweats and arthralgia. Genitourinary involvement occurs in 2-20% of cases. Brucellosis should be considered in patients with epididymitis and possible exposure.
Extensive lymphadenopathy in an HIV-positive patient with multicentric Castleman’s disease

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The case showcases a 53 year old male who has been seropositive for HIV since 2013. The patient is known with paranoid delusions which has made it difficult to assess compliance for antiretroviral therapy. Last measured CD4 count was low. He presented with fever and night sweats and lymphadenopathy on a previous CT-scan made for a suspected recurrent pneumonia. PET-CT scan showed extensive lymphadenopathy suggestive for a Castleman's disease, which was confirmed with histology and immunohistochemistry of an excised lymph node. The patient will be treated with rituximab and valganciclovir. ART will be continued.

Conclusion: newly diagnosed multicentric Castleman's disease in an HIV-positive patient. PET-CT imaging showing extensive lymphadenopathy. Treatment with rituximab and valganciclovir.
Mycotic aneurysm, caused by a clostridium septicum in a patient with coloncarcinoma

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Introduction: Abcess formation is a common finding in new colorectal cancer. A rare micro-organism, associated with this condition, is clostridium septicum. We present a patient which coloncarcinoma, who developed a mycotic aneurysm caused by a clostridium septicum infection.

Case: A 71 year old male presented with abdominal pain and gastro-intestinal obstruction, based on colonic ascendens carcinoma. Computed tomography (CT) imaging showed abcess formation around the tumour, but also fat infiltration and a small amount of peri-aortic gas. The patient was admitted to a surgical ward, the abcess was drained and a doubleloop ileostoma was made. Blood en abcess cultures were taken and amoxicillin/claviculanic acid started. Bloodcultures showed clostridium septicum, the abcesscultures Streptococcus anginosus.

The patient developed a post-operatieve paralytic ileus. A second CT-scan showed a massive mycotic aneurysm (diameter 6cm of the infra-renal aorta) with severe gass formation. Together with the bloodcultures, it pointed to a clostridium septicum aortitis. Amoxicilline/clavulanic acid was continued and the day after a rifampicin-drenged aorta-bifurcation prothesis was implanted. The procedure was complicated by tearing of the infra-renal aneurysm with rupture of a renal artery and a spontaneous jejunall perforation. Cultures were taken from the aortic aneurysm, which also showed the clostridium septicum bacteria. Due to the complications, and ongoing infection, the patient died 5 days later.

Conclusion: Mycotic aneurysm caused by clostridium septicum is a rare and life-threatening complication of abcessformation especially in colonic cancer. With positive cultures and signs of aortitis appropriate antibiotic therapy and prompt surgical intervention are warranted.
Neurologic signs during treatment of herpes zoster ophthalmicus: meningitis or acyclovir intoxication?

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Introduction: Herpes zoster results from reactivation of latent varicella zoster virus (VZV), characterized by painful, unilateral vesicular skin lesions in a restricted dermatomal distribution. Herpes zoster ophthalmicus is situated in the trigeminal ganglion and can lead to visual loss. Therefore, treatment with acyclovir is recommended.

Case: An 88-year old female was diagnosed with left-sided herpes zoster ophthalmicus. Parenteral acyclovir was administered, with initially satisfying clinical response. On the 7th day of admission, the patient demonstrated slow speech and confusion. CT-scan of the brain offered no explanation for the acute change in mental state. Additionally, a lumbar puncture showed an elevated leukocyte count and low-positive VZV PCR in the cerebral spinal fluid (CSF). The consulted neurologist suggested herpes zoster encephalitis. Nevertheless, acyclovir had been adequately dosed for 7 days before the cerebral complaints started. Additional laboratory tests showed acute kidney failure, leading to the diagnosis of acyclovir toxicity causing kidney failure and encephalopathy. Acyclovir was discontinued, and hereafter the confusion faded. The patient recovered fully.

Discussion: It has been described that during a herpes zoster infection, the VZV PCR in CSF can be low positive, without the presence of meningitis or encephalitis. At the same time, acyclovir can cause cerebral toxicity consisting of encephalopathy, especially in case of additional renal failure. This case emphasizes the need to be critical in regard to results of additional testing. In addition, our case emphasizes the importance of frequent checks of kidney function during acyclovir-treatment.
An unusual cause of atypical chest pain

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Case: A 74-year old woman with a history of hypertension and coronary bypass surgery 10 years earlier presented in the emergency department with atypical chest pain. The pain had been present for one day and she reported no trauma or dyspnea. On physical examination, she had no fever and palpation of the sternum was painful. There was swelling and tenderness on the distal end of the old sternotomy scar. Laboratory investigations showed an elevated CRP (183 mg/L) and leukocytosis. ECG and cardiac enzymes were normal. Chest x-ray and urinalysis showed no abnormalities. The patient was discharged from the emergency department and returned to the outpatient clinic a few days later. CRP increased to 314 mg/L and blood cultures revealed a Staphylococcus aureus. Differential diagnosis included myalgia, pleuritis, sternitis and mediastinitis. Chest CT-scan showed a presternal abscess. The patient was treated with intravenous flucloxacilline and surgical drainage of the abscess and removal of cerclage wires was performed. Pus cultures also showed a Staphylococcus aureus. Three weeks before diagnosis the patient had rhinitis with scabs in her nose, which was probably the primary infection focus.

Discussion: Infectious complications after coronary bypass surgery usually occur within one month to one year after the operation. Only two case reports have been published on late infections which present more than 10 years after the sternotomy. Both cases describe immunocompromised older patients with multiple comorbidities.

Conclusion: This case illustrates an unusual cause of chest pain and a rare late complication of coronary bypass surgery.
An unusual Salmonella reservoir in an ill returned traveller

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Description: A 31 year old pregnant woman (13+4 weeks gestation) presented herself at the emergency department because of fever (up to 41.5°C) and chills. 28 days before, she returned from a family visit to Jakarta and Bali, Indonesia. She was vaccinated three years ago against hepatitis A, B and typhoid fever. During this stay, she and her partner suffered of gastroenteritis. Since our patient was pregnant, she did not receive any antibiotics at the local hospital. Laboratory results showed leucocytosis (15.0*10^9/L) and elevated CRP (76mg/L). Malaria and amoebic liver abscess were excluded and she was admitted for observation. Blood cultures revealed a multiresistant Salmonella group B (non-typhoidal). She was treated with ceftriaxone iv for one week, followed by azithromycin orally. One day after switch to oral therapy she had a relapse of Salmonella bacteraemia and ceftriaxone was restarted. Seven days later, a gynaecological ultrasound showed a nonviable pregnancy and she had a spontaneous abortion. Salmonella PCR on placental tissue revealed that the placenta was the reservoir for the ongoing Salmonella infection. PET CT did not reveal any other localization of the infection.

Discussion: Women are at increased risk for food-born infections due to decreased immunity during pregnancy. Infectious diseases that can complicate pregnancy are usually remembered by the mnemonic TORCHes. However, this case shows that other (intracellular) pathogens not typically associated with the TORCH list can cause vertical transmission. It is important to keep this in mind when confronted with a pregnant traveller with fever.
Case report: A 37-year-old Dutch woman (originally from the Philippines) visited Arizona and California in the USA for three weeks. One week after returning, she developed a sore throat, coughing and fever. On physical examination she looked ill and erythema nodosum was present on the dorsal side of her feet. The laboratory results showed increased inflammatory parameters. Chest CT showed multiple subpleural consolidations. The patient was treated with penicillin and ciprofloxacin and because coccidioidomycosis (Valley Fever/'stofkoorts') was taken into account, fluconazole was added. Coccidioidomycosis was confirmed by a positive sputum culture. She was treated with fluconazole for 3 months and she fully recovered.

Discussion: There are two types of coccidioidomycosis-causing fungi namely Coccidioides immnitis and Coccidioides posadasii. It is a common cause of community acquired pneumonia in the Southwest USA, Mexico and certain parts of South America but quite rare in other parts of the world. Most infections are acquired through soil disruption and subsequent inhalation of airborne arthroconidia. This case shows the importance to consider local endemic diseases if patients present after travelling, also if it concerns first world countries like the USA. It is uncertain whether antifungal treatment shortens the course of the illness or prevent complications. Guidelines states to treat 2 groups of patients. Those with severe disease as well as patients with risk factors for developing severe and/or complicated disease. Some experts include patients of African or Philippine descent, like our patient, in this last group since these populations are at increased risk of extrapulmonary complications.
Fascioliasis mimicking pyogenic abscesses.

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A twenty-six-year-old Caucasian female, without relevant medical history, was seen for a second-opinion. Earlier, she was admitted in two different hospitals, because of fever, weightloss and abdominal discomfort. First symptoms were noted six weeks after return from Bali, Indonesia, where she had been working at a biological farm. A tentative diagnosis of amebic and later pyogenic liver abscesses was made by initial physicians and treated accordingly. Aspirated material showed leucocytes without bacteria present and a negative Entamoeba histolytica PCR. Cultures and repeated triple-faeces-tests (TFT) remained negative. She had received oral metronidazole and intravenous ceftriaxone, followed by six weeks of iv. Meropenem. At presentation in our hospital she was afebrile with unremarkable physical examination apart from hepatomegaly. Marked eosinophilia (40%) was noted, with liver enzymes increased in a cholestatic pattern. CT and MRI of the abdomen showed multiple longitudinal hypodense lesions throughout the liver. The largest had multiple components that contained debris and increased in size over time from two centimetres at presentation to seven centimetres. With the evidence now available – persistence of fever, liver ‘abscesses’, eosinophilia (which was not consistently present) failure of treatment thus far, Fasciola hepatica infestation was highly likely. Fascioliasis was confirmed by the presence of IgG against Fasciola hepatica in paired serum samples. With informed consent patient was treated with oral triclabendazole (20 mg/kg, in 2 divided doses) Two weeks later patient started feeling better. Fascioliasis remains a diagnostic challenge with travel history and eosinophilia as clues and a negative TFT as potential pitfall.
Staphylococcus aureus bacteremia and a retrocardial mass.

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A 79 year old male with two times a coronary artery bypass graft operation in his medical history was admitted because of dyspnea and a fever. Because of on demand cardial ischemia he was admitted at the cardiology department. Laboratory findings showed raised inflammatory parameters. Blood cultures showed Staphylococcus aureus for which the internal medicine department was consulted. Patient received high dose flucloxacillin intravenously. Transesophageal ultrasound was negative for endocarditis. Dissemination investigation via PET/CT-scan revealed a large retrocardial mass. Additionally a MRI- scan and a CT-scan of the chest were made. The CT-scan showed that possibly contrast was leaking out of the venous graft of the LIMA inside the retrocardial mass. The suspicion of an infected aneurysma spurium of the venous graft was raised. Other possibilities were malignancy, lymphoma or an abscess. Because the patient had recurrent fever and the inflammatory parameters remained elevated he was referred to the chest surgeons of the Medical Centre of the University of Leiden. They performed a thoracotomy and the mass was found to consist of a large infected hematoma. Debridement was performed. When the patient was stabilized he was replaced to the Alrijne hospital where the antibiotic treatment was continued. The inflammatory parameters declined rapidly and he remained without fever. In conclusion, source control still is the main treatment of an infection.
Apparent IBD: remain aware of other 3-letter conditions

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Case presentation: A not particularly talkative 22-year-old male of Surinamese descent presented with fever, abdominal pain, diarrhoea and 20 kg weight loss in three months. His weight was 45 kg. Laboratory testing revealed anaemia (Haemoglobin 6.3 mmol/L, MCV 71) and elevation of the inflammatory markers (CRP 110 mg/l). Abdominal-CT showed ileocaecitis with lymphadenopathy and mesenteric fat infiltration. Severe IBD or bacterial enteritis were considered most likely. Treatment with prednisolone and azithromycin was considered. Immediate colonoscopy showed pancolitis with deep ulcerations of the caecum and ascending colon suggesting severe IBD or infectious colitis. He was noted to have a productive cough; the X-ray revealing extensive cavitating opacities in the left upper lobe and apical part of the lower lobe. He now reported exposure to tuberculosis when questioned. Subsequent pulmonary-CT confirmed the presence of multiple cavitating lesions and nodules in both lungs with a miliary distribution pattern. Meanwhile HIV, amoebiasis and strongyloides tests were negative. Obviously pulmonary tuberculosis with a tuberculosis enterocolitis was now very likely. Diagnosis was confirmed by positive sputum PCR and culture and compatible colon histology. Tuberculostatic treatment with good clinical improvement was initiated. His weight increased from 45 to 62 kg in 6 weeks supervised (DOT) treatment. This case illustrates the necessity of continuing awareness to differentiate between IBD such as Crohn’s disease and intestinal inflammatory colitis in particular tuberculosis. Symptoms are nonspecific, so are laboratory, radiology and colonoscopy findings. Final diagnosis depends on a meticulous diagnostic work-up with premature introduction of immunosuppression as a potentially lethal pitfall.
Heart benumbing floods in Ho Chi Minh City

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A 27-years old man was referred to the emergency department with complaints of myalgia, headache, fever, nausea, vomiting and watery diarrhea since 3 days. Ten days before, he returned from Vietnam. On the last day of his stay, showers turned the by rats engaged streets of Ho Chi Minh city into rivers and constrained our patient to wade through knee height flooded streets. On physical examination he had a temperature of 39.4°C, a low blood pressure, mild tachycardia and a normal respiratory rate, with no specific site of infection. Laboratory examination demonstrated Leukocytes 16.5x10^9/L, CRP 336 mg/L, eGFR 50 kl/1.73m² and bilirubin 17 µmol/L. The patient was treated according to sepsis protocol. Shortly after hospitalization, our patient was admitted to the ICU because of persistent distributive shock despite fluid resuscitation. Transesophageal echocardiography revealed global cardiac hypokinesia. Together with minor electrocardiography abnormalities and troponin-T levels of 0.878 µg/L, myocarditis was highly suspected. Presence of leptospirosis as a cause was confirmed by PCR in blood and urine. Within three days, inotropic support was seized, antibiotics were switched to doxycycline and the patient fully recovered. Yocarditis is a well-documented cardiac manifestations of leptospirosis. Death due to myocarditis is reported in approximately 25% of fatal cases. Nevertheless, presence of myocarditis in leptospirosis patients appears to be underestimated or even unrecognized because pulmonary or hepatorenal disease outshines its presence. Clinicians should be aware of probable cardiac involvement in severe leptospirosis. Vice versa, in specific cases, leptospirosis should be in the differential diagnosis of myocarditis.
East African trypanosomiasis in The Netherlands

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Background: African trypanosomiasis is caused by protozoan parasites and transmitted by the tsetse fly. *Trypanosoma brucei gambiense* causes a chronic condition while infection with the more virulent *Trypanosoma brucei rhodesiense* leads to an acute form where death can occur within months. There is a hemolymphatic stage followed by a second stage involving the central nervous system, with symptoms fitting the name 'sleeping sickness'.

Methods: A 56-year-old woman was seen on the ER because of headache, general malaise and fever 10 days after she returned from Tanzania. On examination there was a chancre on the left wrist and a fever. Bloodwork showed a pancytopenia, increased liver enzymes and urine analysis was positive for protein and blood. Malaria antigen test was negative but the thick smear surprisingly showed trypomastigotes. Lumbar punction was negative for trypomastigotes. *Trypanosoma brucei rhodesiense* was diagnosed and the patient was treated with suramin (urgently imported from Switzerland) for 4 weeks in total. No central nervous system involvement occurred and she recovered completely. Outpatient follow-up will be for 2 years including lumbar punctions.

Results: Suramin is the first choice of treatment for stage 1 and has 95% rate of curing the disease. Pentamidin is a more toxic alternative. Stage 2 requires melarsoprol which has a 90-95% cure rate but also a 5% mortality.

Conclusion: Trypanosomiasis is rarely seen outside west and east-Africa. The initial symptoms are similar to more common infectious diseases. Diagnosis is usually made by thick smear. Without treatment an infection will always be fatal.
Acute feverish renal failure and proteinuria in a 23-year old Armenian refugee living in a refugee center caused by Hantavirus

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Background: Hantavirus with renal syndrome (HFRS) is a condition that leads to fever, acute nphritis, oliguria and in rare cases an hemorrhagic shock syndrome. In (Northern) Europe it is caused by Hantaviruses from the family Bunyaviridae (Puumelavirus) and transmission occurs mostly via aerosolized excreta from the Myodes Glareolus, a rodent living in afforested areas. The incubation period is mostly 2 weeks. The diagnosis is through IgG and IgM ELISA serological tests. In most cases HFRS is self limiting.

Methods and Results: A 23-year old man presented to the emergency room complaining of fever, abdominal pain and new onset oliguria. At the time the patient (Armenian) was living in an refugee center for 5 years (former airforce compound). Laboratory findings showed an eGFR of 19 with proteinuria, no previous laboratory results were available. The next day the patient had a diuresis of more than 2 liters/24 hours and, despite fluid support, his eGFR dropped even further. Urine analysis showed mild proteinuria without erytrocyturia or dysmorphic erytrocytes. Abdominal ultrasound showed no abnormalities. A biopsy of the kidney was scheduled. Positive ELISA IgM and IgG for Hantavirus were found. The renal function normalised completely after 1 week and the biopsy of the kidney was cancelled.

Conclusion: This case illustrates the importance of considering Hantavirus as an causative agent in acute glomerulonefritis, especially in patients living in or near afforested areas and/or in refugee centers. Furthermore, serological confirmation of Hantavirus can prevent invasive diagnostic procedures like a kidneybiopsy.
Cholangitis: microbiology and antibiotic susceptibility, does amoxicilline/clavulanic acid outperform cefuroxime and should metronidazole be added to cover anaerobic bacteria?

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Background: Depending on patterns of resistance and hospital preferences empiric antimicrobial therapy for cholangitis consists of either amoxicilline/clavulanic acid or cefuroxime, which is often supplemented with metronidazole to cover the anaerobic bacteria. Enterococcus spp. are not covered in the cephalosporin regimen.

Methods: We extracted data on patients diagnosed with cholangitis during the period 2004-2016 from the electronic healthcare database of the Reinier de Graaf Hospital.

Results: A total of 344 patients were hospitalized for cholangitis. During 431 hospital admissions 1,030 blood cultures were taken. After exclusion of unrelated, contaminated and duplicate cultures and those lacking antimicrobial susceptibility a total of 214 positive blood cultures were available for analysis. Enterobacteriaceae n=212 (79.4%), Enterococcus spp. n=38 (14.2%), Pseudomonas aeruginosa n=7 (2.6%) and anaerobes n=6 (2.3%) were most frequently encountered. Antibiotic susceptibility was 65.5% to amoxicilline/clavulanic acid and 92.3% with the addition of gentamicin. This was 55.0% to cefuroxime and 80.5% with the addition of gentamicin to cefuroxime. None of the 17 patients who tested positive for Enterococcus spp. and had inadequate antibiotic coverage worsened as a result. If Enterococcus spp. were excluded, cefuroxime provided better coverage (96.1%) than amoxicilline/clavulanic acid (66.0%). With gentamicin added results were similar (94.2% and 96.1% respectively).

Conclusion: The prevalence of anaerobic species in blood cultures of patients with cholangitis was low and routine addition of metronidazole to cefuroxime might not be necessary. However, the prevalence of Enterococcus spp. was 14%. Optimal antimicrobial therapy depends on the appreciation of the pathogenic potential of enterococcus species.
Five years of experience in structured bedside consultation in patients with a Staphylococcus aureus bacteremia: a retrospective cohort study.

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Background: Staphylococcus aureus bacteriemia (SAB) is a common and severe disease. Every year around 84 patients are diagnosed with a SAB in the Rijnstate Hospital, The Netherlands. From 2012 on, all patients receive a structured bedside consultation. We analyzed the effect of this structured policy in diagnostic and therapeutic intervention on the relapse free survival of patients with a SAB.

Methods: We performed a retrospective cohort study, in which we collected data from all patients with a SAB from 2009 until 2016. Only patients above 18 years are included.

Results: In total 657 patients were included. From 2012, 418 patients with a SAB were seen. 328 patients (78%) had a complicated SAB. The 30 days mortality from 2012 is 24% (101 patients), from which 81 patients (80%) had a Comorbidity Charlson Index above 3 and 80 patients (79%) suffered from a complicated SAB. In total 312 patients (75%) received an echocardiography and 201 patients (48%) a PET-CT-san. In 139 patients (35%) a metastatic infection was seen: endocarditis in 39 patients (28%), spondylodiscitis in 42 patients (30%), osteomyelitis in 9 patients (6%) and an infection of artificial material in situ in 31 patients (22%).

Conclusion: This study shows the high mortality of SAB and demonstrates that a large majority of patients have a complicated SAB with a lot of metastatic infections. This complicated course will determine the duration and route of treatment. Data from 2009-2011 and further statistical analyses, including relapses and treatment strategies, will follow.
A Thai woman with cervical lymphadenopathy and an ‘indeterminate’ IGRA

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A 54-year-old Thai woman without relevant medical history presented with generalised pain, fever and cervical lymphadenopathy. Her complaints had developed over several months and were progressive. On physical examination she had painful cervical lymphadenopathy and erythema nodosum on her extremities. Laboratory results showed inflammation (BSE 120mm/hr, leucocytosis 13.2 x10^9/l, CRP 45 mg/l), HIV serology was negative and the IGRA result was ‘indeterminate’. Imaging did not show any additional abnormalities. A cervical lymph node was removed and culture revealed Mycobacterium abscessus. M. abscessus is a rapidly growing, multidrug-resistant, nontuberculous mycobacterium. Generalised infection with M. abscessus is extremely rare in immunocompetent patients. A literature search showed several cases of patients from East Asia with similar symptoms associated with M. abscessus infections. In a recent study looking at adult-onset immunodeficiency in nontuberculous mycobacterial infections the majority of patients was found to have anti-interferon-gamma autoantibodies. Our patient turned out to have similar autoantibodies against interferon-gamma as described in the literature. These autoantibodies also block interferon-gamma production in the IGRA test and explain the indeterminate result. The trigger for production of these autoantibodies remains unknown, but genetic factors are strongly suspected to be involved because all patients identified to date are Asian-born. Our patient was treated with a combination of several antibiotics intravenously for weeks. She had a quick recovery but her susceptibility to infection remains elevated. This case demonstrates that an ‘indeterminate’ IGRA result may be a clue to underlying immunodeficiency. Anti-interferon-gamma autoantibodies are associated with generalised opportunistic infections in patients from Asian countries.
An uncommon cause of hemolytic anemia

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Case: A 70-year old patient was admitted to our Internal Medicine ward because of dyspnea and malaise. Two weeks previous to his admission he had an upper respiratory tract infection, without full recovery. His medical history included vitiligo, hypertension and a systolic souffle because of an aortic valve stenosis. His vitals were normal, although he looked rather pale. Besides a heart murmur there were no other abnormalities. Laboratory results showed an hemoglobin of 5.0 mmol/L, bilirubin of 20 umol/L, LDH of 558 E/L, haptoglobin of <0.2 g/L and the direct Coombs test was positive (anti-IgM and -C3d positive). Of all viral serologic tests, Cytomegalovirus (CMV) showed positive anti-IgM and anti-IgG.

Bone marrow biopsy was normal. The diagnosis hemolytic anemia due to acute CMV infection was made.

Discussion: CMV is a common virus responsible for a broad spectrum of symptoms, depending on the immunologic status of the host. In most immunocompetent individuals primary CMV infection is asymptomatic or presents as a mononucleosis syndrome. In the immunocompromised patients however, CMV infection can cause significant morbidity and mortality, including hemolytic anemia. In immunocompetent hosts hemolytic anemia due to CMV infection is unusual. The exact pathophysiology is unclear, although direct Coombs test positivity indicates an autoimmune-mediated mechanism. Controversy exists regarding therapeutic management. Watchful waiting, corticosteroids and anti-viral treatment have been proposed. We closely monitored our patient without prescribing medication. After two months he recovered and his hemoglobin increased to 6.7 mmol/L.

Conclusion: CMV infection should be considered in patients with a hemolytic anemia.
First human case of Seoul hantavirus infection in The Netherlands

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Introduction: Hantaviruses are rodent-borne viruses with worldwide distribution. Human infection most often occurs by inhalation of virus-contaminated rodent excreta. Clinical syndromes include haemorrhagic fever with renal syndrome and cardiopulmonary syndromes. In Europe, evidence for circulation of Seoul virus in wild and pet rats increased past years. Incidental cases of Seoul hantavirus have been described in the UK, Belgium and France. Here, we report the first human case of Seoul virus infection in The Netherlands.

Case: A 28-year-old man presented with fever (38.6oC), tachycardia (113/min), vomiting, diarrhea and back pain. He had a medical history of Gamma-Hydroxybutyrate dependence. Laboratory results showed increased plasma C-reactive protein, thrombocytopenia, and elevated liver enzymes. Kidney function, chest X-ray and urinalysis were normal. He had not been abroad, however, mentioned that he had been bitten regularly by rats at his work in a rat farm and at home by rats he kept for his reptiles. Under the presumed diagnosis of leptospirosis ceftriaxone and metronidazole were started. Blood cultures remained negative. Serological tests ruled out viral hepatitis and leptospirosis, but high antibody titres to Seoul virus were found indicating recent infection. Six out of ten rats found at his house were tested positive for Seoul hantavirus and negative for Dobrava and Puumala. The patient recovered completely.

Conclusion: Our case presented with nonspecific clinical symptoms for a hantavirus infection with gastro-intestinal symptoms and pronounced elevation of liver enzymes, however without haemorrhagic symptoms. This case illustrates the importance of clinical awareness for zoonotic infections, especially when rats are involved.
Pulmonary actinomycosis

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A 72-year-old man, with a history of COPD, presented with dyspnoea, coughing, weight loss, thoracic pain and elevated inflammatory markers. He had not responded to initial treatment with trimethoprim/sulfamethoxazole for suspected pneumonia. Computed tomography showed fibrotic destructive changes in the right upper lobe and PET-CT was suspicious for lung carcinoma with post obstructive infection without mediastinal lymphadenopathy. Bronchoscopy however did not reveal any abnormalities, sampling and a bronchial lavage was performed. Detection of galactomannan in the alveolar lavage came back positive and treatment for suspected invasive aspergillus with voriconazole was initiated. Culture did not grow aspergillus species but did show actinomyces odontolyticus. Histology yielded nonspecific inflammation with granulocytic components. Subsequently voriconazole was discontinued and the patient was started on benzylpenicillin six million units per day intravenously for treatment of pulmonary actinomycosis. Blood cultures and bronchial lavage cytology remained negative. Dental screening revealed caries and bone defects in 4 dental elements. Pulmonary actinomycosis should be considered in the differential diagnosis of non-resolving lobar pneumonia or a lobar mass suspicious for malignancy. The prevalence of pulmonary actinomycosis is higher in patients with pre-existent pulmonary disease and caries denture. The diagnosis of actinomycosis is challenging because the bacteria are anaerobe and should be cultured protractedly. Also a lot of patients have been treated with antibiotics before or during the culture. Furthermore because actinomyces is present in the oral cavity, false positives are frequently seen. Treatment with antibiotics is effective but should be prolonged.
Closed-loop modes for mechanical ventilation: commonly applied or left unused? A nationwide survey

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Background: The most recent modes for mechanical ventilation are called closed-loop modes, which are able to automatically adjust certain respiratory settings. Although closed-loop modes appear to be safe and efficient and new types keep emerging, it is unclear to what extent these modes are actually used on Intensive Care Units (ICUs). The aim of this study was to explore current practice of closed-loop ventilation on Dutch ICUs and, if applicable, to analyze the arguments for not using closed-loop modes.

Methods: A short survey was conducted among all non-pediatric ICUs in The Netherlands. Participants could answer the questions either by phone or by e-mail. Use of closed-loop modes was classified as frequent, occasionally or never, if respondents stated they had used these modes in the last week, in the last month/year, or never, respectively.

Results: The response rate of the survey was 82% (72 of 88). Respondents had access to a closed-loop ventilation mode in 58% of the ICUs (42 of 72). Of these ICUs, 43% (18 of 42) frequently applied a closed-loop ventilation mode, while 57% (24 of 42) never or occasionally used it. Reasons for not using these modes were lack of knowledge (40%), insufficient evidence reporting a beneficial effect (35%) and lack of confidence in the mode (25%).

Conclusion: While industry continues to develop new closed-loop modes, implementation of these modes in clinical practice seems to lag behind. Various barriers could play a role, and these issues all need attention in future investigations.
A randomized trial on the effect of acetylsalicylic acid on the systemic inflammatory response in human endotoxemia

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Background: Acetylsalicylic acid (ASA) use is associated with a beneficial outcome in patients with sepsis and pneumonia. Platelet reactivity and prostaglandins both play a pivotal role in the human immune response, and therefore ASA treatment may modulate the inflammatory response, thereby affecting outcome in infections.

Methods: To evaluate the effect of low dose ASA on the innate immune response we performed a parallel randomized controlled study in 20 healthy male volunteers. The subjects were randomized to seven days of treatment with either placebo or 80mg ASA daily. On the seventh day, a systemic inflammatory response was elicited in all subjects by an intravenous bolus of 1 ng/kg purified E. Coli endotoxin, followed by infusion at 1 ng/kg/h for 3 hours. We measured plasma levels of cytokines, thromboxane and measured platelet reactivity

Results: Treatment with ASA resulted in an 50-100 % increase of plasma levels of the pro-inflammatory cytokines TNF, IL-6 and IL-8 (p=0.0005, p=0.01 and p=0.01 is interaction term of treatment group and time by two-way ANOVA). Treatment with ASA lowered plasma levels of thromboxane B2 below detection limits. Platelet reactivity was not affected by ASA use, nor did it relate to cytokine responses.

Conclusion: A seven day course with low dose ASA resulted in an enhanced pro-inflammatory immune response in experimental systemic inflammation in humans. Speculatively, this augmented immunopotency may contribute to improved pathogen clearance or prevent sepsis-induced immunoparalysis. As such these observations may explain the observed beneficial outcome in sepsis and pulmonary infections.
Hyperammonemic coma in non-cirrhotic critically ill patients


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Altered mental status may complicate the course of critically ill patients. Here, we present a case series of ICU/ER patients with coma due to hyperammonemia. Metabolic hyperammonemic encephalopathy is a well-recognized entity in patients with liver failure, however this had been ruled out in the patients reported. Initial causes of hospital admissions of the cases included acute liver failure (1), pancreatitis (3), pneumonia (1), and gastro-enteritis (1). The patients lost consciousness during their ICU stay and one of them also suffered from epileptic seizures. Ammonia at presentation ranged between 128-324 µmol/l. Alternative explanations such as medication intoxication were absent. Concomitant delirium was treated with anti-psychotics, but this could not completely resolve consciousness. After administration of sodium benzoate and repletion of essential amino acids neurological status improved. One patient was previously diagnosed with an inherited metabolic disorder (lysinaric protein intolerance). We hypothesize that disturbance of the urea cycle may occur in critically ill patients without liver failure. Factors such as hypocaloric intake or protein hyperalimentation, bacterial overgrowth and catabolic state such as during febrile periods may play a role in decompensation. In conclusion, hyperammonemic coma (serum ammonia >100 µmol/l) may be a complication in non-cirrhotic critically ill patients and is probably still under-recognized despite several effective and available treatment options.
Systemic Capillary Leak Syndrome; A Rare but Potential Lethal cause of Shock

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Case Description: A 65-year old Caucasian male with a history of hypertension presented at the ED with a severe undifferentiated shock (RR 76/38mmHg, temperature of 34.9°C, severe vasoconstriction and oliguria). He complained about sudden onset lower abdominal pain and dyspnea. Detailed history was unremarkable except for a nonproductive cough and mild fatigue for a few days. CT Aorta and EKG were unremarkable. Laboratory investigation showed Hb 13.5mmol/L, Ht 0.65 L/L, leucocytes 15 mmol/L, CRP 8mg/L, creatinine 193mmol/L, albumin 17g/L and lactate of 2.7mmol/L. Patient started on antibiotics and received 7L of crystalloids which temporarily stabilized the situation. Eight hours after admittance blood pressure gradually decreased. Blood investigation showed Hb 14.6mmol/L, Ht 0.77 L/L, albumin 6g/l and lactate of 5.2mmol/l. Based on the combination shock, hemoconcentration and low albumin the diagnosis SCLS was made. Patient received supportive care with crystalloids and vasopressors. After recovery from the shock patient was treated with diuretics to prevent fluid overload. Patient had a full recovery. MGUS was present (IgG type Kappa). Patient was started on monthly Immunoglobulins and had no further recurrences. Discussion We describe a severe case of Systemic Capillary Leak Syndrome. This potential fatal Syndrome is a rare idiopathic disease with recurrent episodes of hypovolemic shock, hemoconcentration and hypoalbuminemia caused by a massive fluid shift to the interstitial space. Most cases are related to a monoclonal gammopathy of unknown significance. Complications are thrombosis, kidney failure, compartment syndrome and cardiopulmonary failure. Early recognition is of vital importance to prevent complications as to prevent recurrences.
Introduction: *Clostridium perfringens* septic shock is frequently fatal with reported mortality rates up to 80%. Early initiation of appropriate therapy and source control reduces mortality. We present a case of septic shock caused by *C. perfringens* infection characterized by extreme fluid resuscitation.

Case description: A 67-year-old male was admitted postoperatively to our Intensive Care Unit (ICU). Previous emergency laparotomy confirmed extensive necrosis of his small bowel and coecum because of superior mesenteric artery occlusion. Resection of affected bowel segments and the ileocecal region followed and embolectomy of the superior mesenteric artery was successfully performed. The first 24 hours of his stay on our ICU was characterized by the need of extreme fluid resuscitation (up to 34 litres) as well as high-dose vasopressors to maintain perfusion pressure. Only after repeated laparotomy, with ultimate resection of almost the entire small intestine, there was a rapid recovery of his clinical condition. Subsequently ascites fluid culture was positive for *C. perfringens*, susceptible for the initiated antibiotic regime. The following days his condition stabilised. After 49 days of hospitalization the patient is currently further recovering at home and able to tolerate oral nutrition.

Conclusion: The course of *C. perfringens* septic shock due to abdominal vascular ischaemia may be fulminant. There is ongoing debate about the optimum dosage of fluid resuscitation in septic shock and the potential harm of excessive fluid administration. This case illustrates that aggressive treatment and optimal source control remains crucial and lifesaving.
An unusual ‘bloody’ finding in a septic patient

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A 78-year-old man was admitted to the Intensive Care unit with sepsis of unknown origin. His medical history revealed an aortic valve revision and UPJ stenosis with nephrostomy drain. After admission patient was unresponsive to fluid challenges, showed persistent hypotension and noradrenaline was started. Initial diagnosis was urosepsis with urine positive for leucocytes and nitrate. Antibiotic treatment with ceftriaxon was started. CT-abdomen was obtained and showed bilateral adrenal haemorrhage (BAH). Immediately after 100 mg hydrocortisone was administered, arterial pressure normalized and the noradrenaline infusion could be stopped. Two days later patient was discharged to the ward, and antibiotic therapy was changed to ciprofloxacin orally. Bilateral adrenal haemorrhage (BAH) is a rare finding which can been seen in critically ill patients. BAH can lead to acute adrenal insufficiency and death. When BAH is recognized promptly and treated appropriately patients can recover quickly. Based on autopsy studies the prevalence of BAH is around 1.1%. The pathophysiology of BAH is unknown. However the hypothesis is that the vascular supply of the adrenal gland is vulnerable for thrombosis or haemorrhagic necrosis in the setting of bleedings associated with severe stress, sepsis and shock. Additional test for adrenal insufficiency should be obtained by patient suspected of BAH, to exclude hormonal causes for adrenal insufficiency. This case shows that in critically ill patients, BAH should be considered as a cause of therapy resistant septic shock. Abdominal CT scanning can be performed to confirm BAH in septic patients with a high index of suspicion of adrenal failure.
Massive metformin intoxication: CVHH or IDH?

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Background: Metformin intoxication results in lactic acidosis associated with high mortality. The Extracorporeal Treatments in Poisoning Workgroup recommends intermittent hemodialysis (IHD) as initial therapy over continuous veno-venous hemofiltration. Recommendation is strong despite a very low level of evidence.

Methods: We describe a case of severe metformin intoxication and the effects of extracorporeal treatments.

Results: A 53 year old patient was admitted to ICU with shock, minimal level of consciousness and metabolic acidosis due to a multi-drug overdose including 76,500mg metformin, 13,000mg acetaminophen, 4,000mg valsartan, 650mg quetiapine, 310mg temazepam and 52mg lorazepam between 1 and 2.5 hours prior to presentation. Kidney function was only mildly reduced. There were no other relevant comorbid conditions. CVVH was started as initial extracorporeal treatment. Because lactate continued to increase with CVVH two runs of IHD were performed. Laboratory results that became available later showed an admission serum metformin level of 340mg/l, which normalized within 26 hours of admission with treatment. From repeated serum metformin levels sampled near the time of switching between extracorporeal treatments we estimate that metformin serum half-life time in our patient was 3.5 hours with CVVH and 2.6 hours with IHD. In our patient extrapolation of these estimates suggests that a therapeutic level 2mg/l of metformin would have been reached 2.5 hours later with CVVH only.

Conclusion: This case study suggests that with current extracorporeal treatment equipment the difference between CVVH and IHD in the treatment of metformin intoxication might be less extensive than previously assumed and that further study is necessary.
Pulmonary aspergillosis associated with influenza viral infection

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Introduction: Every year we have to combat Influenza outbreaks causing severe morbidity and mortality. In intensive care patients aspergillosis colonization is common but does not cause morbidity often. However, during the outbreak of Influenza in 2016, we found several patients with clinical significant pulmonary aspergillosis as a post influenza complication.

Case report: A 56 year old male, without medical history or medication, presents with 1 week diarrhoea and abdominal pain. Because of respiratory and renal failure due to septic shock, he is admitted to the intensive care unit. Mechanical ventilation, antibiotics and renal replacement therapy were initiated. Microbiological analysis confirmed an influenza A infection and pulmonary Staphylococcus aureus infection. At first his clinical condition improved, but after 10 days his respiratory condition worsened. A bronchoalveolar lavage (BAL) was performed and white, raised, creamy plaques were seen, suspected for aspergillosis. Cultures of the BAL fluid showed Aspergillus fumigatus. Fluconazol was initiated and the patient responded to the therapy and was successfully weaned from the mechanical ventilator. Three weeks after admission, the patient suddenly developed a severe, uncontrollable lung bleeding. Autopsy showed invasive pulmonary aspergillosis as the cause of death.

Discussion: In immunocompetent hosts invasive aspergillosis is rare but has been described in combination with influenza A infections. If aspergillus colonization is present in patients with influenza A infection, especially in mechanically ventilated patients, early treatment of aspergillus should be initiated. Massive haemoptysis due to aspergillus infection is known and a major risk for death due to pulmonary aspergillosis.
A 26-year old male with atypical hemolytic uremic syndrome

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A 26-year old man with an unremarkable medical history was admitted to the emergency department with nausea and fatigue which had progressed over a period of two weeks. Laboratory results showed acute renal failure and a Coombs negative hemolytic anemia. The thrombocyte count was 142x10⁹/L. ADAMST13 activity was normal and shiga toxin serology was negative.

Secondary thrombotic microangiopathy (TMA) was suspected, possibly caused by hypertension due to pre-existing nephropathy (like IgA nephropathy). Renal biopsy showed extracapillary proliferation and intraluminal thrombosis but negative IgA and C₃ immunostaining. At this stage atypical hemolytic uremic syndrome (aHUS) was suspected. Plasmapheresis was initiated after admission. After five days of plasmapheresis treatment, serum LDH had decreased, but patient had become dialysis dependent. He was transferred to the VU Medical Centre for treatment with eculizumab. After two months of eculizumab treatment there was a biochemical remission of TMA and renal function improved to an eGFR of 30 ml/min.

Heterozygote mutations were found in the coding sequence for complement factor H, in line with the diagnosis of aHUS. aHUS is a rare disease characterized by uncontrolled activation of the alternative complement pathway. The formation of membrane attack complex (MAC) causes endothelial activation, thrombosis and intravascular hemolysis. In 60-70% of cases, genetic mutations are found in regulatory proteins of the alternative complement pathway. Eculizumab is a drug which blocks cleavage of C₅, inhibiting the production of MAC. Phase II trials have demonstrated promising results of this orphan drug. However, it’s high costs warrants a strict selection procedure.
Acenocoumarol and (non-uremic) calciphylaxis: what’s the link?

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Case: An 82-year-old Caucasian female presented with two necrotic lesions on her right leg. Her medical history included obesity, diabetes mellitus, hypertension, mechanic heart valve implantation, and chronic kidney disease (MDRD of 30 mL/min). Medication comprised acenocoumarol, metoprolol, simvastatin, furosemide and oxazepam. A biopsy showed an image of calciphylaxis. Acenocoumarol was replaced by a low molecular weight heparin (LMWH) and calcium homeostasis was restored by prescribing cinacalcet. Unfortunately, the patient died two weeks later, and no autopsy was allowed.

Discussion: Calciphylaxis is a rare disease that consists of calcifications in the blood vessels, which lead to necrotic lesions of the skin. It is associated with end-stage renal disease. However, it also occurs in patients with earlier stages of renal disease or in normal renal function, known as non-uremic calciphylaxis. The suggested risk factors for non-uremic calciphylaxis are numerous, consisting of white race, female sex, obesity, diabetes mellitus, use of a vitamin K antagonist, and malignancy, among others. Pathophysiological studies demonstrate that vitamin K antagonists interfere in calcium metabolism, as vitamin K is normally involved in the inhibition of calcium deposition in blood vessels. However, existing epidemiological studies lack adequate designs to confirm this association.

Conclusion: Calciphylaxis can also occur in earlier stages of renal disease or in normal renal function, known as non-uremic calciphylaxis. Although risk factors for this condition have yet to become fully established, increasing evidence points out that vitamin K antagonists may play a role.
Hydration Status in Patients on Hemodialysis, assessed by modified Bio-Electrical Impedance Analysis (BIA): Back to Basics

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Background: Previous attempts to assess tissue hydration in patients on hemodialysis (HD) by bioelectrical impedance analysis (BIA) have failed because of incorrect assumptions regarding the relationship between body water volumes and total body electrical resistance (TBER). Aim of this study was to test the performance of a modified BIA model that quantifies tissue hydration in terms of TBER standard deviation scores (SDS).

Methods: TBER was measured in 74 patients (42 men and 32 women), before and after HD. Normal values were obtained in 144 controls. Results of patients on HD were expressed as TBER standard deviation scores (SDS), i.e. the number of SD difference between the actually measured TBER (TBERₘₐₓ) and the predicted normal TBER (TBERₙₒᵣₙ). In this model a SDS > +2 represents dehydration, and a SDS < -2 represents overhydration, both with a probability of 95%. The correlation of TBER and changes in body water induced by ultrafiltration (UF) was examined in 18 patients.

Results: TBER-SDS was abnormal in 31% of patients before and in 46% patients after HD. TBER changes were inversely related to UF volumes, with R² values > 0.90 in most patients.

Conclusion: Tissue hydration, expressed as TBER-SDS, was abnormal in a large subset of patients, before as well as after HD. Changes in TBER during HD were strongly correlated with UF volumes. These observations suggest that this modified BIA model may be helpful to optimize fluid management and UF volume prediction in patients on HD.
A disappearing cause of acute kidney injury

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**Background:** Acute kidney injury (AKI) has a wide range of possible causes. The differential diagnosis is heavily influenced by the clinical setting in which AKI occurs. We present a rare cause of AKI that is primarily associated with obstetric complications.

**Case:** A 32-year-old woman was admitted after placental abruption with fetal demise at 33 weeks pregnancy. Her medical history included two caesarean sections. She developed extensive bleeding and diffuse intravascular coagulation and was admitted to the ICU for resuscitation. Due to uncontrollable bleeding, she underwent emergency laparotomy, which showed a uterine rupture. After suturing of the rupture, the patient stabilized. However, in the hours following surgery, she developed oligo-anuria despite adequate circulation. Due to persistent anuria, haemodialysis was started. Contrast-enhanced computed tomography showed a hypointense renal cortex, suggestive of renal cortical necrosis (RCN). Haemodialysis was required for four weeks, after which renal function recovered to a glomerular filtration rate of 26ml/min.

**Discussion:** RCN is a rare cause of renal failure, especially in developed countries. It is characterized by oligo-anuria with typical computed tomography findings of a hypointense renal cortex in early stages and cortical calcifications in later stages. It is traditionally associated with obstetric complications, notably peripartum haemorrhage and puerperal sepsis. Other causes include hypercoagulation and major surgery. With improving maternal care, the incidence of RCN is falling around the world. As its prognosis is markedly poorer than many other causes of AKI, it is important that clinicians remain vigilant for this diagnosis in at-risk patients.
Case report: Acute renal failure and granulomatous lymphadenopathy

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Case: A 41-year-old patient presented with acute kidney injury and microscopic haematuria. He had a history of childhood asthma, allergies, and several work related small trauma due to his work in construction. Since 2 years he was treated for sarcoidosis with prednisone because of mediastinal lymphadenopathy with granuloma, without other organ involvement. Despite prednisone 40mg daily he still complained of weight loss, arthralgia, and fatigue. He presented in the emergency room with fever, arthralgia, erythema nodosum and acute renal failure (decline in eGFR from 87 to 23 ml/min/1.73m²). Urine sediment evaluation showed red blood cells >50/field; dysmorphic red blood cells >40%; white blood cells 5-10/field; no casts. Serum calcium was normal and on the day of admission ANCA revealed positive. Granulomatosis with polyangiitis was diagnosed based on MPO-ANCA titer of 127E/ml. Renal biopsy showed focal segmental necrotizing and sclerosing glomerulonephritis without immuundeposits leading to the diagnosis of an MPO-ANCA associated vasculitis (AAV). The patient was treated with methylprednison 1000mg intravenously for 3 days, oral cyclofosfamide, followed by oral prednison. Renal function improved (eGFR 49 ml/min/1.73m²) and MPO-ANCA titer declined to 10E/ml. After a re-evaluation of the biopsy of the intrathoracal lymph nodes, silica particles were identified within the granuloma. The previously mentiononed diagnoses sarcoidosis was confuted.

Conclusion: Work related exposure to silica is associated with acute kidney injury caused by AAV. Our hypothesis is that work related silica exposure led to mediastinal and hilar granuloma forming, which later on triggered the development of AAV.
Better think twice

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A 63-year old woman was referred to our hospital with clinical features of a nephrotic syndrome and proteinuria of 10 gram/day. The medical history consisted of urothelial carcinoma of the bladder in 2012, treated with cystectomy and ileal conduit construction. A kidney biopsy was performed, showing a membranous glomerulopathy (MGN). Several additional tests were performed to differentiate between idiopathic and secondary forms of MGN. Anti-phospholipase A2 Receptor Antibodies (PLA2R) in serum were negative. PET/CT scan showed a pelvic mass and lymphadenopathy. Histology of the pelvic mass appeared to be metastatic urothelial cancer. Based on the findings at PET/CT, and absence of anti PLA2R, the nephrotic syndrome was considered to be a case of cancer-associated MGN. Palliative treatment with carboplatin was started. After three months of treatment, there were no signs of improvement of the MGN. Moreover, the patient developed a pulmonary embolism. A CT scan showed no progression of metastasis. To ascertain that this was not a primary form of MGN, histological PLA2R staining on the kidney biopsy was performed. This showed diffuse staining for PLA2R antibodies, indicating that this was indeed a case of primary MGN. In a patient with MGN, absence of anti-PLA2R in serum does not exclude a primary form of MGN. Moreover, in patients with a clinical condition suggesting secondary MGN, additional staining has to be considered if there are therapeutic consequences. This case emphasizes the findings of previous studies in which sensitivity of glomerular PLA2R staining is higher than serum anti-PLA2R (0.78 versus 0.68).
How obtaining a careful medical history opens your eyes: the TINU syndrome

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Introduction: Tubulointerstitial nephritis (TIN) is an inflammatory condition that causes acute kidney injury. Causes are underlying auto-immune disease, infections or medication. The combination of tubulointerstitial nephritis and uveitis (TINU syndrome) is a less common cause of TIN. Acute kidney injury in combination with uveitis made us suspect the diagnosis.

Case: A 43-year-old woman, referred by the ophthalmologist, presented with symptoms of nausea, weight loss and extreme fatigue. Blood pressure was 108/70 mmHg, pulse 80/min and no signs of edema. Laboratory results showed acute kidney injury (eGFR 24 ml/1.73m²), hemoglobin level of 5.0 mmol/L and elevated erythrocyte sedimentation rate (110 mm/hour). Leukocyturia was present, no dysmorphic erythrocytes. Ultrasound showed normal sized kidneys. Antineutrophil cytoplasmic antibodies were found positive and a-dsDNA-IIF slightly positive. Kidney biopsy revealed tubulointerstitial nephritis and interstitial fibrosis. As the patient was recently diagnosed with uveitis we suggested TINU syndrome. After four weeks of treatment with prednisolone 60mg/day, kidney function returned to normal.

Discussion: TINU syndrome was first described in 1975. Although the pathogenesis is not fully understood, modified C-reactive protein may be involved. Patients may present with systemic symptoms such as fever, weight loss and anemia. The disorder has been associated with positive antineutrophil cytoplasmic and antinuclear antibodies as seen in vasculitis. Treatment with high dose prednisolone can recover renal function, some case reports even show spontaneous recovery of renal function.

Conclusion: TINU is a rare cause of acute kidney injury. The combination with uveitis opened our eyes to the diagnosis, as confirmed by the kidney biopsy.
Abdominal pain of non-mesenteric vascular origin: The Nutcracker Syndrome

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Case: A 45-year-old healthy female was evaluated for postprandial abdominal pain and 10-kg weight loss. She reported increase in pain in response to NSAID’s and developed ‘fear of eating’. Laboratory analysis showed isolated isomorphic erythrocyturia with a marked orthostatic component. CT-angiography demonstrated compression of the left renal vein between the aorta and the superior mesenteric artery (SMA), consistent with the ‘Nutcracker Syndrome’ (NS). A bilateral renal artery stenosis due to fibromuscular dysplasia (FMD) was found as well, for which she refused additional imaging to rule out cervical involvement and intracerebral aneurysms. Other causes of abdominal pain were excluded by endoscopy and (duplex)-imaging.

Discussion: NS presents with abdominal pain and orthostatic albuminuria and/or hematuria (either microscopic or macroscopic) of non-glomerular origin. The postprandial nature of the pain in this case is intriguing, however, although not typical it has been reported before. We hypothesize the pain results from renal hypoxia due to diminished efferent and afferent flow; the first being obstruction of the renal vein due to increased flow in the SMA in response to eating, and the latter being renal artery stenosis and NSAID. Furthermore, weight loss increases renal vein obstruction by increasing the angle between aorta and SMA, thereby eliciting a vicious circle. The albuminuria/hematuria is thought to result from rupture of thin-walled varices into the collecting system. Treatment options consist of conservative, endovascular or surgical therapy.

Conclusion: NS is a rare vascular cause of abdominal pain and should be considered in presence of abdominal pain and non-glomerular erythrocyturia.
An enlightening case of flash oedema

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A 79-year old male patient attended our emergency department with acute dyspnea. Physical examination revealed hypertension and oliguria. His medical history contains cardiac ischemia, hypertension, a cerebrovascular event and chronic kidney disease based on vascular complications. Also he was known with the syndrome of Leriche. Biochemical testing revealed an acute-on-chronic kidney injury (creatinine 502 µmol/L, known with stable creatinine of 120 µmol/L). Ultrasound showed a right-sided renal atrophy and a normal left kidney. Echocardiography demonstrated a slightly diminished ejection fraction and collapse of the inferior vena cava. On admission he was initially treated with diuretics for acute left-sided-heart failure. However, after two days the clinical presentation remained unaltered. A Magnetic Resonance Angiography of the renal arteries was performed and enucleated bilateral renal artery stenosis (RAS). Immediately after stenting of the left renal artery, clinical presentation and kidney function improved. Acute pulmonary oedema can be life-threatening and has a broad differential diagnosis. Cardiac failure or ischemia and severe sepsis or septical shock are most common. In RAS, retention of salt and fluid by acute release of renine can lead to acute pulmonary oedema, known as Pickering syndrome. Although RAS is a rare cause of pulmonary edema (<2% of all cases), it is an increasingly common and often unanticipated finding in elderly patients.

**Conclusion:** Flash oedema can be a life-threatening complication of RAS. It is important to recognize Pickering syndrome excluding cardiac and pulmonary causes of respiratory insufficiency. Stenting of the stenotic renal artery provided immediately resolution of symptoms and kidney function.
A case of rivaroxaban-associated acute tubulointerstitial nephritis

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An 82-year old tulip farmer, with a history of hypertension, a total AV-block with DDDR pacemaker and recently diagnosed with atrial fibrillation, presented with acute renal failure. He complained about malaise, fatigue and loss of appetite since starting rivaroxaban 3 weeks ago. He had a negative family history and denied use of over the counter medication. At physical examination the patient appeared euvoemic. Laboratory examination showed an acute renal failure with hyperkalaemia (MDRD 8mL/min/1.73m², creatinin 573µmol/L, urea 27.8µmol/L, potassium 6.3mmol/L, sodium 136mmol/L), without ECG changes and increased infection parameters. A urine sediment contained 0-5 erythrocytes, >50 leukocytes and >50 bacteria with negative urine culture, and 24u urine analysis revealed 0.1gr proteinuria with a calculated creatinin clearance of 10mL/min/1.72m², and no Bence Jones protein. Both kidneys had normal size on ultrasound and there were no signs of post-renal obstruction. Hemodialysis was initiated, rivaroxaban discontinued and a kidney biopsy was performed. The kidney biopsy demonstrated an extensive tubulointerstitial nephritis (TIN), likely due to rivaroxaban. After discontinuation of rivaroxaban and treatment with prednisolone, renal function improved. Some years after the introduction and widespread prescription of direct oral anticoagulants (DOACs), its potential side-effects gradually become apparent. This case report underlines that a TIN is a potential side effect that should be taken into consideration in case of acute renal function decline. This case is provisionally accepted as a case report in Neth J Med
A previously healthy 38-year old male was seen at the emergency department with a two-day history of left upper flank pain and fever. He did not have any symptoms of dysuria or hematuria. On physical examination revealed hemodynamically stable patient with a temperature of 38.4°C and a tender left flank. Laboratory examination showed leukocytosis, two-fold elevated LDH, slightly elevated aminotransferases and an increased C-reactive protein level, the renal function was normal. Urinary analysis was unremarkable. Computed Tomography showed a wedge-shaped perfusion defect that involved both the cortex and medulla. The diagnosis of left renal infarction was made. Anticoagulant therapy and analgesics were initiated. Urine and blood cultures showed no growth. There was no evidence of hypercoagulability, renal artery or cardio-embolic disease. The patient was discharged a few days later in good condition. During the last follow-up visit he experienced no abdominal complaints and his renal function was normal.
A 78 years old woman was referred with weakness. She had had symptoms of fatigue, nausea, and loose stools for a few days. Physical examination showed no neurologic abnormalities, no fever, and a blood pressure of 145/95 mmHg. Laboratory testing showed a hemoglobin of 5.9 mmol/L, thrombocytopenia (49x10⁹/L), evidence of hemolysis (lactate dehydrogenase 872 U/L; haptoglobin <0.1 g/L; and fragmentocytes 1++; Coombs negative) and acute kidney failure (creatinin 227 umol/L). Urinalysis showed proteinuria and leukocyturia. A diagnosis of thrombotic microangiopathy (TMA), possibly thrombotic thrombocytopenic purpura (TTP), was made and plasmapheresis was started. Atypical hemolytic uremic syndrome was thought less likely since the lack of neurological symptoms. After 3 sessions of plasmapheresis, thrombocytes and lactate dehydrogenase had normalized. ADAMTS13 activity then turned out to be 58%. The diagnosis of TTP was rejected and plasmapheresis was discontinued.

Drug-induced TMA or a viral infection were also considered. Ciprofloxacin, which she had recently used for a urinary tract infection, is associated with TMA. However, this seemed an unlikely cause, since she had used ciprofloxacin several times before and had stopped using it several weeks before. However, she had elevated IgM parvoB19 levels, consistent with a recent infection, whereas serology for HIV, hepatitis B, CMV and EBV was negative. We therefore concluded she had microangiopathic hemolytic anemia (MAHA) and thrombocytopenia caused by parvoB19 infection. ParvoB19 has been associated with MAHA, but usually in immunocompromised hosts. The reason for the severe course in this patient remains unknown, but symptoms diminished spontaneously, and she recovered completely.
Hypoglycemia: not only in diabetics

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A 68-year old man presented to the emergency department with a hypoglycemic coma. His medical history included a non-functional grade 2 neuro-endocrine tumor of the pancreas with metastases to the liver for which he was treated with somatuline and everolimus. His other medication included pancreatin, phytoenadione and fluticasone furoate nose spray. General physical examination did not show any abnormalities. Laboratory results showed a serum glucose of 1.9 mmol/L and pre-existing elevated alkaline phosphatase and gamma-GT levels. The patient was admitted to the hospital. A C-peptide and insulin level were measured during hypoglycemia, both turned out to be markedly elevated. This confirmed the diagnosis insulinoma. We concluded that the non-functional neuro-endocrine tumor transformed into a functional tumor. Despite treatment with glucose infusion, dexamethasone, diazoxide and gavage, patients’ glucose levels remained very low. We decided to start chemotherapy with streptozocin and doxorubicin in order to revert the hypoglycemia. After 6 cycles of chemotherapy the patient decided to stop the treatment due to side effects including fatigue, anorexia and mucositis. He no longer needed glucose-enhancing treatment. The CT-scan demonstrated a partial response at that moment. The transformation of a non-functional neuro-endocrine tumor into a functional tumor is a very rare phenomenon. Only a few cases have been reported. The pathophysiology is not well understood. In patients with metastatic non-functional neuroendocrine tumors presenting with hypoglycemia, one should keep this paraneoplastic cause in mind.
Case report: a patient with pulmonary metastasized malignancy develops sudden dyspnea and a hissing sound...

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A 53-year old male was admitted to our A&E Department with sudden increase in dyspnea. The patient was diagnosed with clear cell renal cell carcinoma two months ago with pulmonary, ossal, hepatic and adrenal metastases, treated with pazopanib and prednisolone. He has experienced a productive cough with brown mucus for weeks, and used 3L oxygen for dyspnea. At the day of admission he suddenly experienced an increment in dyspnea, ‘around 3 p.m.’. The patient noticed retrosternal pain, waxing and waning with breathing. He could not lie supine because of the dyspnea, and slept in sitting position. Physical examination demonstrated a respiratory rate of 20/min, O₂-saturation of 96%, and diffuse rhonchi. Most inspirations were accompanied by a hissing sound, resembling venting of a bike tire valve. Chest radiograph revealed a lucent streak between heart and pericardium. Computed tomography (CT) confirmed presence of pneumopericardium, caused by perforation of the pericardium by one of many necrotizing metastases. The patient developed frank tachycardia. The cardiologist performed echocardiography. Pericardial drainage would not improve the situation, and because CT did not show any response to the palliative immunotherapy, oncologists and cardiologists saw no therapeutic options. Therefore palliative care was initiated to palliate dyspnea, with continuous i.v. morphine. The tachypnea and dyspnea became ‘bearable’ for the patient. On 4th day of admission the patient deceased peacefully. Pneumopericardium is a rare complication of pulmonary metastases with few case reports and indicates a very poor prognosis, regardless of intervention. Early identification allows for timely palliative care.
Ongoing remission 21 years after high-dose chemotherapy for oligo-metastatic breast cancer; what can we learn from this patient?

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Introduction: Metastatic breast cancer is generally considered incurable. Some patients, however, show an exceptional response to treatment and enjoy long-term survival in good health.

Case: We present a 32-year-old woman carrying a pathogenic BRCA1 mutation who presented with pain located at the sternum and a hoarse voice due to paralysis of the laryngeal recurrent nerve three years after mastectomy of the left breast because of breast cancer. A CT-scan of the chest revealed enlarged mediastinal lymph nodes on the left side and a 6 cm mass in the left upper lobe of the lung. The diagnosis was limited (oligo) metastases of the breast cancer. She received high-dose cyclophosphamide, thiotepa, and carboplatin (CTC) with peripheral blood progenitor cell support in the context of a clinical trial and achieved normalization of all symptoms and a complete radiological remission. She subsequently received locoregional consolidation radiation to the left mediastinum and apical lung. Currently, she is still in remission 21 years after treatment with high-dose chemotherapy and consolidation radiotherapy.

Discussion: The excellent outcome of this patient despite distant metastases falsifies the hypothesis that metastatic breast cancer is universally fatal. The individual contribution of local and systemic treatment in the context of oligo-metastatic disease needs further clarification. Furthermore, BRCA1 and BRCA2 gene mutations sensitize tumors to DNA double strand break inducting agents, such as CTC. A randomized clinical trial studying the effect of high-dose chemotherapy in oligo-metastatic breast cancer with a BRCA-signature is currently open for accrual in The Netherlands Cancer Institute (clinicaltrials.gov NCT01646034).
Tailoring treatment to the individual patient with metastatic colorectal cancer based on a comprehensive drug screen on patient-derived tumor organoids, the SENSOR study

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Background: Companion diagnostics, such as DNA profiles or protein expression assays, that are used to allocate targeted therapy to the individual patient have often proven insufficient to boost clinical outcome. In this study, we will evaluate if drug response of patient-derived tumor organoids, 3D cultures of cancer cells, are predictive of treatment response in the same patient, and can thereby be used as a platform to select treatment for the individual patient.

Methods: The SENSOR study is a mono-center, prospective, intervention study. Patients with metastatic colorectal cancer can be included and will undergo a tumor biopsy at baseline. Biopsies are used to generate organoid cultures and are subsequently subjected to a drug screen with eight targeted anti-cancer drugs. If a more than 10-fold reduction in organoid viability is observed in vitro for one of the drugs, the patient will be offered treatment with that specific compound after he/she has no regular treatment options left.

Results: A preliminary screen on a test panel of 20 tumor organoids has demonstrated differential drug sensitivity, where genotype-based predictions matched our in vitro observations. The study has been initiated November 2016 and has since then accrued 6 patients, who are currently being screened for drug sensitivity.

Conclusion: If this platform is capable of matching the right patient to the right drug, this will result in reduced attrition rates for new targeted compounds, better application of new and currently registered targeted therapies and an overall improvement in the treatment of patients with cancer.
Impact of comorbidities in addition to classic prognostic factors on breast cancer specific mortality: a competing risk prediction model in patients from the TEAM trial

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Background: Treatment decisions in breast cancer (BC) are often based on the risk of dying due to BC versus the risk of dying due to other causes. This study aimed to assess the impact of specific comorbidities on breast cancer specific mortality (BCSM) in patients with BC participating in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial.

Methods: Dutch and Belgian postmenopausal, hormone receptor positive, early BC patients enrolled in the TEAM trial were included. Baseline covariates included patient, tumor and treatment characteristics and specific comorbidities (ICD-10 classification). A Fine and Gray competing risk regression model was used to analyze covariates associated with the cumulative incidence of BCSM.

Results: A total of 3160 patients were included (median age at diagnosis: 63.5 years, median follow up: 10.2 years). Ten-year cumulative incidence was 16.6% for BCSM and 13.7% for other cause mortality (OCM). In multivariable analysis with OCM as competing event, BCSM was associated with increasing age (subdistribution Hazard Ratio (sHR) 1.04, 95% CI 1.03-1.05), presence of diabetes mellitus (sHR 1.52, 1.17-1.99), mood disorders (sHR 1.76, 1.03-3.01), previous transient cerebral ischemic attack (sHR 1.56, 0.92-2.62), peripheral atherosclerotic disease (sHR 0.42, 0.14-1.38) and chronic obstructive pulmonary disease (sHR 1.37, 0.96-1.97), increasing tumor size (T1 reference; T2 sHR 1.30, 1.07-1.58; T3/T4 sHR 1.37, 0.97-1.93) and nodal stage (No reference; N1 sHR 1.15, 0.94-1.41; N2/N3 1.79, 1.29-2.48).

Conclusion: In addition to classic prognostic factors, specific comorbidities influence the risk of breast cancer specific mortality and should be included in prediction models.
Improved diagnosis of malignant pleural mesothelioma in pleural effusion using flow cytometry

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Background: The diagnosis of malignant pleural mesothelioma (MPM) is hampered by a lack of robust and clinically utilizable markers to diagnose MPM. Patients with MPM often present with pleural effusion, however, fluid cytology analysis by the pathologist has poor sensitivity of about 25%, frequently necessitating invasive diagnostics such as taking a pleural biopsy. The current study evaluated a flow cytometric method to improve the diagnosis of MPM in pleural effusion.

Methods: A flow cytometry-based assay using melanoma cell adhesion molecule (MCAM) to identify tumor cells in the pleural effusion of MPM patients was optimized, validated and explored clinically. The assay was investigated in 1) a MPM cohort consisting of patients with histology-confirmed MPM (n=27), and 2) a control cohort of patients with pleural effusion and alternative diagnoses (n=22). The ability of the flow cytometric assay to detect MPM tumor cells in pleural effusion was compared with routine diagnostics by the pathologist.

Results: The malignant nature of MCAM-positive cells in pleural effusions from MPM patients was confirmed. The flow cytometric assay had superior sensitivity (48%) to standard cytological analysis (15%) for detecting MPM tumor cells (p=0.03), along with a specificity of 94%. In exploratory analyses the absence of tumor cells in pleural effusion appeared to be associated with worse overall survival.

Conclusion: Our flow cytometric assay was more sensitive to diagnose MPM than routine cytological analysis. Flow cytometric analysis of pleural effusion may also be a promising marker for the prognostication of MPM patients deserving further study.
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High dose of neoadjuvant chemoradiation for patients with potentially resectable esophageal cancer: a retrospective study

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Background: Standard treatment for potentially resectable esophageal cancer consists of five cycles of carboplatin and paclitaxel with concurrent radiotherapy (41.4 Gy), followed by esophagectomy. This treatment regimen yields a 5-year disease-free survival rate of 44%. It remains unclear whether dose-intensification leads to better outcomes. The aim of this study is to analyze the disease-free survival and toxic effects of a higher dose of chemoradiation.

Methods: Medical records of patients treated between January 2008 and December 2014 were studied retrospectively. The neoadjuvant therapy consisted of six cycles of carboplatin (area under the curve = 2 mg/ml/min) and paclitaxel (50 mg/m² of body-surface area) and concurrent radiotherapy (50.4 Gy given in 28 fractions of 1.8 Gy each, 5 days per week), followed by esophagectomy.

Results: A total of 181 patients were included, of which 72% underwent a resection. At a median follow-up of 26.3 months, the patients who underwent a resection had not yet reached the median disease-free survival time. The disease-free survival rates at 3 and 5 years were 56% and 52%, respectively. The most common grade 3 acute toxicity due to the chemoradiation was leukopenia (29%). The postoperative mortality rate within 30 days after surgery was 4%. A pathological complete response was achieved in 35% of patients.

Conclusion: Neoadjuvant chemoradiation consisting of six cycles of carboplatin and paclitaxel with concurrent radiotherapy (50.4 Gy) for patients with potentially resectable esophageal cancer is well tolerated and effective. In addition, the pathological complete response rate was relatively high.
An unusual presentation of metastatic breast cancer

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Case: A 66-year-old woman presented with progressive dyspnea d'effort. Her medical history was remarkable for estrogen receptor-positive (ER+) pT3N2M0 ductal carcinoma in 1995 for which she received mastectomy, radiation, adjuvant chemotherapy and anti-hormonal treatment. A CT-scan of the thorax showed a 70 mm intracardiac mass and pleuropericardial effusion. Transthoracic echocardiography did not show outflow obstruction and thrombosis was excluded as a possible cause by MRI of the heart. A primary cardiac malignancy was considered unlikely based on MRI imaging. Additional scans showed ascites, bone and liver metastases. Cytology and histology of the pleural effusion and bone lesions, respectively, did not show malignancy. Subsequently, cytology of ascites demonstrated ER+ adenocarcinoma cells, due to late metastases of her previous breast carcinoma. In addition, the tumor marker CA 15.3 was elevated (642 kU/l). Due to the extensive disease the intracardiac mass was considered a metastasis of breast cancer. Patient was unfit to receive palliative chemotherapy and anti-hormonal therapy was initiated. She deceased several weeks after presentation.

Conclusion: We present a case of an unusual metastasis, located in the heart, 21-years after the first presentation of breast cancer. This case demonstrates the unpredictable metastatic behavior of breast cancer. So, in cancer patients with symptoms of heart failure, metastatic cardiac deposits must be considered in differential diagnosis, especially in patients with a medical history of breast cancer.
Junctional escape rhythm due to neoadjuvant chemotherapy for breast cancer

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A 48-year old female with a blank medical history was diagnosed with breast cancer, cT2N1, estrogen and progesterone receptor negative and HER2 positive. She was started on neoadjuvant chemotherapy (doxorubicin/cyclophosphamide). Three days after the first course of chemotherapy, she presented to the emergency department with syncope. She complained of dizziness, nausea and blurred vision, but no vomiting, chest pain or palpitations. On cardiac rhythm observation she had a junctional escape rhythm of 30 beats per minute. An MRI of the brain excluded metastases of the breast cancer in the brain as origin of the symptoms. A nuclear imaging study prior to the first course of chemotherapy showed a normal ejection fraction at a heart rate of 57 beats per minute. On admission, an echocardiogram and cycle-ergometry showed no evidence of an underlying cardiac disorder. Borrelia serology was negative, excluding Lyme carditis as the cause of the rhythm disorder. Also other virus serology (HIV, viral hepatitis and lues) was negative. Myocardial MRI showed no structural heart defects or myocardial disorders. Doxorubicin was depicted as the cause for the junctional escape rhythm. The chemotherapy scheme was adjusted avoiding anthracycline agents. An implantable loop recorder was implanted to observe rhythm disorders. The patient remains under out-patient control of the oncologist and cardiologist. In conclusion, in patients receiving anthracycline chemotherapeutic agents, new-onset cardiac rhythm or conduction disorders might be attributed to the chemotherapy.
Background: The optimal treatment strategy for patients with asymptomatic incurable metastatic colorectal cancer is unknown. Particularly, the potential benefit of surgery of the primary tumour is extensively debated. Comparative Effectiveness Research, by using country as instrumental variable, could provide clues to the best treatment strategy.

Methods: Population-based cohorts (2007-2013) from The Netherlands and Norway including all patients with incurable synchronous metastatic colorectal cancer were compared on treatment strategy and overall survival. Using country as an instrumental variable (pseudo-randomisation), we assessed the effect of different treatment strategies on mortality within the first year. Analyses were adjusted for age, gender, localisation, year of diagnosis, and localisation of metastases.

Results: We included 16,144 Dutch patients and 5,052 Norwegian patients. The proportion of patients with surgery of the primary tumour was 38.6% in The Netherlands compared with 51.5% in Norway (p<0.001). Of all Dutch patients, 58.4% received chemotherapy compared with 21.4% of Norwegian patients. Radiotherapy was given in 10.2% of Dutch patients compared with 11.2% of Norwegian patients. With The Netherlands as a reference category, the adjusted HR for overall survival was 0.98 (95% CI 0.93-1.03; p=0.36). Instrumental variable analysis showed an adjusted OR of 1.00 (95% CI 0.98-1.03; p=0.72).

Conclusion: The present international comparison shows variation in treatment strategy between The Netherlands and Norway. However, we did not observe a difference in overall survival between these two countries. Instrumental variable analysis showed no benefit of a treatment strategy with more surgery of the primary tumour on mortality within the first year.
Background: FMF is the oldest and most prevalent hereditary auto-inflammatory disease. Due to immigration FMF also occurs in non-Mediterranean regions, but data are scarce. In the present study the clinical, demographic, and genetic characteristics of patients with FMF in a teaching hospital in Amsterdam are described.

Methods: Case records of patients with FMF, who met the Tel-Hashomer diagnostic criteria, were analysed retrospectively. The international disease severity score was used.

Results: Between 1990-2012, 53 patients were identified, 28 (52.8%) were female. The mean age was 29.1 years (14.8 - 43.4). Main ethnicity was Turkish (n=38; 71.7%). Mean age at onset of symptoms was 13.8 years (2.8-24.7) and at time of diagnosis 22 years (8-35.9). Mean time from onset of symptoms to diagnosis was 8.2 years (5.2 - 11.2 years). Most prominent symptoms were peritonitis (n=48, 90.6%) and fever (n=43; 81.1%). The mean CRP and ESR during acute attacks were 133 mg/l (28-237) and 37 mm/first hour (13-62) respectively. One patient developed amyloidosis as a complication. 17 (32.1%) patients underwent abdominal surgery before diagnosis. Most patients (91.7%) received colchicine treatment and were responsive (81.2%). Most patients classified their disease as a mild disease (41.5%). MEFV-gene mutation analysis was performed in 45 patients: 30 patients (66.7%) were heterozygote and the most frequent mutation was M694V (20%).

Conclusion: FMF is diagnosed in relative young patients. The delay between the initial symptoms and diagnosis is 8.2 years. Disease manifestations and genetic distribution of our FMF patients are comparable to those in Mediterranean regions.
Five year outcomes of remission steered treatment in early rheumatoid and undifferentiated arthritis patients

**Background:** To assess 5 year outcomes of induction therapy followed by disease activity score (DAS)-remission steered treatment in early arthritis patients.

**Methods:** 610 early rheumatoid arthritis (RA) or undifferentiated arthritis (UA) patients were included, starting induction therapy methotrexate (MTX) and tapered high dose of prednisone. Early DAS-remission (ER) (DAS<1.6 at 4 months) patients could stop prednisone and also MTX if remission persisted at 8 months. Patients not in ER were randomized to MTX+sulfasalazine+hydroxychloroquin e+low dose prednisone (arm 1) or MTX+adalimumab (arm 2), 50 patients (not randomized) were treated ‘outside of protocol’ (OP). Four-monthly treatment adjustments aimed at DAS<1.6: DAS<1.6 taper/stop medication and DAS=1.6 restart/intensify. Outcomes were (drug-free) remission (DFR) percentages.

**Results:** 295/610 (48%) patients achieved DAS-remission at 5 years: 220/387 (57%) in ER, 31/83 (37%) in arm 1, 29/78 (37%) in arm 2 (p=0.768 arm 1 vs arm 2) and 15/50 (30%) in OP. 134/610 (22%) patients achieved DFR: 105/387 (27%) in ER, 9/83 (11%) in arm 1, 12/78 (15%) in arm 2 (p=0.374 arm 1 vs arm 2) and 8/50 (16%) in OP. DAS-remission percentages were similar in RA and UA patients and autoantibody positive (+) vs negative (-) patients. More UA patients (33% UA vs 19% RA, p<0.001), anti-citrullinated protein antibodies (ACPA)? (31% ACPA? vs 15% ACPA+, p<0.001) and rheumatoid factor (RF)? (48% RF? vs 17% RF+, p<0.001) achieved DFR.

**Conclusion:** Induction therapy followed by 5 years DAS-remission steered treatment resulted in 48% DAS-remission and 22% DFR in early arthritis patients. More UA and autoantibody negative patients achieved DFR.
A 64-years old patient was referred to our department with since three months complaints of muscle pain, severe muscle weakness and strong elevated creatinine kinase (CK) levels. Patient had a history of coronary heart disease and he used atorvastatin. Muscle weakness was progressive and patient was severely impaired in daily functioning. There were no swallowing problems. Physical examination showed symmetrical atrophy and weakness grade 4 of the proximal muscle groups and grade 2 of axial muscles. Reflexes were normal, there was no arthritis, no skin rash or abnormal results on heart, lungs or abdomen examination. Laboratory tests showed elevated CK (7894 U/l) and normal CRP, BSE and TSH. ANA, ENA and additional myositis blot were negative. Electromyography showed active myositis and dynamometry showed severe muscle weakness. Muscle biopsy revealed necrotizing myopathy without concomitant lymphocytic infiltrates. PET-scan was performed to exclude malignancy. Except diffuse muscle activity there were no pathological findings. Finally, anti-HMGCR antibodies turned to be positive. Diagnosis of immune mediated necrotizing myopathy due to statin use was made. After start of steroid treatment CK levels dropped and muscle strength increased. Immune mediated necrotizing myopathy due to statin use is an acquired auto-immune disease, characterized by severe symmetrical proximal muscle weakness and very high CK levels (mean CK 10.333 U/l). Anti-HMGCR antibodies are highly specific and have not been found in patients with statin use without myopathy or in patients with a self-limiting statin intolerance. Long-term treatment with glucocorticoids often combined with other immunosuppressive drugs or immunoglobulin's is required.
The giant miracle of metabolic imaging

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Introduction: 18FDG PET may play a role in the management of atypical giant cell arthritis (GCA). Case A 58-year old Serbian man was referred to our outpatient clinic due to unexplained weight loss and an anemia. He had been unwell for 3 months. He complained of night sweats and had little energy. He did not have a headache, visual disturbances or jaw claudication. In the evenings he had a temperature of 38 C. His travel history was unremarkable. On physical examination he did not have a fever and there was no lymphadenopathy. Laboratory results revealed a sedimentation rate of 120 mm after 1h; Hb 5.5 mmol/l, normal and kidney function. There was no M-protein. HIV, hepatitis, EBV/CMV serology were negative, as was a Mantoux test. An additional CT scan of the thorax and abdomen did not show any abnormalities. Due to ongoing inflammation and weight loss without a diagnosis, a 18FDG PET was performed and revealed uptake in the entire aorta continuing along the aortic bifurcation to the common iliac veins suggestive for a large vessel vasculitis. It was classified as giant cell arthritis on clinical criteria. The patient improved rapidly after introduction of high dose steroids.

Discussion and conclusion: In the absence of typical clinical symptoms the classification of isolated inflammatory syndromes is a challenge. Frequently the results of radiological studies are ultimately fruitless and time-consuming. As in the present case 18FDG PET may particularly useful in cases of GCA with an atypical presentation.
Complete deletion of the GPIHBPl gene in two siblings with familial hyperchylomicronemia syndrome

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Case: A 27-year old male (index patient) and his 22-year-old sister are attending the lipid out-patient clinic. As a 3-day infant he presented at the neonatal clinic with jaundice. Blood withdrawal showed lipemic serum and triglycerides >70 mmol/L, which was confirmed by repeated measurements. The diagnosis of familial hyperchylomicronemia syndrome (FCS) was made. A medium chain triglyceride (MCT) diet was initiated. Since his third year he experienced repeated episode of pancreatitis due to non-adherence to his diet. His sister was diagnosed with FCS immediately after birth. Despite the advice for adhering to an MCT diet, she also suffered recurrent episodes of pancreatitis because of non-adherence. The parents are consanguine and have no lipid abnormalities. Initial genetic analysis showed no mutations in LPL or APOC2 gene. Because of improved diagnostics genetic analyses was repeated, showing a total deletion of the GPIHBPl gene in the 2 siblings and heterozygote deletion in the parents.

Discussion: FCS is a rare autosomal recessive disorder, mostly caused by a mutation in the LPL gene. Other FCS-causing mutations affect the genes encoding for apoC-II, apoA-V, LMF1 and glycosylphosphatidylinositol-anchored high-density-lipoprotein-binding protein1 (GPIHBPl). GPIHBPl is a binding site for lipoprotein lipase (LPL) on the endothelial surface and acts as a transporter for LPL across the endothelial cells to the capillary lumen. Patients with FCS caused by compound heterozygous and homozygous missense GPIHBPl mutations have been prescribed previously. However, to our knowledge, this is the first description of patients with a complete deletion of the GPIHBPl gene.
Use of a single baseline versus multi-year 24-hour urine collections for estimation of long-term sodium intake and associated cardiovascular and renal risk

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Background: Reduction of sodium intake has been shown to lower blood pressure, but data from cohort studies on the association with cardiovascular and renal outcomes are inconsistent. These studies have estimated long-term sodium intake using a baseline measurement, which may be inaccurate considering day-to-day changes in sodium intake. We compared a single versus multiple follow-up 24-hour urine samples for investigation of the relation between sodium intake and long-term cardiorenal outcomes.

Methods: We selected adult subjects with an eGFR >60 mL/min and an outpatient 24-hour urine between 1998-1999. Sodium intake was estimated using a baseline sample and the average of samples that were collected during a 1, 5 and 15-year follow-up. We used Cox-regression analysis to investigate the relation between sodium intake and cardiovascular (cardiovascular events or mortality) and renal outcome (dialysis, transplantation, >60% eGFR decline or mortality).

Results: We included 574 subjects with 9,776 24-hour urines. Average age was 47 years, 46% were male. Median follow-up was 16.2 years. Average 24-hour sodium excretion, 170 mmol, was equal among all 4 methods (p=0.98). However, relative to a single baseline measurement, 48-50% of the subjects had a >34 mmol different sodium intake with long-term estimates. Consequently, 45-50% switched between salt intake tertiles and hazard ratios for cardiorenal outcomes changed up to 60% using 1-15 year estimates.

Conclusions: Relative a single baseline 24-hour sodium measurement, the use of multiple 24-hour urine samples resulted in different estimations of individual sodium intake, which had significant consequences for the association between sodium intake and long-term outcome.
Lifelong Apixaban Treatment for Venous Thromboembolism is cost-effective in The Netherlands

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Background: Dutch guidelines advise lifelong anticoagulant treatment with direct oral anticoagulants (DOACs) or vitamin K antagonists (VKAs) for patients with venous thromboembolism (VTE) who do not have high bleeding risk. The aim of this study was to analyze the economic effects of lifelong treatment of apixaban in The Netherlands, based on updated and adapted previous modelling exercises for use of apixaban in acute VTE-patients.

Methods: We performed a cost-effectiveness analysis (CEA) simulating a population of 1,000 VTE patients. Two different treatment strategies were tested: lifelong apixaban treatment vs. no treatment after the first 6 months (base case analysis). In scenario analysis, the initial treatment period of 6 months with LMWH/VKA was also included. We calculated the incremental cost-effectiveness ratio (ICER) in costs (€) per quality adjusted life-year (QALY), with one QALY defined as one year in perfect health. To account for any influence of the uncertainties in the model a probabilistic sensitivity analysis (PSA) was conducted, in which the ICER was recalculated 2,000 times while varying all input parameters over their range.

Results: The model showed a significant reduction in recurrent-VTE and no increase in major bleeding events for lifelong treatment. Deterministic results showed ICERS of €9,830/QALY and €8,231/QALY in the base case and scenario analysis, respectively. In the PSA, a probability of being cost-effective at a willingness-to-pay threshold of € 20,000/QALY of 70.4% and 79.5% respectively resulted.

Conclusion: Lifelong treatment with apixaban is effective and cost-effective in Dutch VTE patients with high recurrent VTE risk.
A 66-year old male was presented to the hospital with a history of fatigue, loss of appetite and fever since three weeks, followed by acute abdominal pain since one day. At presentation, the patient was hypotensive and tachypneic. Laboratory investigation showed a raised C-reactive protein, leukocytosis with atypical lymphocytes, elevated transaminases and lactic acidosis. The suspicion of intestinal ischemia was confirmed by computed tomography, revealing massive portal vein thrombosis. Antithrombotic therapy was initiated, surgery was performed and followed by a complicated recovery phase. Since there had been no immobilization or other apparent thrombophilic risk factors, common tests for inheritable and acquired thrombophilia were performed, showing no abnormalities. However, the cytomegalovirus (CMV) serology was in accordance with an acute infection, which was in line with the symptoms of the patient in the weeks preceding hospital admission. The seroprevalence of a CMV infection in adults is reported to be 65%. Symptoms may vary from mononucleosis-like symptoms to a severe disseminated infection in immunocompromised patients. Thrombo-embolic events are not well known, but have been reported in more than hundred patients with an acute CMV infection of which most were immunocompetent. It is postulated that an acute CMV infection causes a hypercoagulable state through a transient elevation of antiphospholipid antibodies, activation of factor X, stimulation of factor VIII and Von Willebrand factor, systemic endothelitis and adhesion of thrombocytes and leukocytes. The relative thrombosis risk of a CMV infection can be deducted through future prospective research, which may affect decisions of the duration of coagulation.
Sodium intake in patients treated for hypertension in secondary care: how does it relate to the recommended maximum sodium intake?


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Background: High sodium intake is associated with hypertension, resistant hypertension, cardiovascular disease, and albuminuria. The recommended maximum sodium intake is 100 mmol/24h in The Netherlands. We investigated sodium intake based on 24h urinary sodium excretion as well as on information obtained during anamnesis in patients treated for hypertension in secondary care.

Methods: We performed a retrospective study in patients treated for hypertension in the outpatient clinic of vascular medicine in the Amphia hospital between January 2012 and March 2016 using 24h urine collections obtained during non-study-related care, intending to represent daily practice. In addition, estimated sodium intake during anamnesis was defined as low, intermediate, high, or very high.

Results: 158 patients collected 24h urine samples for analysis of sodium excretion. Mean age was 59.1 years and 48.1% was male. Median sodium excretion in 24h urine was 148 mmol. 122 patients (77.2%) had an excretion above 100 mmol/24h, of which 36 patients (22.8%) had an excretion above 200 mmol/24h. Males had a higher median 24h urinary sodium excretion than females (179 versus 118 mmol, p = <0.001). 67.6% of the patients with an estimated sodium intake defined as ‘low’ during anamnesis had a 24h urinary sodium excretion above 100 mmol.

Conclusion: The majority of patients treated for hypertension in secondary care is consuming more sodium than recommended. Thus, further efforts to lower sodium intake should be taken in these patients. Furthermore, estimation of sodium intake by means of anamnesis is unreliable, urging the need of estimating sodium intake by using 24h urine collections.
A 53-year old woman was referred with progressive pain of a blue toe without other symptoms. She had a history of deep venous thrombosis and pulmonary embolism three years earlier and used anticoagulants. She was non-smoking. Physical examination showed blue discolorisation of the right middle toe. Laborotary investigations showed mild leukocytosis with eosinophilia, mild thrombocytosis, and no other abnormalities, including normal CRP and ferritin. Ankle-brachial index was normal, but toe pressure was diminished in the symptomatic toe. Skin biopsy revealed no signs of inflammation or embolism. Additional laboratory testing showed no coagulation disorders, while eosinophilia and thrombocytosis was progressive. Suspecting a myeloproliferative disorder, we performed a bone marrow examination. Histopathology showed proliferation of large megakaryocytes and increased number of spindle-shaped mast cells (>25%). Immunophenotyping the mast cells revealed increased expression of CD117, with CD2 and CD25 co-expression. PCR showed mutations in both JAK2-V617F and KIT-D816V. The constellation of findings met the diagnostic criteria of essential thrombocytosis as well as systemic mastocytosis. Conclusively, we diagnosed Systemic Mastocytosis with Associated clonal Hematological Non-Mast cell-lineage Disease (essential thrombosis), SM-AHNMD. Treatment with carbasalatcalcium resulted in resolution of symptoms and hydroxyurea myelosuppression normalised thrombocyte level. Regarding the systemic mastocytosis, preventive advices were given. In this case, a blue toe was the only current sign of systemic mastocytosis with associated essential thrombocytosis. The essential thrombocytosis dictated the presentation and treatment. The case illustrates the importance of performing a complete blood count in patients with a blue toe syndrome as part of the work-up for treatable causes.
Medical students’ and doctors’ professionalism and societal role modeling: what are the boundaries between professional versus private life?

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Background: Due to blurring of private and professional boundaries, medical professionalism and doctors’ function as a societal role model is increasingly being discussed by public media. However, expectations of professional behavior during students’ and doctors’ spare time are only vaguely eluded to, if described at all. We wondered if there were any guidelines concerning this aspect of professional behavior. We performed a literature search to look for any information on this subject.

Methods: We searched for any relevant legal regulations and jurisprudence. Furthermore, we reviewed the guidelines of the national federation of Dutch Medical Doctors’ (KNMG), as well as guidelines from two teaching hospitals and guidelines of other civil servant organizations. All legal regulations and guidelines were reviewed whether they address the topic of medical professional behavior in professionals’ private time.

Results: Legal regulations only extent to either confidentially breaches, or criminal activities which makes one unfit to be a doctor, for example sexual abuse or murder. None of the medical guidelines provides any framework or consensus about what is considered as either as professional or unprofessional behavior of a medical employee ‘off duty’.

Conclusion: Despite the lack of clear legislation and guidelines by professional organizations pertaining to this issue, many unwritten rules and expectations exist. The contemporary social debate will improve societal, organizational and individual awareness regarding the issue of the so far blurred professional behavior boundaries between students and doctors’ private and professional life.
A rare combination of Cushing syndrome and nephrotic syndrome.

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Case: A 56-years old female patient presented with progressive edema and facial swelling. In the past she was suffering from depression, for which she used olanzapine and fluoxetine. On physical examination she had a remarkable moon-face and pitting edema of the lower limbs. No other abnormalities were found. Laboratory results showed a low serum potassium of 3.1 mmol/L (normal 3.5-4.8), a slightly elevated creatinine of 117 umol/L and a low serum albumin of 28.3 g/L (34.0-46.0). In 24 hours urine a total protein of 4.25 g/24 hours was measured. Dexamethasone suppression test showed a cortisol level of 2088 nmol/L (normal < 300) and an elevated ACTH -level of 60.9 pmol/l. On a chest X-ray no abnormalities were found. Finally a PET scan was performed which was suspicious for a stage IV primary lung carcinoma. Via bronchoscopy the diagnosis small cell lung cancer was confirmed. The patient was treated with a sodium restricted diet, furosemide, spironolactone and metyrapone were initiated. The edema resolved and the cortisol level decreased. After starting chemotherapy the symptoms disappeared and the cortisol level normalized.

Discussion: Cushing syndrome due to ACTH producing malignancies is a rare phenomenon, but mostly observed in small cell lung cancer. Malignancy is a well-known cause of nephrotic syndrome. Only two cases have been described with both the syndromes in one patient before.

Conclusion: We present a case of Cushing syndrome and nephrotic syndrome in a patient with disseminated small cell lung cancer.
Evidencio: implementing prediction models into medical practice

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Background: Prediction models are research-based tools that can complement medical decision-making. Although prediction models were repetitively shown to outperform clinical judgement, their application in medical practice is still limited. Evidencio is a novel online platform that aims to improve clinical implementation of prediction models by facilitating model creation, validation, and integration. Here, we present three models to exemplify the potential of the Evidencio platform in internal medicine.

Methods: The online Evidencio development kit was used to create user-friendly calculators based on model coefficients published in the literature. The first model was built to estimate individual prognosis in patients who had surgery for invasive breast cancer. The second model includes ultrasound parameters to predict the probability of axillary lymph node metastasis in early breast cancer patients. The third model was built to predict individual pharmacokinetics of trastuzumab-emtansine in patients with HER2 positive metastatic breast cancer.


Conclusion: With these three models, we show how Evidencio can be used to predict individual prognosis, treatment outcome, and individual pharmacokinetics. We encourage researchers and clinicians to use prediction models on a regular basis to complement medical decision-making.