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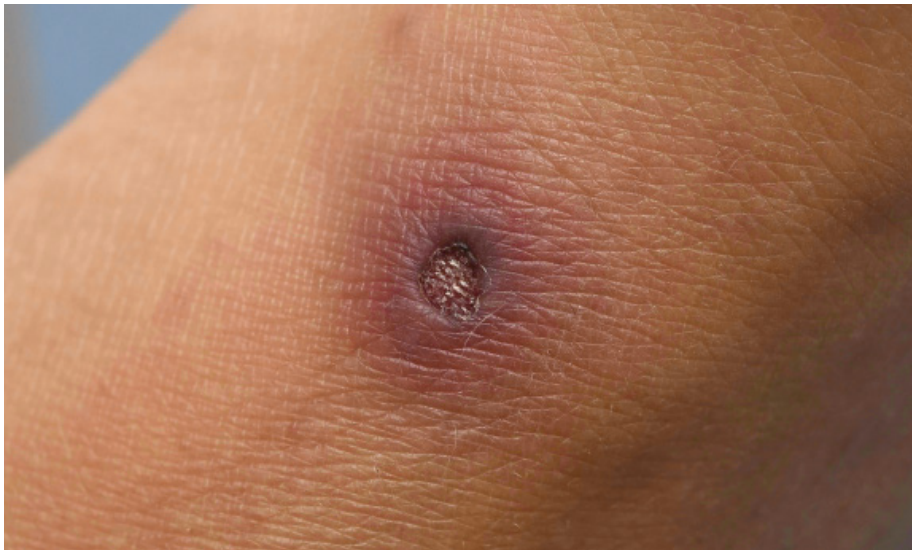

A skin lesion after a visit to South Africa; what is your diagnosis?

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EDITORIAL

Pharmacological awareness benefits patients

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Whereas the tool of the surgeon is the scalpel, internists cure, or at least treat, with medication. However, in the past decade our toolbox has grown so rapidly that it is becoming more and more difficult to handle. The result: adverse drug events (ADE). In a meta-analysis by Hakkarainen et al., it was demonstrated that in an outpatient population up to 2% of all admissions or emergency visits are due to ADE, many of which were potentially preventable.[1] The most important risk factor for ADE in hospitalised patients is the number of drugs they use and the start of a new drug during admission.[2] Patients on cancer treatment sometimes start three new drugs during admission just to treat their nausea. In the current issue, Schoffelen et al. explain how various drugs given in cancer therapy may interact with each other.[3]

Prescription errors and drug-drug interactions are potentially preventable as a cause of ADE. Computerised prescriber order entry may help in prevention but depends on adherence and completeness.[4] We need to do better. In the current issue of the journal, Bosma et al. demonstrated that adding a pharmacologist to the team present during rounds on the intensive care unit leads to further improvement in medication care for patients and on top of this to a decrease in costs.[5]

Luckily most patients admitted do not end up in the ICU unit, but also on general wards and in the outpatient clinic patients might benefit from better pharmacological awareness. Apart from drug interactions, knowledge on pharmacokinetics and pharmacodynamics is becoming more and more important especially in a patient population that is gradually ageing. As Ross and Maxwell stated: 'Good prescribing requires a sound understanding of the principles of clinical pharmacology, knowledge of medicines, appreciation of uncertainty and good judgement, ideally based on experience'.[6] Intensifying training in pharmacology ultimately will lead to better patient care.

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REVIEW

Recent developments in the diagnosis and therapy of well-differentiated neuroendocrine tumours

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ABSTRACT

Well-differentiated neuroendocrine tumours (NETs) of the digestive tract are being increasingly detected, which is partly explained by the increased use of endoscopic and cross-sectional imaging as well as improved recognition at histopathological evaluation. After the discovery of this relatively indolent type of epithelial malignancy over 100 years ago, their sporadic occurrence and divergent biological behaviour at multiple primary sites have hampered dedicated studies into NET pathogenesis and testing of drug efficacy in well-designed clinical trials. The last decade, however, has seen significant improvements in the NET field regarding our understanding of their pathophysiology. This has been substantiated by novel and exciting diagnostic and therapeutic options, including superior positron emission tomography imaging, treatment with unlabelled and radiolabelled somatostatin analogues and inhibitors of the mammalian target of rapamycin and vascular endothelial growth factor pathways. This review summarises contemporary studies within NET patients, which have enriched our clinical repertoire for this disease and have been instrumental in securing a remarkable improvement of overall survival within recent years.

KEYWORDS

Neuroendocrine tumour, carcinoid, peptide receptor radionuclide therapy

INTRODUCTION

Despite their reputation as uncommon malignancies, neuroendocrine tumours (NETs) are nowadays increasingly encountered across the practices of endocrinologists, oncologists, gastroenterologists, surgeons and pulmonologists.[1] Different tumour subtypes at multiple sites are linked due to their common origin of neuroendocrine cells within the pulmonary and gastrointestinal tracts. Research has clearly delineated the separate genetic backgrounds and biological behaviours of NETs originating at different primary locations in terms of proliferative potential and hormone production. These insights have resulted in a paradigm shift in patient treatment according to tumour subtype and clinical syndrome. Consequently, any medical professional dealing with NETs should be well informed about the NET phenotypes and how the emerging therapies can be best applied to the individual patient suffering from this disease.

EPIDEMIOLOGY

NET is a rare malignancy that comprises 1-2% of all gastrointestinal and pulmonary malignancies.[2,3] A prospective, nationwide study on the occurrence of gastrointestinal and pancreatic NETs in Austria revealed an annual incidence ratio of 2.4 per 100,000 persons.[2] According to a national cancer registry in the UK the incidence of gastrointestinal NETs is 1.3 per 100,000 and has markedly risen during the past four decades.[4] Recently, a large population-based USA registry showed an incidence of all NETs of 7.0 per 100,000 persons in 2012, which is over 6-fold higher compared with the 1970s. This increment was seen across all age groups, tumour sites, stages and grades. In the past two decades, the 20-year limited-duration prevalence of NETs also rose 8-fold to 0.048%.[5] The increased detection of the disease is likely explained by the rise in the use of endoscopic investigations and cross-sectional imaging combined with

an increased awareness among pathologists to consider a diagnosis of NET.

TUMOUR SITES, GRADING AND STAGING

Classically, NETs have been subdivided according to the origin of the primary tumour.[6] Tumours were historically classified as arising from the embryonic foregut, midgut or hindgut. Foregut NETs comprise lung, thymic, stomach, duodenal and pancreatic tumours. Midgut NETs arise from the neuroendocrine cells of the small intestine distal to the duodenojejunal flexure, the appendix and the ascending colon. NETs of the hindgut originate in the distal colon or rectum. Tumours originating from the gastrointestinal tract are commonly called gastroenteropancreatic NETs (GEP-NETs). Despite contemporary imaging techniques, about 5-10% of metastasised NETs have an occult primary tumour.[7] Neuroendocrine neoplasms can arise in organs outside the pulmonary and digestive tract and features of neuroendocrine differentiation can be observed in a subset of common malignancies, such as breast and prostate cancer, but these neoplasms are generally not classified as NET.

One of the key features of NET is the considerable difference in biological behaviour ranging from indolent rectal tumours to the highly malignant small cell lung cancer. As such, grading of NETs is crucial for estimation of prognosis and for choice of appropriate anti-proliferative management. The current World Health Organisation (WHO) grading system divides NETs into three subgroups depending on histopathological evaluation of the mitotic index and the Ki67 index.[8,9] In the case of lung NETs the presence of necrosis is also taken into account.[10] Tumours with grade 1 (low) or grade 2 (intermediate) are generally considered well-differentiated and are accompanied by the best prognosis. Grade 3 or poorly differentiated tumours with a high mitotic and/or Ki67 index display aggressive behaviour, which is why this subtype is also classified as neuroendocrine carcinoma (NEC). An additional tumour group of grade 3 NET is incorporated in the new WHO 2017 grading system which is comprised of histologically well-differentiated tumours that harbour a high proliferative index, i.e. Ki67 index above 20%. This review will focus primarily on well-differentiated tumours. Staging occurs according to a TNM-based system with localised disease representing stages I and II, invasion into adjacent structures (T4) or lymph node metastases (N1) denoting stage III and distant metastases (M1) are the hallmark of stage IV disease.[8,9]

PATHOPHYSIOLOGY

In a minority of cases, NETs can develop within the context of several inherited syndromes.[11] Notably, patients with multiple endocrine neoplasia type 1 (MEN1), caused by germline mutations in the *MEN1* gene, have a predisposition for developing pancreatic and bronchopulmonary NETs. Hereditary susceptibility to pancreatic NETs (PanNETS) is also encountered in Von Hippel-Lindau disease, tuberous sclerosis complex and neurofibromatosis type 1.

Similar to other malignancies, much has become known about disease-causing genes through next-generation sequencing studies. First, exome sequencing of PanNETs revealed a predominance of mutations in *MEN1* (44%) as well as mutations in the interacting telomere-altering genes *ATRX* (α thalassaemia/mental retardation syndrome X-linked) and *DAXX1 (*death-domain-associated protein) in a mutually exclusive pattern in 43% of patients.[12] Signalling of the kinase mammalian target of rapamycin (mTOR) is involved in a subset of patients, as pathway-activating mutations have been detected in 15% of PanNETs. Recently, whole-genome sequencing of PanNETs identified four mutational signatures revealing pathogenic alterations in pathways of chromatin remodelling, DNA damage repair, the mTOR pathway and telomere maintenance.[13]

For midgut or small intestinal NETs exome sequencing identified a variety of single nucleotide mutations with low penetrance; gene copy number alterations appeared to be more common.[14] Genetic changes were clustered within several growth factor pathways, such as the transforming growth factor-β (TGF-β), platelet-derived growth factor and epidermal growth factor. Inactivating alterations in the cell cycle regulator *CDKN1B* (cyclin-dependent kinase inhibitor 1B), the gene encoding p27 and responsible for MEN type 4, were the most prevalent at 8% of tumours.[15] Similar to PanNETs, signatures of genetic aberrations detected in midgut NETs were grouped in the mTOR pathway, DNA damage repair and chromatin remodelling.[14] Further studies have confirmed that small intestinal NETs appear to be caused by epigenetic rather than genetic dysregulation.[16]

In well-differentiated lung neuroendocrine tumours, also termed bronchial carcinoids, there is again a molecular signature involving chromatin-remodelling genes.[17] Prevalence of disease-causing mutations therein was high with over 60% of tumours affected and was accompanied by significant loss of heterozygosity at several affected genes. Consequently, alterations in chromatin-remodelling, mTOR pathway and DNA repair mechanisms appear key factors in the pathogenesis of NETs.

HORMONAL SYNDROMES

NETs can be divided into 'functional' and 'non-functional' tumours. Functional NETs produce bioactive peptides and hormones resulting in specific symptoms whereas non-functional NETs can present with mechanical effects, i.e. bowel obstruction or ischaemia. Non-functional NETs are also frequently discovered incidentally during diagnostic procedures. Patients with functional NETs can present with a range of clinical symptoms related to hormonal secretion by the tumour. Next to production of hormones that are physiologically produced by neuroendocrine cells, functional NETs can also produce hormones that are normally secreted by endocrine glands, i.e. ectopic hormone production. Patients should be asked about the occurrence of these symptoms as they require specific treatment and can potentially impair prognosis.[18]

The classic hormonal syndrome encountered in patients with NETs is the carcinoid syndrome.[19] Patients present with cutaneous flushes and diarrhoea due to vasodilation and increased gut motility, respectively. NETs can secrete a variety of amines and peptides that elicit these symptoms, but serotonin or 5-hydroxytryptamine is the most well-known mediator causing carcinoid syndrome.[20] It is produced by the enterochromaffin cells in the small intestine and its overproduction is predominantly encountered in midgut NETs, although primary tumours at other sites can also secrete this amine. Besides its vasodilatory and peristaltic effects, serotonin is also the most likely mediator producing mesenteric and right-sided cardiac fibrosis, which are exclusive features of carcinoid syndrome.[21]

PanNETs arise from the islets of Langerhans and as such are able to produce pancreatic peptides. Hypoglycaemia can be a severe and potentially life-threatening complication of insulin-producing PanNETs also known as insulinomas.[22] Physicians should also be aware of Zollinger-Ellison syndrome, caused by a gastrin-producing duodenal or pancreatic NET with clinical sequelae of severe gastric acid hypersecretion, i.e. multiple peptic ventricular or duodenal ulcers.[23] Glucagon release by the tumour can lead to diabetes mellitus, cachexia, glossitis and a typical rash termed necrolytic migratory erythema.[24] Production of vasoactive intestinal peptide (VIP) or calcitonin by PanNETs can trigger severe life-threatening secretory diarrhoea.[25] Rare clinical syndromes encountered in NETs are caused by ectopic hormone production including hypercalcaemia due to parathyroid hormone-related peptide (PTHrP),[26] the syndrome of inappropriate antidiuretic hormone, Cushing's syndrome due to adrenocorticotrophic hormone[27] and acromegaly caused by growth hormone-releasing hormone.[28]

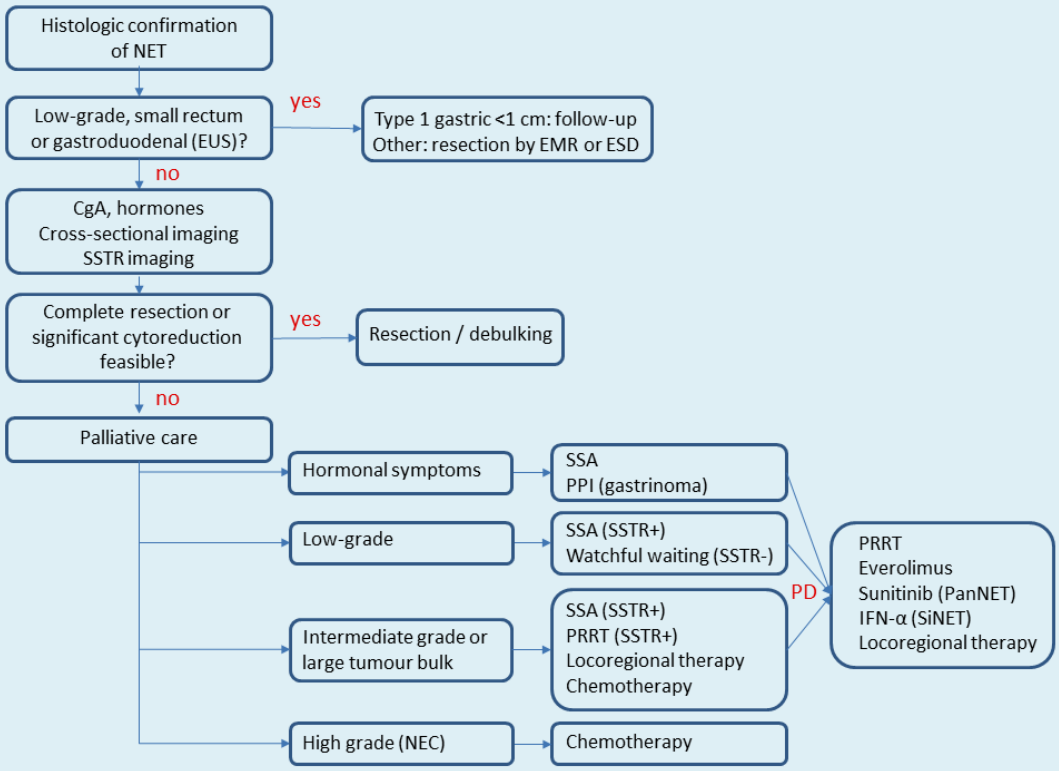
DIAGNOSIS

A diagnosis of NET can be suspected because of incidental findings during endoscopic or cross-sectional imaging or following symptom-directed investigations into the sequelae of tumour mass or hormone release. Central to the diagnosis of all NETs is histological evaluation of tumour tissue.[29] Primary or metastatic lesions should be biopsied or resected when feasible for confirmation of diagnosis and determination of the tumour grade. Histologically, well-differentiated NETs display an organoid arrangement of cells, with a nesting, trabecular or gyriform pattern and stain positive for neuroendocrine markers, particularly synaptophysin and chromogranin A.[6] These immunohistochemical markers are key to diagnosis and their increased application has likely contributed to the observed rise in incidence of NET.[5] In the case of an unknown primary tumour, staining for TTF1 (lung NET), CDX2 (midgut NET) and ISL-1 or PDX-1 (PanNET) can guide the pathologist and clinician towards a likely source.[29]

When the diagnosis is confirmed, routine measurements of glucose, renal and liver function, calcium and blood cell counts should be accompanied by determination of chromogranin A (CgA) levels and, in case of highly proliferative NET, neuron-specific enolase levels. Sensitivity of serum CgA in NET patients is reported to be 50-90% with an average of 73%,[30-32] but for those patients with elevated levels these markers can be used for follow-up as they may represent changes in tumour volume or biology. Importantly, false-positive findings are frequently encountered, since elevated levels can be caused by medication, most notably proton pump inhibitors, atrophic gastritis or renal failure.[33] As such, clinicians should refrain from CgA measurements for NET screening in patients with a low a priori probability of NET. Hormonal analysis should be guided by symptoms; in the case of an apparent clinical syndrome dedicated investigations are indicated with measurement of the serotonin metabolite 5-hydroxyindolacetid acid in 24-hour urine collection, insulin and C-peptide during hypoglycaemia in a supervised 72-hour fast, glucagon, gastrin, VIP, PTHrP, 24-hour urinary free cortisol excretion, cortisol after 1 mg dexamethasone overnight or insulin-like growth factor 1. If the family history is suspicious or positive for hereditary NET-related syndromes, dedicated genetic testing should be requested accordingly.

Tumour staging for the presence of metastases should be performed in all NETs (*figure 1*). Low-grade gastric or rectal NETs smaller than 1 cm carry an excellent prognosis and for these tumours staging with endoscopic ultrasound will

Figure 1. *Evaluation and management of NET patients*



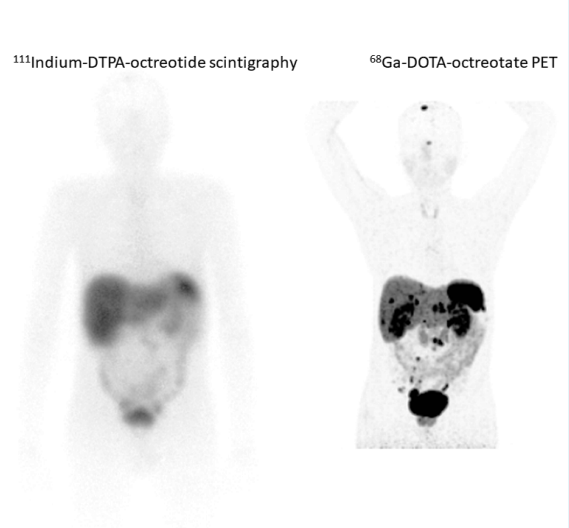
Proposed diagnostic and treatment steps for patients with NET. EUS = endoscopic ultrasound; EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection; CgA = chromogranin A; SSA = somatostatin analogue; PD = progressive disease; PPI = proton pump inhibitor; SSTR = somatostatin receptor; PRRT = peptide receptor radionuclide therapy; PanNET = pancreas NET; SiNET = small-intestinal NET; IFN-α = interferon-alpha.

be sufficient.[34,35] In all other cases, cross-sectional imaging with computer tomography (CT) or magnetic resonance imaging (MRI) is preferred as initial staging.[34-39] On top of this, somatostatin receptor imaging is advised. Low-grade and a subset of high-grade NETs have a high expression of the somatostatin (SS) type 2 receptor (SSTR2A) which can be used for molecular imaging. Following the introduction of somatostatin receptor scintigraphy (SRS) with ^{111}In-DTPA-octreotide (Octreoscan®) in the 1980s, this modality has been extensively used due to its superiority over cross-sectional images for NET.[40] Besides tumour staging, the uptake on scintigraphy can assist in the management of patients, for example for the decision on local or systemic treatment. More recently, dedicated NET centres have adopted the use of ^{68}Ga-DOTA-SS analogue positron emission tomography CT (PET-CT), which is more sensitive and patient-friendly than Octreoscan[41] (*figure 2*). Implementing this diagnostic modality instead of anatomic imaging or Octreoscan® can change management decisions in up to a third of patients.[7] SRS gradually becomes negative in more aggressive tumours such as NECs, limiting their yield in poorly differentiated tumours. Alternatively, glucose metabolism increases in these tumours, making them avid on ^{18}fluoro-deoxyglucose PET imaging.[42] As such, selective PET imaging can be applied according to the tumour grade, whereas some centres even advise to perform imaging with both PET tracers. Additionally, radio-labelled exendin-4, a glucagon-related peptide 1 receptor agonist, has specifically been developed for the detection of insulinomas.

MANAGEMENT

The primary goal of the management of a patient with a NET is cure and consequently the possibility of complete resection should be evaluated.[43,44] For small gastroduodenal NETs or colorectal NETs this might be achieved through endoscopic resection. As an exception, type 1 or atrophic gastritis-related gastric NETs below 1 cm can be managed conservatively with follow-up endoscopy.[34] As many gastroduodenal and colorectal NETs grow into the submucosa, endoscopic mucosal resection or endoscopic submucosal dissection should be employed by an experienced gastroenterologist.[34,35] Many NETs unfortunately present at advanced stages marked by unresectable or disseminated disease, with

Figure 2. *Somatostatin receptor imaging in a patient with stage IV midgut neuroendocrine tumour*



^{68}Ga-SSA PET images are marked by a higher sensitivity than ^{111}In-DTPA-octreotide scintigraphy, which could significantly impact upon clinical decision making.

a predominance of liver and bone metastases.[45] In selected cases of hepatic metastases, especially in young patients, complete surgical resection or ablation can still be attempted as surgical cytoreduction of NET carries an excellent prognosis.[46] If surgical resection is not considered feasible, tailored palliative care should ensue. Again, tumour grading is highly relevant as some grade 1 tumours might not show growth over time whereas most grade 3 tumours require aggressive anti-proliferative treatment.

Treatment of well-differentiated NETs with conventional chemotherapy has little success. For most grade 3 NECs chemotherapy with platinum-based regimens with etoposide is the first-line treatment of choice.[47] Regimens including the DNA-alkylating agents streptozocin or temozolomide have been studied and can be considered for progressive and/or bulky and/or symptomatic intermediate- to high-grade PanNETs and NECs.[48,49] Temozolomide with or without capecitabine has also been studied in single arm or retrospective series of well-differentiated non-pancreatic NETs, where encouraging responses have been observed.[50] The indolent nature in the majority of well-differentiated NETs clearly make them unsuitable for toxic chemotherapy and targeted treatment has been highly desired. Only in the last decade have significant improvements been made in this field based on large, international, randomised clinical trials with hormonal or targeted therapy (*figure 3*).

As stated before, NETs are generally characterised by a high expression of SSTR, although expression levels may vary considerably among tumours and between different types of tumours. To date, five SSTR subtypes have been identified.[51] The SSTR2A subtype is expressed at the highest level and explains the successful application of the somatostatin analogues (SSA) octreotide and lanreotide, which are analogues preferentially binding to SST2, in the medical treatment of patients with NET. Specific treatment of hormonal symptoms started in the 1980s with octreotide, an SSA with a favourable half-life compared with its natural counterpart. Subcutaneous injection of octreotide decreased carcinoid syndrome-related symptoms in the majority of patients.[52] Nowadays, long-acting SSA octreotide and lanreotide are indicated for all patients with carcinoid syndrome in the palliative setting and can be implemented for other NET-related hormonal syndromes.[45] SSTR imaging should be employed to check for tumoral SSTR2A status. Importantly, patients with carcinoid syndrome who undergo surgery should be treated with high-dose intravenous SSA in order to prevent a carcinoid crisis, a state of haemodynamic instability due to the massive release of vasoactive hormones.

At the time of SSA introduction, it was also found that daily interferon-alpha (IFN-α) injections ameliorated hormonal symptoms and produced modest anti-proliferative effects in midgut NETs. IFN-α treatment, however, is accompanied by extensive side effects, most notably flu-like symptoms.[53] For gastrinomas, treatment with proton pump inhibitors successfully diminished acid-related complications and has become the first-line treatment of choice.[23] As somatostatin analogues do not abolish clinical symptoms in all patients with carcinoid syndrome, additional treatment is required beyond toxic cytoreductive strategies. A recently developed drug that inhibits serotonin synthesis, telotristat ethyl, offers novel options as it decreased carcinoid syndrome-associated diarrhoea and flushes in a subset of patients.[54]

Apart from suppression of hormone secretion, clinical observations have shown that SSA may also inhibit tumour growth in patients with NET. This led to the first placebo-controlled, double-blind clinical trial in NET. In the PROMID trial octreotide LAR was compared with placebo in SSTR-positive midgut NET patients; 95% of the tumours were grade 1.[55] Patients receiving the SSA had a median progression-free survival of 14 months as compared with 6 months in the placebo group, whereas overall survival was not affected. This was followed by the CLARINET trial in which patients with SRS-positive enteropancreatic NETs and a Ki67 below 10% were randomised to treatment with long-acting lanreotide or placebo.[56] Lanreotide also significantly delayed progression-free survival to a median of 33 months compared with 18 months in patients receiving placebo.[57]

The use of gamma-emitting radiolabelled SSAs in NET diagnostics paved the way for treatment with beta-emitting

radiolabelled SSAs. Peptide receptor radionuclide therapy (PRRT) has mainly been performed using the radionuclides ^{90}Yttrium-DOTA-octreotide and ^{177}Lutetium-DOTA-octreotate. The latter beta-emitting radionuclide has a favourable safety profile with regard to renal and haematological toxicity and has been applied by most dedicated centres in the last 15 years. After many retrospective series, the first randomised, multicentre phase 3 trial was recently published.[58] The NETTER-1 trial proved the efficacy of PRRT with ^{177}Lutetium-DOTA-octreotate in patients with well-differentiated, SSTR-positive midgut NETs that were progressive on a standard dose of octreotide LAR. Compared with patients on high-dose octreotide LAR patients receiving PRRT had an increase in progression-free survival. Although an objective response was only obtained in 18% of patients treated with PRRT, it predominantly induces prolonged tumour stabilisation. PRRT with ^{177}Lutetium-DOTA-octreotate was well tolerated with mostly transient side effects. Similar survival data have been shown for SSTR-positive NETs of other origins, with the best responses obtained in PanNETs.[59] Besides the anti-proliferative outcomes, PRRT positively affected quality of life, symptoms and functioning in patients.[60] Concerns for long-term sequelae have been raised with reports on increased occurrences of myelodysplastic syndrome and acute leukaemia, but the latest data show that these risks for ^{177}Lutetium-DOTA-octreotate are acceptable at 1.5% and 0.7%, respectively, after a median follow-up time of 64 months.[61] No therapy-related renal failure was observed.

In recent years, we have also seen the advent of oral molecular targeted therapy. As NETs are typically hypervascularized, treatment with anti-angiogenic drugs has also been evaluated for NET. The tyrosine kinase inhibitor sunitinib, which displays activity against VEGF receptors amongst others, has been shown to increase progression-free and overall survival in patients with advanced, well-differentiated PanNET,[62] making this an option for patients with progressive disease. Sunitinib appeared less effective in patients with advanced lung or midgut NETs.[63] The key role of the mTOR pathway in the pathogenesis of NET has fuelled trials with everolimus, an mTOR inhibitor. Growth stabilisation by everolimus has been demonstrated in both pancreatic NETs[64] as well as in lung and gastrointestinal NETs.[65] In two pivotal trials in patients with advanced, well-differentiated, progressive tumours everolimus increased progression-free survival to a median of 11 months compared with four or five months in patients taking placebo.

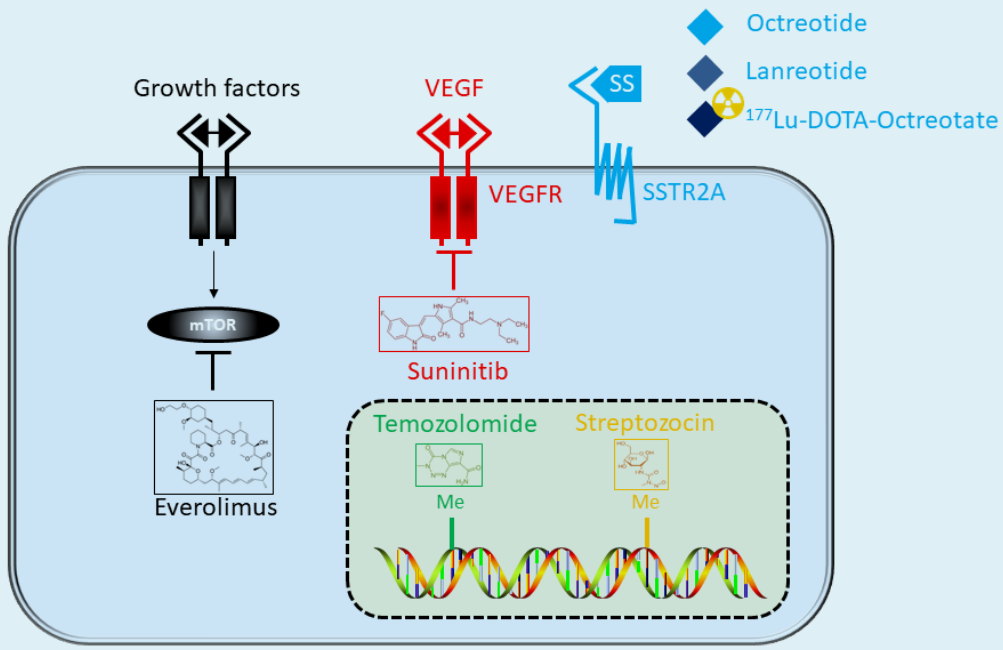
Given the indolent nature of NETs locoregional therapy, particularly targeting the liver, can be administered. Due to the predominant vascular supply by the hepatic artery, NETs are particularly susceptible for treatment with embolisation procedures. Options for treatment of NET metastases include radiofrequency ablation, transarterial embolisation or transarterial chemoembolisation.[66] All three can provide tumour relief and improvement of hormonal symptoms in patients; no large series have compared efficacy between these treatments in NETs. A recent development incorporates radiolabelling of microspheres with ^{90}Yttrium or ^{166}Holmium for local radioembolisation of liver metastases, a technique known as selective internal radiation therapy.[67]

Choices among these different treatment options should preferably be discussed in a multidisciplinary team meeting with participants who have ample experience in dealing with NET (*figure 1*). Advanced non-functioning, asymptomatic, low-grade tumours can be safely monitored with a watchful waiting policy employing longitudinal imaging as a subset of these tumours shows little if any spontaneous growth. In low to intermediate grade or functional NETs that are SSTR positive, treatment with a long-acting SSA is generally preferred due to its tumour-stabilising and anti-hormonal effects accompanied by a good tolerability. In case of tumour progression on SSA therapy the optimal treatment sequence is unclear due to the lack of data. However, the progression-free survival and responses obtained with PRRT appear to exceed that of targeted therapy and at no significant increase of toxicity, making this a reasonable second-line option. Following progression after PRRT or in SSTR-negative tumours, everolimus or in the case of PanNET sunitinib can be administered. Patient characteristics and the ever-changing behaviour of individual tumour lesions should always be taken into account, necessitating a comprehensive view in an experienced multidisciplinary team.

PROGNOSIS

For many years, the lack of specific treatment options for NETs was instrumental in a disappointing outcome and prognosis for patients, despite the indolent nature in a subset of tumours. Consequently, median overall survival for all NETs between 1973 and 2004 was only 75 months.[68] By 2012, these estimates had already increased to up to 112 months, with most notable improvements detected in patients with advanced GEP-NET.[5] Presumably, the availability of improved diagnostic and therapeutic strategies together with the centralisation of care into dedicated NET centres have contributed to better patient outcome. Concerning the latter, several specialised NET centres have published their data on overall survival for stage IV, well-differentiated GEP-NETs which exceeds 100 months.[69,70]

Figure 3. *Treatment targets and options in the NET cell*



Unlabelled or radiolabelled somatostatin (SS) analogues have become key treatment modalities for the control of hormone secretion or growth. Inhibition of the mTOR pathway with everolimus is registered for progressive lung, pancreatic and midgut NETs, whereas the tyrosine kinase inhibitor sunitinib is registered for progressive PanNETs. Alternatively, chemotherapy regimens including the alkylating agents temozolomide and streptozocin present alternatives for progressive or large volume intermediate- to high-grade PanNETs.

CONCLUSION

Several milestones have emerged recently in the NET field with the improvement in understanding of the genetic background, superior diagnostic modalities and the first randomised, multicentre clinical trials. This provides the clinician with emerging options for their patients with a NET, which can improve both survival and hormonal symptoms. We are only at the brink of properly understanding the heterogeneity of this disease and how to predict which patients will respond to particular therapies. Hopefully, further insights into tumour biology, including the epigenetics and control of hormonal stimuli, will pave the way towards optimal patient treatment strategies for NETs in the future.

DISCLOSURES

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REVIEW

Drug-drug interactions with aprepitant in antiemetic prophylaxis for chemotherapy

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ABSTRACT

In the current guidelines to prevent chemotherapy-induced nausea and vomiting, multiple antiemetic drugs are administered simultaneously. In patients who receive highly emetogenic chemotherapy, aprepitant, an NK_1-receptor antagonist, is combined with ondansetron and dexamethasone. Aprepitant can influence the pharmacokinetics of other drugs, as it is an inhibitor and inducer of CYP3A4. Some anticancer drugs and other co-medication frequently used in cancer patients are CYP3A4 or CYP29C substrates. We give an overview of the metabolism and current data on clinically relevant drug-drug interactions with aprepitant during chemotherapy. Physicians should be aware of the potential risk of drug-drug interactions with aprepitant, especially in regimens with curative intent. More research should be performed on drug-drug interactions with aprepitant and their clinical consequences to make evidence-based recommendations.

KEYWORDS

Antiemetic prophylaxis, chemotherapy, drug-drug interactions

INTRODUCTION

Over the last years, great improvements have been achieved in the control of chemotherapy-induced nausea and vomiting (CINV). A new group of antiemetics, the neurokinin-1 (NK_1) receptor antagonists, has been developed. In combination with 5-HT3 antagonists and dexamethasone, this treatment prevents 70-80% of CINV.[1] In the last years the international guidelines of the American Society for Clinical Oncology (ASCO), Multinational Association of Supportive Care in Cancer (MASCC), the European Society of Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN) were updated.[2,3]

The antiemetic regimens implemented in the Netherlands, based on scientific evidence, availability and costs, are shown in *table 1*. Patients on highly emetogenic chemotherapy (> 90% of the patients experience CINV in the absence of antiemetic prophylaxis) receive a standard antiemetic regimen of three medications: ondansetron, aprepitant and dexamethasone. The addition of aprepitant to ondansetron and dexamethasone has significantly increased efficacy in controlling nausea and vomiting.[4-6] With moderately emetogenic chemotherapy (30-90%), the prophylaxis involves a 5-HT_3-receptor antagonist (ondansetron) and dexamethasone. Low emetogenic chemotherapy (10-30%) only requires antiemetics on the day of administration, without specific preference for one class of drugs. When patients experience breakthrough or refractory symptoms another drug can be added, e.g. olanzapine or metoclopramide.[2,3] Olanzapine might soon become part of the standard regimen for highly emetogenic chemotherapy.[7] In patients who have anticipatory CINV or extreme anxiety, lorazepam or another anxiolytic drug can be administered, prior to and during the chemotherapy.[8]

In the international guidelines, several drugs are included in the standard regimens, which are not yet implemented in our national or local guidelines[9] because they are not yet available or not reimbursed due to high costs, such as fosaprepitant, rolapitant, netupitant, palonosetron and NEPA, a combination of netupitant and palonosetron. Fosaprepitant is an intravenous prodrug of aprepitant, which showed non-inferiority of a single intravenous dose of fosaprepitant compared with oral administration of aprepitant for three days.[10] Palonosetron is a newer 5-HT3-receptor antagonist with a longer half-life than ondansetron (40 vs 3 hours), with superior efficacy in moderately and highly emetogenic chemotherapy.[11-13]

Besides the better prevention of CINV, the concurrent use of several antiemetic drugs simultaneously, especially

Table 1. *Emetogenic potential of the most used intravenous chemotherapeutic drugs with the most frequently used prophylactic antiemetic regimen*

Emetic risk	Chemotherapeutic agents	Antiemetic agents	
		Acute phase	Delayed phase
High	Cisplatin (> 50 mg/m²), cyclophosphamide (> 1500 mg/m²), combination of anthracycline-cyclophosphamide	Day 1: 5-HT_3-receptor antagonist and aprepitant 125 mg and dexamethasone 8-12 mg	Day 2-3: Aprepitant 80 mg and dexamethasone 8-12 mg Day 4: Dexamethasone 8-12 mg
Moderate	Carboplatin, cisplatin (< 50 mg/m²), cyclophosphamide (< 1500 mg/m²), cytarabine (> 1000 mg/ m²), dacarbazine, doxorubicin, ifosfamide, irinotecan, oxaliplatin	Day 1: 5-HT_3-receptor antagonist and dexamethasone 8 mg	Day 2-3: 5-HT_3-receptor antagonist and dexamethasone 8 mg
Low	Cytarabine (< 1000 mg/m²), docetaxel, etoposide, 5-fluorouracil, gemcitabine, methotrexate, mitomycin, paclitaxel, pemetrexed, topotecan	Day 1: 5-HT_3-receptor antagonist, or dexamethasone 8 mg, or dopamine-receptor antagonist	

including aprepitant, may pose an increased risk of drug-drug interactions.[14] Here, we will discuss the complexity and clinical significance of possible drug-drug interactions with aprepitant in anti-cancer treatment.

Pharmacokinetic drug-drug interactions due to aprepitant

Aprepitant is a moderate inhibitor of CYP3A4 during the chemotherapy treatment,[15] while after a three-day treatment with aprepitant it induces CYP2C9, and to a lesser extent, CYP3A4.[16] The induction effect is maximum at three to five days after the last dose of aprepitant, and thereafter gradually declines over two weeks.[17] The most important interactions are due to the effect of aprepitant on other drugs, i.e. on the other antiemetics, mainly dexamethasone, on anticancer drugs, and other drugs that are frequently used in this population (painkillers, anticoagulants, and psychoactive drugs) (*table 2*).

Interactions between aprepitant and anticancer drugs

Aprepitant could potentially influence the pharmacokinetics of anticancer drugs that are CYP3A4 or CYP29C substrates. Known substrates of CYP3A4 include cyclophosphamide, docetaxel, erlotinib, etoposide, gefitinib, ifosfamide, irinotecan, imatinib, paclitaxel, tamoxifen and vinca alkaloids. Some of the anticancer drugs are metabolised by multiple CYP enzymes, such as CYP3A4, CYP2B6 and CYP2C9 for cyclophosphamide, and CYP3A4 and CYP2D6 for tamoxifen.[18] Several of these compounds are pro-drugs, e.g. irinotecan, cyclophosphamide and ifosfamide, of these, cyclophosphamide and ifosfamide need the CYP3A4-enzyme to be activated.[19-21] No chemotherapeutic drugs are predominantly metabolised by CYP2D9.[18] Here we will give an overview of the most important current data on potential drug-drug interactions with anticancer drugs.

Several studies have investigated the metabolism of cyclophosphamide during co-administration of aprepitant. Although one of the studies found a greater exposure to cyclophosphamide,[22] no important difference in the exposure of the active (4-OH) metabolite was found, only lower exposure to its neurotoxic metabolite.[22-24]

Aprepitant is suspected to increase the risk of encephalopathy when co-administered with ifosfamide, but just a few case reports and retrospective studies are available.[25-30] Only one case report showed pharmacokinetic data, but these are difficult to interpret.[25] Further studies are needed to confirm this effect on the pharmacokinetics of ifosfamide and a causal relation with an induced risk of encephalopathy. However, if encephalopathy develops during a course containing ifosfamide, a different antiemetic regimen should be considered in subsequent treatment.

The effect of aprepitant on the pharmacokinetics of irinotecan and its active metabolite SN-38 was studied in a pilot study. The maximum concentration and the area under the concentration time curve (AUC) of SN-38 were slightly higher when co-administered with aprepitant (23.5 vs 18.8, and 18 vs 15, respectively), but this difference does not seem to be clinically relevant.[31]

Pharmacokinetic studies of vinorelbine combined with aprepitant showed no difference in AUC on day 1 compared with day 8, excluding a clinically relevant inhibiting effect.[32] Likewise, aprepitant did not influence the pharmacokinetics of docetaxel.[33]

Among the anticancer drugs, not only chemotherapeutic agents are CYP substrates, but also many of the oral

Table 2. *Drug-drug interactions with antiemetics, examples of drugs that are frequently prescribed in cancer patients and of which pharmacokinetic data are available*

Drug	Interaction	Clinical relevance
Dexamethasone *(CYP3A4 substrate)*	2.2-fold increase of the area under the concentration time curve (AUC) of dexamethasone[36]	Dose adjustment: 50% dose reduction of dexamethasone
Ifosfamide *(CYP3A4 substrate)*	Data difficult to interpret[25-30]	Not enough data available
Irinotecan *(CYP3A4 substrate)*	Slight increase of maximum concentration and AUC of SN-38 (active metabolite)[31]	No clinically relevant changes in exposure, no dose adjustments needed
Oxycodone *(CYP3A4 substrate)*	Significant increase of AUC of oxymorphone (active metabolite)[41]	Monitoring for adverse effects
Warfarin *(CYP2C9 substrate)*	Decrease of international normalised ratio (INR) (-14%)[42]	Coumarin derivatives: within normal variation, though recommendation for extra monitoring INR during 2-3 weeks
Ethinyl oestradiol and norethindrone *(CYP3A4 substrate)*	Decrease in AUC of substrates[17]	Use an alternative or back-up method of contraception up during a month
Quetiapine *(CYP3A4 substrate)*	Increase of quetiapine levels, with somnolent state[43]	Consider dose reduction

kinase inhibitors. However, most of them will not often be used concomitantly with aprepitant, due to their lower emetogenic impact. One of these compounds, erlotinib, was shown to have a relevant drug interaction with aprepitant when it was used off-label for pruritus. Erlotinib had a two-fold higher serum level, which could increase toxicity as well as efficacy.[34]

For many other chemotherapeutic agents which are CYP3A4 substrates, there is a theoretical interaction with aprepitant, but no clinical studies have been performed to investigate this effect, for example for doxorubicin, etoposide, gefitinib, imatinib, paclitaxel, vinblastine or vincristine.[35]

Interactions between aprepitant and other antiemetic agents

Due to the moderate inhibition of CYP3A4 by aprepitant, the metabolism of dexamethasone is decreased, leading to a 2.2-fold increase of the AUC of dexamethasone.[36] High-dose dexamethasone gives a high risk of serious adverse effects, such as infections and mental disturbances.[37] In the guidelines, it is recommended that the dose of dexamethasone is decreased by 50% when combined with aprepitant. Pharmacokinetic studies with aprepitant did not reveal a different effect for oral versus intravenous dosing of dexamethasone.[38]

Ondansetron, the other compound of the three-drug combination to prevent CINV with highly emetogenic agents, is also a substrate of CYP3A4, as well as CYP1A2 and CYP2D6.[39] In contrast to dexamethasone no clinically relevant pharmacokinetic interaction was observed when co-administered with aprepitant.[40] This can be explained by the fact that the other CYP enzymes are alternative routes for ondansetron when CYP3A4 is blocked.

Interactions between aprepitant and other medications

Other CYP3A4 or CYP2C9 substrates that are frequently used by cancer patients and therefore could potentially have an interaction with aprepitant include oxycodone (CYP3A4), coumarin derivatives (CYP2C9), and hormonal contraceptives (CYP3A4).[14,35]

In pharmacokinetic studies with oxycodone, its active metabolite oxymorphone had a significantly higher AUC (+34%), but this did not result in more adverse effects (e.g. respiratory depression, sedation, constipation, nausea or vomiting).[41] It seems reasonable not to make preventive dose adjustments, but to monitor patients more closely during combined therapy.[17]

All studies on coumarin derivatives were done with warfarin instead of acenocoumarol or phenprocoumon. From five days after the first administration of aprepitant (three-day schedule), the S-warfarin plasma levels were decreased, with a maximum difference at day 8 (-34%), resulting in a lower international normalised ratio (INR) of -14%.[42] A point of discussion is whether this is a clinically relevant effect, taking into account the normal variation in INR. In daily practice, extra INR monitoring for two or three weeks after aprepitant administration is recommended.

There is also an effect of aprepitant on hormonal contraceptives due to CYP3A4 induction. A pharmacokinetic study showed a long-lasting (three to four weeks) decrease in the AUC of ethinyl oestradiol and norethindrone (> 60%). Patients should be advised to use an alternative or back-up method of contraception for up to one month after the last dose.[17]

Psychoactive agents are often used by patients with cancer, but most of these drugs are metabolised by CYP2D6, so are not susceptible for CYP inhibition or induction due to aprepitant. Quetiapine is an exception of a psychoactive drug that has been demonstrated to have a clinically relevant drug-drug interaction with aprepitant. This drug is a CYP3A4 substrate and has showed higher plasma levels when co-administered with aprepitant.[43]

DISCUSSION

In this review, we give an overview of the potential risk of clinically relevant drug-drug interactions with aprepitant, an NK_1-receptor antagonist. In particular, it can influence the pharmacokinetics of other drugs, including oncolytic drugs, as it is initially an inhibitor and later on an inducer of CYP3A4. When CYP-enzyme induction leads to lower exposure of its substrate, this could theoretically result in loss of effectiveness. The same holds true for enzyme inhibition when a pro-drug needs CYP enzymes to form the active drug. So far, it is not known if this will result in clinically relevant changes during chemotherapy combined with aprepitant. Because it takes several days before enzyme induction reaches its effect, the effect depends on the timing of the different drugs. However, when a serious interaction occurs, this might be unrecognised since pharmacokinetic results are not usually available. In curative regimens, such as bleomycin-etoposide-cisplatin for carcinoma of the testis, this potential risk should be avoided. So far, only a few pharmacokinetic studies have investigated these serious potential interactions. In our hospital, when we suspect an interaction between a chemotherapeutic drug in a therapy with curative intent, we have decided not to use aprepitant until studies have demonstrated that the anti-tumour effects are not decreased.

Apart from the need for more data on the effects of aprepitant, newer NK_1-receptor antagonists, such as netupitant and rolapitant, which interfere less with CYP enzymes compared with aprepitant, might be safer options. Several phase III studies have shown good responses of rolapitant compared with placebo.[44,45] However, no studies were powered to compare the efficacy and safety of aprepitant, netupitant (in the combination with palonosetron as NEPA) and rolapitant.[46] Moreover, for the two newer agents very few studies have been conducted to prove that they might have less impact on the pharmacokinetics, and thus the effect and toxicity, of chemotherapeutic agents. Besides, these agents are not yet available in the Netherlands.

In conclusion, it is crucial that more studies on drug-drug interactions with aprepitant and their influence on pharmacokinetics are performed. Therapeutic drug monitoring of oncolytic drugs could be useful to assess the clinical relevance of the interactions. However, it is crucial that more research is done to define the concentration-effect relationships. This knowledge should then put into perspective the clinical consequences and recommendations for each drug, such as dose adjustments (for example for dexamethasone when co-administered with aprepitant), avoidance or extra monitoring. In the meantime, physicians should be aware of the potential risk of drug-drug interactions with aprepitant, especially in regimens with curative intent. Close collaboration between oncologists and pharmacists is essential for safe drug administrations during chemotherapy.

CONCLUSIONS

Aprepitant, an NK_1-receptor antagonist, is now standard treatment in patients receiving highly emetogenic chemotherapy, combined with ondansetron and dexamethasone. Aprepitant is an inhibitor and inducer of CYP3A4, so it could influence the pharmacokinetics of CYP3A4 substrates, including chemotherapeutic drugs. The new NK_1-receptor antagonists netupitant (in the combination with palonosetron as NEPA) and rolapitant might be safer options, as they interfere less with CYP enzymes compared with aprepitant. However, they do not have EMA approval at this moment. More studies should investigate these potential drug-drug interactions to provide data on their clinical relevance. High awareness of these risks among oncologists and close collaboration with pharmacists could increase the safety of cancer patients receiving highly emetogenic chemotherapy. This is especially true in regimens with curative intention.

DISCLOSURES

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ORIGINAL ARTICLE

Pharmacist interventions during patient rounds in two intensive care units: Clinical and financial impact

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ABSTRACT

Introduction: The risk of prescribing errors and related adverse drug events (ADE) on the intensive care unit (ICU) is high. Based on studies carried out in North America or the UK, a clinical pharmacy service can reduce ADEs and lower overall costs. This study looks into the clinical and financial impact of interventions made by pharmacists during patient rounds in two ICU settings in the Netherlands.

Materials and methods: A quality improvement study was performed in a general teaching hospital (GTH) and a university hospital (UH) in the Netherlands. The improvement consisted of a review of medication orders and participation in patient rounds by an ICU-trained pharmacist. The main outcome measure was the proportion of accepted pharmacist interventions. Secondary outcome measures were the clinical relevance of the accepted interventions, the proportion of prevented potential ADEs (pADE) and a cost-benefit ratio.

Results: In the GTH 160 patients and in the UH 174 patients were included. A total of 332 and 280 interventions were analysed. Acceptance of the interventions was 67.3% in the GTH and 61.8% in the UH. The accepted interventions were mostly scored as clinically relevant, resulting in 0.16 and 0.11 prevented pADEs per patient. The cost benefit was €119 (GTH) and €136 (UH) per accepted intervention.

Conclusion: This clinical pharmacy service in two ICUs resulted in high numbers of accepted and clinically relevant interventions. Our model appeared to be cost-effective in both ICU settings.

KEYWORDS

Adverse drug event, clinical pharmacist intervention, intensive care unit, cost-benefit ratio, cost avoidance, cost saving

INTRODUCTION

As patients and medication are complex on the intensive care unit (ICU), the risk of prescribing errors and related adverse drug events (ADEs) is high.[1-6] Kopp et al.[5] found that the medication errors, leading to preventable ADEs at the ICU occurred mostly at the process of prescribing. 'Lack of drug knowledge' and 'inadequate monitoring' were the most common proximal causes of errors. ADEs are associated with extra treatment needs, extended hospital stay, morbidity and mortality and they induce extra healthcare costs.[7,8] Estimations of the ADE cost price vary from €970, based on a German micro-costing study (extended hospital stay of 2.9 days)[7] to €4395, based on an American study by Bates in 1997[9] (extended hospital stay of 4.6 days).

Over the last 30 years, clinical pharmacists have become part of the multidisciplinary team in the ICU, especially in North America.[10,11] They provide a wide range of

patient care services with the aim of maximising patient safety and optimising patient outcomes.[12-14] Interventions performed by clinical pharmacists significantly reduce ADEs.[15-17] Direct patient care by clinical pharmacists at the ICU is associated with shortened length of hospital stay, lower overall costs and may even contribute to reduced mortality.[18-20] However, these findings are not generalisable as such, since these studies were performed in North America and their setting is different from the European setting. Whereas the American pharmacists have been intensively involved in critical care for many years,[21] in Europe most hospital pharmacies do not have a clinical pharmacy service. As a result Europe has about 17 times less pharmacists, i.e. 1.1 hospital pharmacists/100 beds. In the Netherlands this number is even lower (0.75 hospital pharmacists/100 beds).[22,23]

Despite the fact that over the last decade the involvement of clinical pharmacists in Dutch ICUs is gradually increasing, information about the benefit of their clinical practice is still missing. One way to evaluate this benefit is by measuring the proportion of pharmacist interventions accepted by physicians during patient rounds. Several studies have measured the proportion of accepted pharmacist interventions on the ICU, as part of their study, with outcomes varying from 71-99%.[16,17,24]

In addition, costs in healthcare are increasing fast, so cost-benefit analyses are required to increase the likelihood that implementation of beneficial healthcare services, such as clinical pharmacy, will actually occur. Up to now, only a few European studies have calculated costs of interventions made by clinical pharmacists in the ICU.[16,21,24] All studies were single centre and the economic outcomes differed greatly between these studies.

Therefore, a prospective quality improvement study was performed in two ICUs in the Netherlands with the primary aim to determine the proportion of pharmacist interventions accepted by physicians during ICU patient rounds. Secondary aims were to determine the clinical relevance of the accepted interventions, the proportion of prevented potential ADEs (pADEs) and the cost-benefit associated with the introduction of ICU pharmacists.

MATERIAL AND METHODS

Study design

An interventional, prospective quality improvement study in two different ICU settings was designed. Since the study was considered a quality improvement study, which did not affect patient integrity, Medical Ethics Committee approval was not needed according to Dutch clinical trial law.

Setting

The study was performed in the adult ICUs of the Haga Teaching Hospital (GTH) from July to December 2008 and the ICU of the Erasmus University Medical Centre (UH) from July to September 2011. These periods were several years apart in order to enable the same pharmacist to implement the same clinical pharmacy service in both settings, including an extensive training period in Erasmus MC (see description of the intervention).

The GTH consisted of a 12-bed ICU and the UH of a 36-bed ICU. The UH ICU was divided into two departments, both treating the same types of medical and surgical patients. Both ICUs were closed format and the medical staff consisted of a team of certified intensivists and residents. The UH ICU also trained ICU fellows. In both ICUs, the ICU staff worked according to national and local guidelines. Both ICUs worked with a Patient Data Management System (PDMS). The GTH ICU used Metavision (Itémedical BV, Tiel, the Netherlands) and the UH ICU used Care Suite 8.2 (PICIS Inc., Wakefield, Massachusetts, USA). Both PDMSs offered a continuous collection and display of vital patient data, such as laboratory values and data from medical devices. Both ICUs had a daily patient round. Before the study, pharmacists primarily fulfilled their role for the ICU from the central pharmacy with limited time spent on the ICU, i.e. pharmacists did not have any role in medication preparation, medication order review or medication reconciliation. Their role was limited to consultation on demand by the ICU doctor. Drug delivery and dispensing to the ICU was done by pharmacy technicians.

Study population

Patients were included when they were staying in the ICU during the patient round in which the pharmacist participated. No exclusion criteria were applied.

Description of the pharmacist intervention

Based on a clinical pharmacist model derived from an American clinical skills program, which was previously practised at an internal ward,[25,26] we developed a proactive ICU pharmacist intervention method. This method consisted of collecting medication orders, patient information, followed by an assessment of appropriateness, indication, duration of therapy, drug dosage and frequency, adjustment to renal function, drug-drug interactions, contraindications, drug omissions and duplicate medication. Furthermore the clinical effects of the patient's pharmacotherapy were analysed. A check on missing (prophylactic) medicines was also performed. During the patient round the collected interventions were discussed with the attending intensivists.

The leading pharmacist (NH) was extensively trained at the GTH ICU for 6 months. In the UH this pharmacist took a period of five months to become familiar with the local ICU guidelines and daily routines. Subsequently, she trained three pharmacists prior to the UH intervention period.

During the 6-month study period in the GTH and the 3-month study period in the UH, patient rounds were attended twice a week. Each included patient in the UH was reviewed once a week and in the GTH twice a week.

Primary outcome measure

The primary outcome measure was the proportion of pharmacist interventions that were accepted by doctors.

Secondary outcome measures

Secondary outcome measures were the clinical relevance and the prevented pADEs of the accepted interventions. The clinical relevance of the accepted interventions was assessed retrospectively in two ways: a clinical relevance score (Overhage method)[27] and a pADE score (Nesbit method),[28] both methods are explained in *table 1*. Two assessors – one intensivist (PM) and one hospital pharmacist (BB) with clinical ICU experience – performed both assessments independently. If the two assessors scored interventions differently, consensus was reached in a consensus meeting.

Overhage method: Severity of reasons for intervention and value of service

This validated method from previous research of pharmacists' clinical activities[26,27] classifies each intervention in two ways: A-E for the severity of the reason for intervention and 1-6 for the clinical relevance of the pharmacist's intervention. Before scoring the interventions with this system, a number of adjustments were made in order to make the scoring method more specific for the ICU setting. Specific examples to assist in the proper classification were added. A summary of the instrument, including the specific ICU adjustments, is shown in *table 1*.

Nesbit method: Prevented pADEs

All accepted interventions were given a pADE probability score, according to Nesbit et al.[28] (*table 1*). We assumed that none of the interventions would increase the likelihood of a pADE.

Preliminary cost benefit analysis

Cost savings and cost avoidance were estimated, summed and compared with cost of service, to calculate the net financial impact on the institution and the preliminary cost-benefit ratio. Where necessary, costs were adjusted to 2014 using the general price index of the Dutch Central Bureau of Statistics in 2014.[29]

Costs, cost avoidance and savings were expressed for the intervention period and subsequently extrapolated to one year (annual costs and savings), per accepted intervention and per monitored patient days.

Cost avoidance

Cost avoidance is achieved whenever an intervention, with the potential to prevent or detect an ADE, is accepted. It refers to an intervention that reduces or eliminates additional expenditure that otherwise may have occurred.[15] We measured the cost avoidance by multiplying the Nesbit pADE scores with the costs of an ADE. The ADE cost was derived from a study by Rottenkolber,[7] which utilised a micro-costing approach based on data from German hospitals[18] and was adjusted to 2014.

Cost savings

Potential cost savings refer to reductions in current spending due to changes in the expenditure on patient treatment.[28] We selected all accepted stop and dose reducing interventions and measured the daily drug costs involved, based on the Dutch medication price list.[30] For non-listed drugs, the internal hospital cost price was used and 6% tax was added.[31] Dosage reduction costs were calculated based on the difference in costs between the original and reduced dosage. The daily drug costs were multiplied by the number of days left on ICU.

Costs of service

The direct labour time spent on this intervention was calculated using the bottom up approach, based on the duration of the preparation and attendance of patient rounds and the time for entering intervention information in the database. The time investment related to training prior to the study period was not included in the cost analysis, as this is normally excluded in an economic evaluation.[32] The direct labour time was multiplied by the unit costs of labour and a marginal mark-up percentage to account for indirect labour time (43%).[31] The unit costs of labour were based on standardised costs per hour: €70.81 (GTH) and €70.27 (UH), which equalled the normative income.

Data collection

Patient characteristics

The following patient characteristics were collected from the electronic patient records: age, gender, length of stay on ICU, type of ICU admission (acute or surgical), APACHE IV score (Acute Physiology and Chronic Health evaluation), SAPS II score (Simplified Acute Physiology Score) and finally whether the patient died in ICU.[33]

Table 1. *Classification of pharmacist interventions according to Overhage[27] and Nesbit[28]*

Intervention severity[27]	**Value of service[27]**	**pADE score, Nesbit method[28]**	
Inappropriateness of the prescription or its deviation from the standard of practice	*Potential impact of pharmacist's intervention on patient care*	*Probability of an ADE occurring in the event pharmacist's intervention was not made*	
A =Potentially lethal	1= Extremely significant	**0.6=high**	**Harm is expected, life threatening**, prevented a potentially fatal or severe reaction, e.g. 10x normal dose; narrow therapeutic range, life-threatening reaction/anaphylaxis
B=Serious	2= Very significant		
C=Significant	3= Significant		
D=Minor	4= Somewhat significant		
E=No error	5= No significance	**0.4= medium**	**Harm is expected, clinically relevant**, prevented a potentially serious reaction, e.g. allergy to drug ordered, allergy information, adjustment of renal failure
	6= Adverse significance		
Standard intervention scores			
E3= Results from drug level monitoring	C3= Missing prophylactic drug [i]		
D3= Missing instructions for use	D4= From IV to oral[i]	**0.1=low**	**Some harm is expected, but poorly clinically relevant;** i.e. prevented a potentially significant reaction. 2-4x normal dose, dose inadequate to produce therapeutic effect, incorrect schedule/route with potential for therapeutic failure/toxicity, duplicate therapy with potential for additive toxicity
D4= Missing strength or quantity	D4= Appropriate recommendation, rejected by the clinician due to specific patient conditions unknown by the pharmacist[i]		
D4= Missing drug for non-serious disease			
B2= Any allergy			
E4= Change to formulary drug			
C2/C3= Dosage adjustment on the basis of creatinine clearance		**0.01 = very low**	**Problem orders**, clarifications, missing information etc.
D3/C3= Dosage change after evaluation of initial order for aminoglycoside			
		0 = zero	**Information only**

ADE= adverse drug event; pADE=prevented potential adverse drug event; [i]new.

Intervention characteristics

The following intervention characteristics were collected: drug involved, patient involved, date, intervention description, response prescriber, intervention accepted and three intervention categories:

(1) Reason for intervention

The reasons for interventions were classified as: drug-drug interaction, inappropriate route of administration, wrong drug choice, no indication, omission of therapy, wrong dosage, duplicate medication, contraindication, administrative error and no error/clarification required.

(2) Type of intervention

The interventions were classified as: addition of a drug (start), stopping a drug, dosage increase, dosage reduction, instructions for use, switch of a drug, switch route of administration, correction of an administrative error (i.e. double administration of prescription in PDMS), information only and finally therapeutic drug monitoring and toxicology screening (monitoring). All of these types together, with the exception of 'information only', are defined as recommendation interventions.

(3) Drug involved

The drugs involved were grouped into the following categories: gastrointestinal medication, antimicrobials, sedatives & pain medication, antithrombotics, medication involving the central nervous system (CNS), cardiac medication (including antihypertensives), and a rest group consisting of other drugs.

Furthermore we counted the number of patients per patient round, the number of patient rounds, the number of monitored patient days (MPD), the number of reviews per patient and finally the number of hours the pharmacists spent on the intervention. An MPD was defined as each patient day in the ICU during which the pharmacist reviewed the patient's medication.[16]

Data analysis

Patient data and clinical pharmacist intervention data were entered into SPSS (IBM SPSS Statistics version 21, IBM Corp. New York) for descriptive data analysis.

For the cost-benefit analysis, a one-way sensitivity analysis was performed for known variables in order to determine the effect of varying these estimates on the preliminary cost-benefit analysis:

For varying the labour costs we used the data of a previous study.[32] For varying the salary costs we used the highest senior hospital pharmacist scale and the lowest point on a basic pharmacist scale. For ADE costs we used previously published costs of an ADE[9] and the Dutch costs for 2.9 extra days on the ICU.[7,34] The ADE probability was varied by ± 50%.[9,15] For the cost savings we reduced the maximum effect of a cost saving intervention to 2 days. Finally we measured what the cost-benefit ratio would be in case of poor acceptance, i.e. acceptance of half of the interventions made by the pharmacist (acceptance = 50%) and in case of high acceptance, meaning 100% of the interventions made by the pharmacist were accepted.

RESULTS

Patient, clinical pharmacist service and intervention characteristics

In the GTH, 160 patients were included and in the UH 174. Patient and intervention characteristics are shown in *table 2*.

During the study period 50 patient rounds were attended in the GTH and 33 in the UH, resulting in 367 and 274 MPD respectively. The number of patients reviewed per patient round was almost twice as high in the UH compared with the GTH. Since the GTH had 1 ICU ward, which was visited twice a week, whereas the UH had 2 ICU wards, which were each visited once a week, the number of reviews per patient in the GTH was higher.

Table 3 shows the intervention categories. Omission of a drug was the most frequently occurring reason for intervention (GTH = 20.8% and UH = 23.6%). 'Stop' and 'Start' interventions were scored most.

Table 2. *Patient and clinical pharmacist service characteristics*

Patient characteristics	GTH (n = 160)	UH (n = 174)
Age (years), mean (SD)	63.8 (15.1)	56.4 (16.7)
Sex, female (%)	65 (40.6%)	63 (36.2%)
Length of stay on ICU (days), median (range)	2 (1-57)	2 (1-76)
Emergency admission, n (%)	129 (80.6%)	132 (75.9%)
Surgical, n (%)	71 (44.4%)	71 (40.8%)
Apache IV, mean (SD)	97.4 (33.6)	70.4 (32.2)
SAPS II, mean (SD)	51.8 (18.0)	41.4 (17.9)
Died in ICU, n (%)	60 (37.5%)	37 (21.3%)
Clinical pharmacist service characteristics		
Number of patients per patient round (mean)	7	13
Number of patient rounds	50	33
Number of monitored patient days (MPD) Number of reviews per patient	367	274
1 time	83 (51.9%)	127 (73.0%)
2 times	32 (20.0%)	25 (14.4%)
3 times	18 (11.9%)	11 (6.3%)
> 3 times	26 (16.2%)	11 (6.3%)

APACHE IV = Acute Physiology And Chronic Health Evaluation IV, ICU = intensive care unit, GTH = general teaching hospital, SAPS II = Simplified Acute Physiology Score II, UH = university hospital.

Table 3. *Intervention categories of accepted interventions*

	GTH (n = 198)	UH (n = 157)
Reason for intervention (% of total)		
Omission of medication	46 (23.2%)	31 (19.7%)
No indication	33 (16.7%)	26 (16.6%)
Wrong dosage	28 (14.1%)	37 (23.6%)
Administrative error	27 (13.6%)	3 (1.9%)
No error / clarification requested	16 (8.1%)	19 (12.1%)
Contraindication	15 (7.6%)	9 (5.7%)
Wrong drug choice	10 (5.1%)	14 (8.9%)
Inappropriate route of administration	10 (5.1%)	7 (4.5%)
Drug-drug interaction	7 (3.5%)	4 (2.5%)
Duplicate medication	6 (3.0%)	7 (4.5%)
Intervention type (% of total)		
Stop	56 (28.3%)	56 (35.7%)
Start	49 (24.7%)	32 (20.4%)
Correction of administrative error	21 (10.6%)	3 (1.9%)
Dosage reduction	19 (9.6%)	18 (11.5%)
Monitoring	16 (8.1%)	6 (3.8%)
Switch route of administration	10 (5.1%)	7 (4.5%)
Switch drug	9 (4.5%)	8 (5.1%)
Dosage increase	8 (4.0%)	14 (8.9%)
Dosage instruction	6 (3.0%)	11 (7.0%)
Information only	4 (2.0%)	2 (1.3%)
Drugs involved (% of total)		
Antithrombotics	26 (13.10%)	15 (9.60%)
Gastro Intestinal medication	37 (18.70%)	43 (27.40%)
Antibiotics, antimycotics & antiviral	36 (18.20%)	23 (14.60%)
Sedatives & pain medication	22 (11.10%)	20 (12.70%)
Blood pressure & cardiac	9 (4.50%)	8 (5.10%)
Central nervous system	18 (9.10%)	9 (5.70%)

GTH = general teaching hospital; UH = university hospital.

Twenty-four (18.0%) different drugs were involved in half of the accepted interventions. Most interventions involved prophylactic drugs, such as low-molecular-weight heparin (LMWH) for thrombosis or proton pump inhibitors (PPIs) for stress ulcers, antimicrobials, sedatives and corticosteroids.

In both hospitals, the medication class most often leading to a pharmacist intervention was gastrointestinal (37 interventions [18.7%] in the GTH and 43 [27.4%] in the UH). For example, the pharmacist frequently advised to stop erythromycin (used as a prokinetic medicine, 16 interventions) and PPIs (6 interventions), with the absence of an indication as underlying reason. Additionally, the pharmacist frequently advised to add PPIs (5 interventions) and laxatives (23 interventions) as prophylactic medication. The second medication group most frequently intervened on were antimicrobials (36 interventions [18.1%] in the GTH and 23 [14.6%] in the UH). This group involved

Table 4. *Number and acceptance of interventions*

Intervention	GTH	UH
All interventions	332	280
Recommendation interventions	294 (88.6%)	254 (90.7%)
Accepted recommendation interventions	198 (67.3%)	157 (61.8%)
Patients with at least 1 accepted intervention	79 (49.4%)	93 (53.4%)
Patients with:		
• 0 accepted interventions	81 (50.6%)	93 (53.4%)
• 1 accepted intervention	31 (19.4%)	45 (25.9%)
• 2 accepted interventions	16 (10.0%)	17 (9.8%)
• 3 accepted interventions	14 (8.8%)	5 (2.9%)
• > 3 accepted interventions	18 (11.3%)	14 (8.0%)

GTH = general teaching hospital; UH = university hospital.

22 different drugs. Pharmacists frequently enquired if there was still an indication for prescribing the antibiotic (9 interventions). They also frequently recommended to reduce the dose of antimicrobial drugs in patients with impaired kidney function (13 interventions).

Primary outcome: Acceptance of the interventions

We observed 198 pharmacist interventions accepted in the GTH and 157 in the UH . Acceptance of the recommended interventions was 67.3% in the GTH and 61.8% in the UH (*table 4*).

Clinical relevance and prevented potential ADE scores

The results of the secondary clinical outcomes are shown in *figure 1* and are explained below.

Clinical relevance of the accepted interventions

The majority of issues, leading to accepted interventions (249 interventions), were given a 'significant' score (GTH: 63.6% and UH: 78.3%) (*figure 1*). Examples of 'significant' issues were 'omission of drug' or 'no indication'. One drug-drug interaction in the GTH that led to an intervention was scored as potentially lethal. This interaction involved four medicines, known for their potential to prolong the QT interval (3dd 500 mg erythromycin, 3dd 1 mg haloperidol, 1200 mg continuous amiodarone, and 3dd 20 mg metoclopramide). These medicines were used simultaneously in an 82-year-old male patient with atrium fibrillation and a heart rate varying from 83-129 bpm. The QTc value, after starting erythromycin, was found to be > 500 msec. After the pharmacist's intervention, erythromycin was immediately switched, the metoclopramide stopped and after a few days the amiodarone was stopped. Twenty-one detected issues leading to accepted interventions were given a 'serious' score (7.1% [GTH] and 4.5%[UH]).

The potential impact of the majority of the accepted interventions (268 interventions) was scored as 'significant' (GTH: 77.3% and UH: 73.2%). For 39 accepted interventions (GTH: 11.1% and UH: 10.8%), the potential impact was 'very significant'.

Prevented potential adverse drug events

In the GTH 22.84 pADEs were calculated and this was 17.73 pADE in the UH, leading to a pADE proportion of 0.16 (GTH) and 0.11 (UH) per patient or 0.52 and 0.57 pADEs per patient round.

Preliminary cost benefit analysis and sensitivity analysis

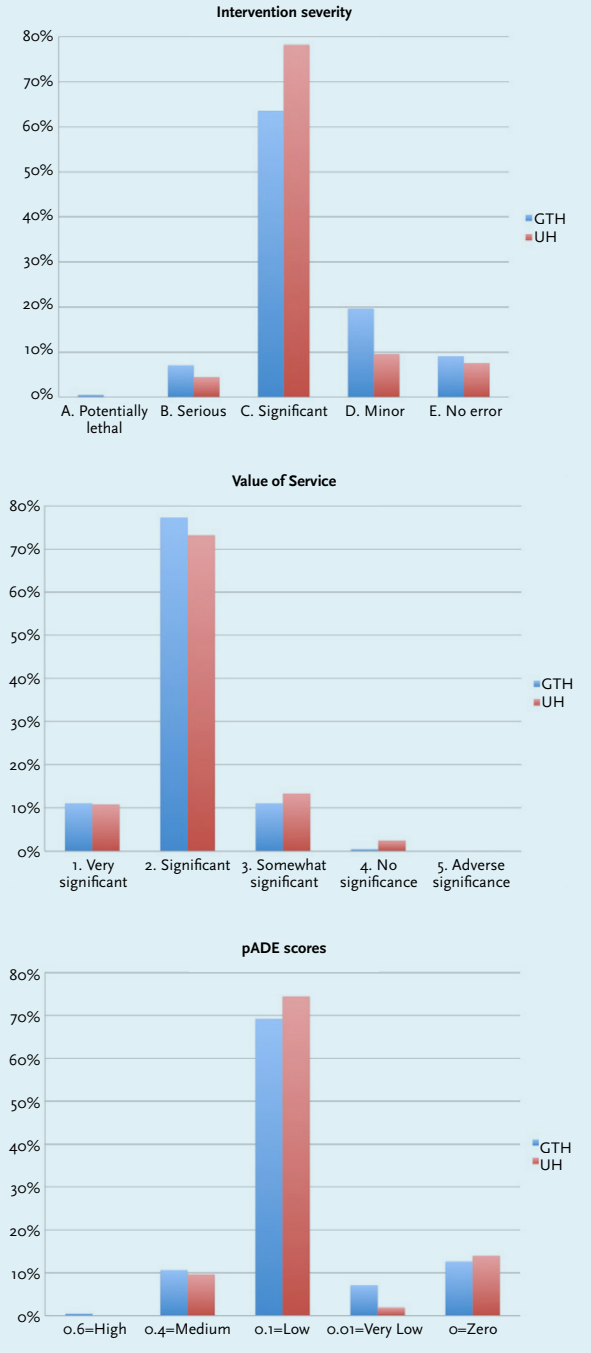
Table 5 shows a positive preliminary cost-benefit ratio of 3.34 (GTH) and 3.23 (UH).

The cost of service was based on 100 (GTH) and 95.1 (UH) direct labour hours spent on the service.

The potential cost savings for medication were based on 77 accepted interventions regarding stopping and dosage reduction in the GTH ICU and 74 in the UH ICU. The multiplied prevented pADE scores, according to Nesbit, were 22.72 (GTH) and 17.64 (UH) respectively and were multiplied by the ADE cost found in literature,[7] which was adjusted to 2014 cost (€1079). This lead to a net cost benefit of €119 (GTH) and €136 (UH) per accepted intervention.

In the sensitivity analysis the cost-benefit remained positive in all measured scenarios. The largest variance was found in cost assigned to an ADE.

Figure 1. *Results of the assessments of clinical relevance (intervention severity and value of service according to Overhage[27] and prevented potential ADE scores, according to Nesbit[28]*



ADE = adverse drug event; GTH = general teaching hospital; UH = university hospital; pADE = potential adverse drug event.

DISCUSSION

To our knowledge, this is the first study looking into the clinical and financial impact of pharmacist interventions in two different ICU settings.

The proportion of accepted interventions in our study was 67.3% in the GTH and 61.8% in the UH. This acceptance was comparable with Klopotowska's study (71%), but lower when compared with American and Belgian research.[15-17,24] Our lower outcome can be caused by the fact that our clinical pharmacy service was relatively new on both ICUs at the time of study. The acceptance rate will probably increase over time when the ICU team and the pharmacists become more adapted to each other. Such a learning curve was found by Klopotowska et al.[16] On the other hand, our clinical model relied on a proactive attitude of the pharmacist during the patient rounds which, as a consequence, led to more 'interfering' interventions the medical staff were unfamiliar with and not always willing to accept. For example, more than half of our interventions were to stop and start interventions. Compared with the literature, these percentages were high.[14,16,17] In contrast, 70% of the interventions made by Leape et al.[17] were more conventional interventions such as 'correction of an order' or 'provision of drug information'. These types of interventions are easily accepted, increasing the overall proportion of accepted interventions.

Our clinical pharmacy model led to a high number of interventions in both hospitals. Compared with Klopotowska's study we found 8 (GTH) to 9 (UH) times more interventions per MPD.[16] In addition, the clinical relevance of the accepted interventions was found to be significant or highly significant in about 85% of the cases. Unfortunately, a direct comparison of the relevance of the interventions between studies was not possible, since rating the clinical relevance of the interventions was not previously done in ICU studies. Nonetheless, compared with a previous study in an internal medicine ward in the Netherlands, the relevance of interventions made in our ICU settings was higher,[26] which can be explained by the critical illness of our patients and their complex poly-pharmacy.

In our study we found a net cost benefit of €119 (GTH) and €136 (UH) per accepted intervention. The cost-benefit ratio remained positive under all conditions examined in the one-way sensitivity analysis. In comparison, Kopp et al.[13] found that the addition of a critical care pharmacist to an ICU generated a cost avoidance of €1497 to €1516 per intervention. This large difference can be explained by the higher cost price used for an ADE (€975 vs. €5999) and the fact that they omitted pharmacist salary expenditures in their study.

Our study had several strengths. It is the first study in ICU patients measuring the acceptance of interventions of a clinical pharmacist service in two different settings. It was a real life, quality improvement study with a considerable number of patients and interventions included, leading to robust results. Finally, clinical relevance and prevented ADEs were determined using a panel consisting of multidisciplinary expertise.

Table 5. *Preliminary cost analysis of pharmacist interventions and sensitivity analysis*

Net cost benefit & cost-benefit ratio		GTH	UH
1.	Costs of service (pharmacist salary)	- € 10,116	- € 9547
2.	Cost savings	€ 5754	€ 10,734
3.	Cost avoidance	€ 28,000	€ 20,134
4. (= 2 +3- 1)	Net cost benefit during intervention period annual (extrapolated) per MPD per accepted intervention	 € 23,638 € 47,276 € 64 € 119	 € 21,321 € 85,284 € 78 € 136
5. (=(2+3):1)	Cost-benefit ratio	3.34	3.23
Sensitivity analysis for cost-benefit ratios			
Time	30 minutes per intervention	2.00	2.20
	15 minutes per intervention	4.00	4.40
Salary	Highest point on hospital pharmacist scale	2.98	3.14
	Lowest point on hospital pharmacist scale	4.77	4.14
ADE probability	50% + 50%	1.95 4.72	2.18 4.29
ADE cost	Based on Bates et al. [9]	18.98	15.15
	Based on 2.9 extra days ICU [7]	17.05	13.68
Cost savings	Lowest point based on 2 days	2.97	2.45
Acceptance	50%	2.45	2.41
	100%	4.75	5.28

ADE = adverse drug event; ICU = intensive care unit; GTH = general teaching hospital; MPD = monitored patient days; UH = university hospital.

Several limitations need to be addressed as well. First, since we did not have a control group in this study, conclusions about the clinical relevance of our model could only be made with caution. But as the main outcome measure was the proportion of accepted recommendations, a control group was not feasible. Second, one could argue that the study was performed several years ago. To date, we are still working in both ICUs in the same manner as was studied, confirming that our study results are still valid. Third, although this study was not a single centre study, conclusions would have been stronger had this study been performed in more than two hospitals over a longer period of time. Finally, the cost-benefit ratio was preliminary and based on a model that estimated cost avoidance of ADEs and estimated prevented costs. For this reason we used the most conservative ADE price.

In conclusion, quality improvement by implementation of a clinical pharmacy service in two different ICU settings resulted in high numbers of accepted and clinically relevant interventions. The service appeared to be cost effective in both ICU settings. This study indicates that this clinical pharmacy service is an effective method for improving patient safety and can be implemented in different ICU settings.

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DISCLOSURES

The authors declare that they have no competing interests. None of them have received honoraria, reimbursement or fees from any pharmaceutical companies in relation to the subject of the study.

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CASE REPORT

Cholesterol embolisms as possible adverse drug reaction of direct oral anticoagulants

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ABSTRACT

The Netherlands Pharmacovigilance Centre Lareb has received two reports of cholesterol crystal embolisms associated with the use of a direct oral anticoagulant (DOAC). The European pharmacovigilance database contains several other cases concerning this association, and one report was published in the scientific literature. Cholesterol crystal embolisms were described in association with the use of several other antithrombotic drugs, although the role as an independent risk factor is not conclusive. The case series described in this article, indicates the possibility of an adverse drug reaction when a patient develops cholesterol crystal embolisms while using a DOAC.

KEYWORDS

Adverse drug reaction, direct oral anticoagulants, cholesterol crystal embolisms

INTRODUCTION

The direct oral anticoagulants (DOACs) dabigatran (Pradaxa®), rivaroxaban (Xarelto®), apixaban (Eliquis®) and edoxaban (Lixiana®) are indicated for the treatment of venous thromboembolisms and prophylaxis of venous and arterial thromboembolisms. Dabigatran directly inhibits thrombin. Apixaban, edoxaban and rivaroxaban inhibit the coagulation factor Xa. Dabigatran and rivaroxaban were granted marketing authorisation in the Netherlands in 2008, apixaban in 2011 and edoxaban in 2015.[1-4]

Cholesterol crystal embolisation (also referred to as cholesterol embolisation syndrome, atheromatous embolisation or atheroembolism), refers to cholesterol crystals originating from an atheromatous core of an atherosclerotic plaque in a large artery, embolising to a distant medium or small artery, leading to mechanical obstruction and inflammation resulting in end-organ damage. Usually several small emboli (microemboli) are released over time. The possible end-organ damage includes renal failure, skin manifestations such as the blue toe syndrome or small cerebral infarctions. The inflammatory response may lead to fever and hypereosinophilia. The diagnostic hallmark is a biopsy showing intravascular cholesterol crystals. Cholesterol crystal embolisation may occur spontaneously or after arterial or other surgical interventions. Thrombolytic and anticoagulant treatment are also associated with cholesterol crystal embolisation, but it is still uncertain whether these are independent risk factors.[5,6]

This article describes cases concerning DOACs associated with cholesterol crystal embolisms from the spontaneous reporting database in the Netherlands maintained by the Netherlands Pharmacovigilance Centre Lareb, the European Pharmacovigilance database EudraVigilance maintained by the European Medicines Agency (EMA), and one case published in the scientific literature. It must be noted that cases from pharmacovigilance databases concern spontaneous reports of possible adverse drug reactions reported by healthcare professionals, manufacturers, patients or others, and the likelihood of a causal relationship can differ between cases.

CASE SERIES

Details of the cases are described below. A summary of the cases is listed in *table 1*.

Table 1. *Cases of cholesterol crystal embolisms associated with direct oral anticoagulants (DOACs), in the Lareb database,[7] EudraVigilance database[8] and scientific literature[9]*

Source [Reference]	Age (or age group)	Gender	Suspect drug(s)	Reported indication	Latency	Reported signs	Biopsy proven	Intervention	Outcome
Lareb database									
[7]	80 years	Male	Dabigatran Edoxaban	Atrial fibrillation	About a week for dabigatran Two days for edoxaban		Skin biopsy	Dabigatran had already been withdrawn, edoxaban was also withdrawn	Not recovered
	≥ 71 years	Male	Rivaroxaban	Atrial fibrillation	Five weeks		Not reported	Not reported	Recovering
EudraVigilance database									
[8]	≥ 71 years	Male	Apixaban	Prophylaxis	About a month	Increased creatinine Increased eosinophil count	Not reported	Dose of apixaban not changed	Not recovered
	≥ 71 years	Male	Apixaban	Prophylaxis	Unknown	Blue toe Renal impairment Increased eosinophil count	Skin biopsy	Statin, prednisolone Action of apixaban not reported	Unknown
	≥ 71 years	Female	Apixaban	Atrial fibrillation	Unknown	Renal impairment Fluctuating hyper-eosinophilia	Renal biopsy	Not reported	Unknown
	≥ 71 years	Male	Apixaban Amlodipine Hydrochlorothiazide / olmesartan	Atrial fibrillation	About eight months	Toe necrosis Aggravated renal failure	Not reported	Withdrawal of apixaban	Unknown
	Unknown	Male	Dabigatran	Atrial fibrillation	Unknown	None reported	Not reported	Not reported	Unknown
	≥ 71 years	Male	Rivaroxaban	Atrial fibrillation	About five and a half weeks after start and one week after withdrawal	Painful, cold, purple left foot	Not reported	Rivaroxaban had already been withdrawn	Recovered
	≥ 71 years	Female	Dabigatran	Unknown	About 7 months	Acute kidney failure Hyper-eosinophilia	Renal biopsy	Withdrawal of dabigatran	Unknown
	61-70 years	Male	Rivaroxaban	Atrial fibrillation	About two and a half months	Aggravated renal failure	Renal biopsy	Prednisolone Action of rivaroxaban not reported	Not recovered
Scientific literature									
[9]	79 years	Male	Dabigatran	Atrial fibrillation	Six weeks	Acute renal failure Elevated peripheral eosinophils	Renal biopsy	Methylprednisolone Withdrawal of dabigatran Haemodialysis	Not recovered

Cases received by Lareb

The Netherlands Pharmacovigilance Centre Lareb received two reports of cholesterol crystal embolism associated with the use of a DOAC.[7]

One case concerned an 80-year-old male. The medical history included aortic graft surgery, myocardial infarction treated with coronary angioplasty, multiple transient ischaemic attacks and atrophy of the left kidney. About one week after starting a DOAC (initially treatment with dabigatran and after five days replacement by edoxaban) for atrial fibrillation, the patient noticed blue discolouration of the toes. At physical examination blue toes and levido reticularis were seen, and the possible diagnosis of cholesterol crystal embolisms was suspected. Laboratory evaluation revealed leucocytes of 7.0 x 10^9/l with slightly elevated eosinophils of 0.7%. Blood creatinine had increased from 140 to 230 µmol/l, with a decrease of MDRD from 41 to 22 ml/min/1.73 m^2. Urinary analysis showed no proteinuria and no urinary sediment abnormalities. At kidney ultrasound there were no visible changes compared with previous investigation. Skin biopsy was performed, and confirmed the diagnosis of cholesterol crystal emboli. Edoxaban was withdrawn. At the moment of reporting, the patient had not recovered. Concomitant medications were pantoprazole, ezetimibe, metoprolol, losartan and rosuvastatin.

The other case concerned a male in the age group 71 years and older, with cholesterol crystal embolisms following administration of rivaroxaban for atrial fibrillation with a latency of five weeks after start. The patient experienced a blue toe, which spontaneously recovered, while continuing the use of rivaroxaban. Concomitant medications were sitagliptin, glimepiride, amlodipine and atorvastatin.

EudraVigilance cases

When excluding the Lareb cases, the European Pharmacovigilance database EudraVigilance contained another eight strongly supportive cases of a DOAC associated with cholesterol crystal embolisms.[8] The reports concerned six men and two women. Ages varied from 70 up to and including 81 years (mean and median 78 years), where in one report only the age 'in his 70s' was reported and in one patient age was unknown. Suspect drugs were dabigatran in two reports, rivaroxaban in two reports and apixaban in four reports. In one report amlodipine and hydrochlorothiazide were also mentioned as suspect drugs. In the other seven reports the DOAC was the single suspect drug. Other possible causes of cholesterol crystal embolisms such as arterial or other surgical interventions were not described in the reports. Latencies were reported in five cases, varying from one month to eight months after start of the DOAC. One report described that cholesterol crystals were observed in a skin biopsy specimen, and three other reports in a kidney biopsy specimen. In three reports the presence of eosinophilia was mentioned.

Case in scientific literature

In the scientific literature one other case was described of cholesterol crystal embolisms associated with the use of a DOAC. This case concerned a 79-year-old male, whose medical history included hypertension and hyperlipidaemia, who developed acute renal failure six weeks after start of dabigatran for atrial fibrillation. Peripheral eosinophils were elevated. Renal biopsy showed cholesterol embolisms. Dabigatran was withdrawn. Renal function did not recover.[9]

DISCUSSION

Cholesterol crystal embolisms were described in association with the use of several other antithrombotic drugs including heparin, low-molecular-weight heparin, warfarin, and thrombolytic therapy.[10-13] The cholesterol embolisation syndrome may occur four to eight weeks after anticoagulation therapy in patients with underlying atheromatous disease.[14]

The role of anticoagulants as an independent risk factor for cholesterol crystal embolisms is, however, not conclusive.[15-17] An article by Tunick et al. retrospectively described the outcome of 519 patients with severe aortic plaque on transoesophageal echocardiography, treated with statins, warfarin or antiplatelet medication. In this study the atheroemboli syndrome occurred in five patients, where only two patients were taking warfarin.[18] Furthermore, an article published in 1987 described a review of 221 cases from the literature with histologically proven cholesterol crystal embolisation. The possible predisposing factor of the use of anticoagulants was reported in 30 patients.[19]

A postulated mechanism on how anticoagulants may induce cholesterol embolisms is by inducing haemorrhage in an atheromatous plaque, or by dissolution of the fibrous cap around the atheromatous core, resulting in the release of cholesterol in the systemic circulation.[13]

Because cholesterol crystal embolisms can occur spontaneously, a coincidental effect of starting a DOAC and spontaneous cholesterol crystal embolisation in the described cases cannot be ruled out, but the time relationships after start of the DOAC in the described cases, supported by a possible mechanism, indicate a possible causal relationship between treatment with a DOAC and cholesterol crystal embolisation.

It is important to realise that when a patient develops cholesterol crystal embolisms while on therapy with a DOAC, this may concern an adverse drug reaction of the DOAC.

DISCLOSURES

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DISCLAIMER

The authors are indebted to the national pharmacovigilance centres that contributed data to the EudraVigilance database, maintained by the European Medicines Agency EMA. The opinions and conclusions, however, are not those of the various centres, nor of the EMA. The information originates from a variety of sources, and the likelihood that the suspected adverse reaction is drug related can vary between cases.

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CASE REPORT

A rare cause of dysregulated metabolic syndrome: cortisol-producing adrenocortical carcinoma

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ABSTRACT

Adrenocortical carcinoma is a rare and highly malignant disease which can cause hypercortisolism leading to dysregulation of blood pressure and glucose levels. Most patients present with advanced disease. We describe the classic presentation of a functional adrenocortical carcinoma in a patient with metabolic syndrome.

KEYWORDS

Adrenocortical carcinoma, hypercortisolism, metabolic syndrome

What was known on this topic?
Adrenocortical carcinomas (ACCs) are rare and frequently aggressive tumours that may be functional (hormone-secreting) and cause Cushing's syndrome and/or virilisation, or non-functional and present as an abdominal mass or as an incidental finding.

What does this add?
Since cortisol-producing ACC, and Cushing's syndrome in general, can mimic the dysregulation of more frequently seen chronic disorders as hypertension and diabetes, we want to remind clinicians that hypercortisolism might underlie this dysregulation.

CASE REPORT

A 75-year-old woman was referred to our hospital because of malignancy with liver metastases suspicious for hepatocellular carcinoma, as determined by CT scan and biopsy. She was known with type 2 diabetes since 2008, until recently well-regulated with dietary measures only. However, in the past months, she was admitted to the referring hospital twice because of congestive heart failure and hyperglycaemic deterioration with an Hb1ac level of 116 mmol/mol, for which metformin and insulin glargine were started. She was taking several antihypertensive drugs (metoprolol, spironolactone, amlodipine and valsartan). Her symptoms at presentation included severe muscle weakness, leading to wheelchair dependency in one month. On clinical examination the patient appeared frail with proximal muscle weakness and haematomas localised at her right breast and arm after a recent collapse. Centripetal obesity and peripheral oedema were present. Blood pressure was 170/95 mmHg, pulse rate 86 bpm and her BMI was 34.3 kg/m^2. Laboratory testing showed: potassium 1.6 mmol/l (reference values 3.5-5.1), sodium 148 mmol/l (136-145), fasting glucose 14.6 mmol/l (4.0-6.1), phosphate 0.19 mmol/l (0.80-1.40), AST 109 U/l (< 31), LD 1381 U/l (< 247) and gamma-GT 964 U/l (< 38). A severe metabolic alkalosis was seen with a pH of 7.61 (7.35-7.45) and a bicarbonate of 47 mmol/l (21-27). Re-evaluation of the CT scan performed elsewhere identified a right-sided adrenal mass invading the right renal vein, inferior vena cava and right liver lobes (*figure 1*), suspicious for adrenocortical carcinoma (ACC) with liver metastases. Pulmonary embolisms were also detected. Additional hormonal testing yielded a serum cortisol level of 2180 nmol/ (200-800), a midnight salivary cortisol level of 339 nmol/l (< 2.8), elevated urinary cortisol excretion at 6232 nmol/24 hours (< 133) and a suppressed adrenocorticotrophic hormone (ACTH) concentration of 1.2 pmol/l (1-55). The serum steroid profile showed increased steroid precursor levels, including androstenedione, progesterone,

Figure 1. *CT abdomen of the patient shows a right-sided adrenal mass, invading the right renal vein, inferior vena cava and right liver lobes, and liver metastases*

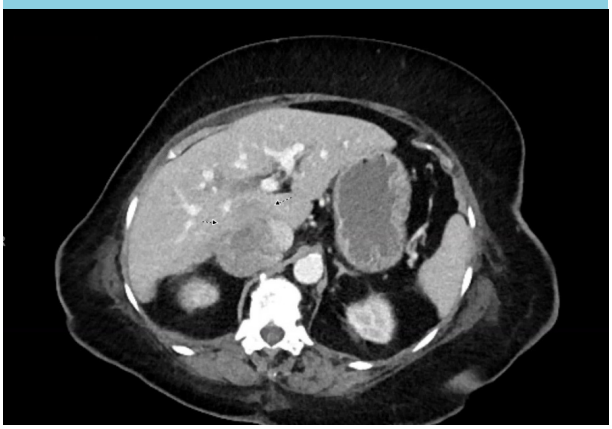
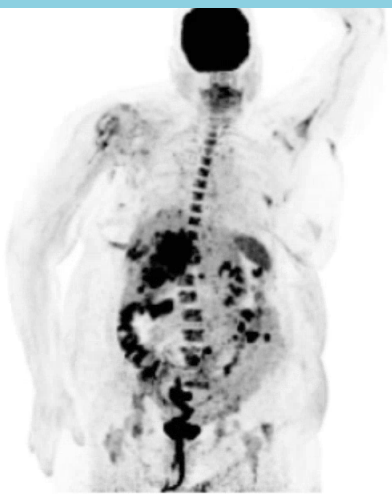


Figure 2. *FDG PET-CT shows greatly enhanced uptake in the right adrenal gland and liver metastases*



17-hydroxyprogesterone, testosterone and oestradiol, while aldosterone levels were suppressed; 24-hour urinary excretion of (nor)metanephrines was not elevated. High uptake in the adrenal tumour and liver metastases was shown on the ^{18}F-fluoro-deoxyglucose positron emission tomography (FDG PET)-CT (*figure 2*). After revision by our pathologist, the liver biopsy was concordant with an ACC with positive Melan-A and synaptophysin staining and a Ki67 index of 20%. In summary, our patient was diagnosed with a stage IV ACC producing cortisol, androgen and oestrogen. Because of her poor performance status she was deemed ineligible for surgery, mitotane or intensive chemotherapeutic treatment. Cortisol excess was treated with metyrapone combined with hydrocortisone suppletion (block and replace therapy). Spironolactone was increased from 50 mg once daily to 150 mg twice daily combined with potassium supplements to treat hypokalaemia. Three days after starting block and replace therapy a biochemical response was seen as evidenced by normalisation of the blood pressure, a lower insulin dose requirement and resolution of alkalosis. Treatment with low-molecular-weight heparin was started for pulmonary embolism. The patient was discharged to a palliative care facility.

DISCUSSION

ACCs are rarely seen with an incidence of 1-2 per million persons/year. Less than 5% of adrenal incidentalomas appear to be ACCs.[1] In adults, ACCs typically present in the fourth to fifth decade as a sporadic tumour, more often in women than in men (male female ratio 2:1). Approximately 60% of ACCs are functional causing a clinical syndrome as a result of an excess of cortisol, androgens, oestrogens or rarely aldosterone. ACTH-independent Cushing's syndrome caused by autonomous cortisol production is most frequently seen (45%) whereas less than 10% of patients present with virilisation alone.[2] The morbidity of Cushing's syndrome can be classified into metabolic, cardiovascular, musculoskeletal, infectious, reproductive, dermatological and neuropsychiatric manifestations.[3] Glucose intolerance is primarily due to stimulation of gluconeogenesis by cortisol, direct suppression of insulin release and peripheral insulin resistance caused by progressive centripetal obesity.[4] Direct stimulation of the mineralocorticoid receptor by glucocorticoid excess, exceeding the capacity of 11-beta-hydroxysteroid dehydrogenase type II in the kidney, causes hypertension, hypokalaemia and oedema.[5] This pseudoaldosteronism was also present in our patient, also evidenced by the metabolic alkalosis. Thromboembolic events are frequently seen, caused by both increased plasma concentrations of clotting factors with activation of the coagulation cascade and inhibition of fibrinolysis.[6] Due to clustering of cardiovascular risk factors, patients are at risk for cardiovascular events.[7] Proximal muscle weakness and osteoporosis are caused by the catabolic effects of hypercortisolism on skeletal muscles and bone, respectively. An increased risk of infections is the result of immunosuppressive effects. An important clinical clue to the presence of hypercortisolism is the simultaneous development and increasing severity of several of the aforementioned symptoms causing considerable morbidity.

Non-functional ACCs are often discovered as incidentalomas. When an ACC is suspected, hormonal evaluation should always be performed, including fasting blood glucose, serum potassium, cortisol, ACTH, 24-hour

urinary free cortisol, dexamethasone suppression test, aldosterone, renin, dehydroepiandrosterone-sulphate (DHEAS), androstenedione, testosterone, 17-hydroxyprogesterone and, on indication, oestradiol in men and postmenopausal women. It is also recommended to measure plasma or urinary (nor)metanephrines to exclude pheochromocytoma.[1] A CT scan can usually distinguish adenomas from ACCs; however, with magnetic resonance imaging local invasion of veins can be identified more precisely. Most ACCs are greater than 4 cm when discovered. Since the liver, lungs, lymph nodes and bones are the most common sites of distant metastases, a CT thorax/abdomen is included in the diagnostic work-up. The role of FDG PET-CT needs to be further determined but studies using PET/CT to compare malignant lesions with adenomas show a high sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 98%, 97%, 100%, respectively.[8] Fine-needle aspiration biopsy is only recommended when an adrenal metastasis of another malignancy is suspected. For histopathological examination, the Weiss system is most commonly used.[9] Ki67 proliferation index as determined using immuno/histochemistry has consistently been related to prognosis.[10] Staging of ACC patients is performed with the ENSAT 2008 staging system.[1]

At presentation, approximately 50% of adult patients have advanced stage III or IV disease.[11] In a palliative or metastasised setting mitotane monotherapy can be considered in patients with low-grade disease, late recurrence or those unfit to undergo chemotherapy. However, a survival benefit has not been proven.[12] Patients undergoing mitotane treatment can experience substantial toxicity, mostly gastrointestinal and neurological, also due to the small therapeutic range of this drug. For patients with aggressive tumours and WHO performance score 0-1, combination chemotherapy including etoposide, doxorubicin and cisplatin with mitotane is advised based on the FIRM-ACT trial that revealed a slight progression-free survival benefit of this regimen over streptozocin with mitotane.[13] In case of Cushing's syndrome, tumour debulking or treatment with metyrapone or ketoconazole, next to the cortisol-lowering effects of mitotane, can be necessary to block adrenocortical cortisol synthesis.[2] Suppletion with hydrocortisone might be necessary on indication. Radiation therapy can be helpful in palliating pain. Overall, the prognosis of ACC is poor with a five-year survival of approximately 55 to 65% for early stage and 10 to 25% for advanced stage disease.[14]

Our case shows a rare cause of worsening of a pre-existing metabolic syndrome with sudden dysregulation of hypertension and diabetes as the clue to the underlying cortisol-producing ACC. Cushing's syndrome is rare and the diagnosis is often delayed because part of its morbidity, namely the metabolic syndrome, has a high prevalence in the general population. The typical combination of Cushing's syndrome features or sudden worsening of symptoms should prompt the clinician to consider hypercortisolism as underlying cause. Since severe hypercortisolism can be lethal, it is essential to start appropriate treatment quickly.

DISCLOSURES

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PHOTO QUIZ

Dystrophy of the fingernails: a diagnostic clue

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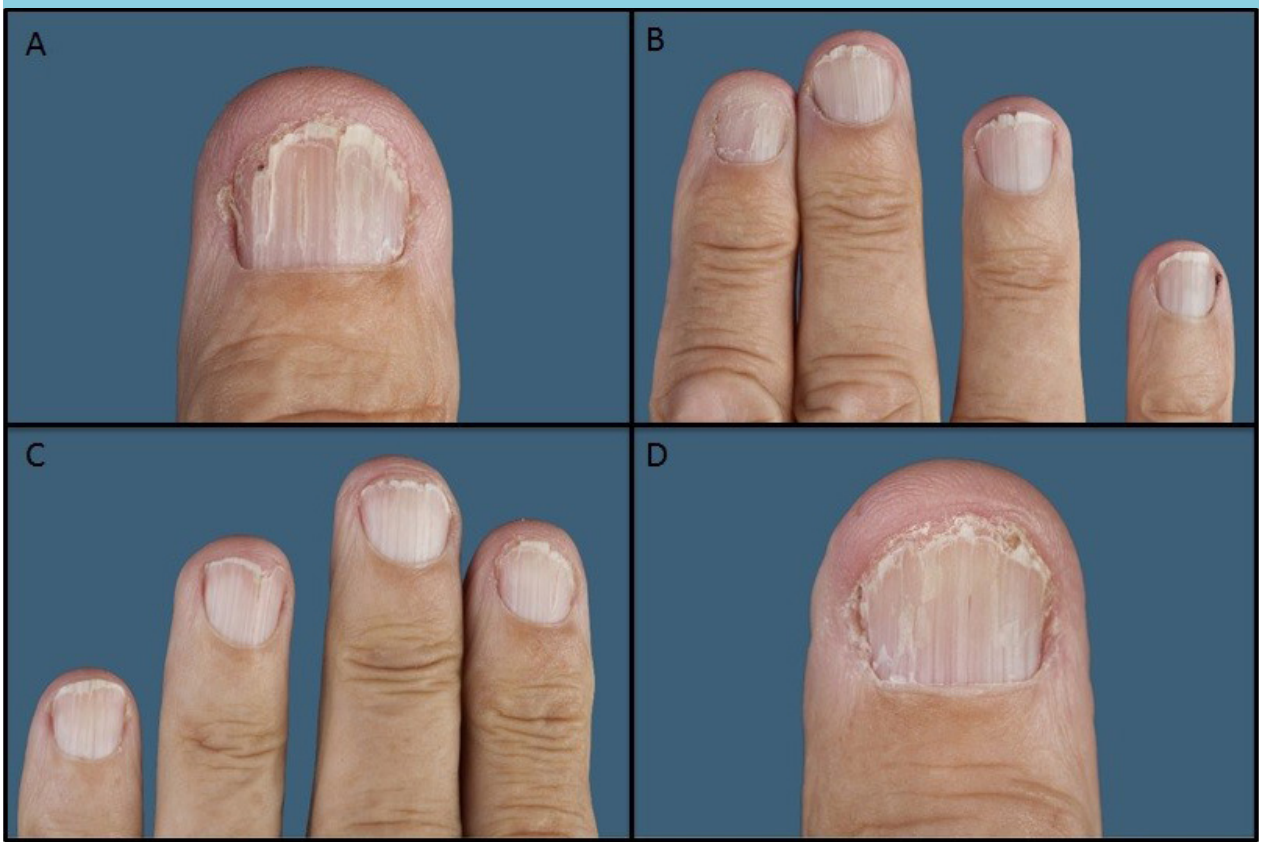
CASE REPORT

A 69-year-old male with a history of monoclonal gammopathy of unknown significance (MGUS) IgM lambda was first evaluated for dyspnoea on exertion in 2014. At that time, this was attributed to mild pulmonary hypertension caused by diastolic heart failure of unknown origin. One year later his dyspnoea was rapidly progressive and he was re-evaluated. Physical examination showed strikingly thin and brittle fingernails on both hands, with longitudinal ridging (*figure 1*). Echocardiography and cardiovascular magnetic resonance were performed.

WHAT IS YOUR DIAGNOSIS?

See page 133 for the answer to this photo quiz.

Figure 1. *Thin and brittle fingernails in a 69-year-old male patient. (A) right thumb, (B) fingers of the right hand, (C) fingers of the left hand, (D) left thumb*



ANSWER TO PHOTO QUIZ (PAGE 132)

DYSTROPHY OF THE FINGERNAILS: A DIAGNOSTIC CLUE

DIAGNOSIS

Echocardiography and cardiovascular magnetic resonance imaging showed signs of amyloid cardiomyopathy. Congo red-stain of abdominal fat pad aspirate samples revealed apple-green birefringence. Since IgM lambda and free light chains (FLC) lambda were elevated, amyloid light-chain (AL) amyloidosis was diagnosed. Additional bone marrow examination showed a lymphoplasmocytic lymphoma. Since he had both lymphoplasmocytic lymphoma and AL amyloidosis, treatment with bortezomib and dexamethasone was started to reduce the production of amyloidogenic FLC. Unfortunately, neither the FLC count nor the nail dystrophy responded to this treatment before it was discontinued because of side effects. He was then treated with dexamethasone, rituximab, and cyclophosphamide. After an initial flare-up, the FLC count decreased somewhat; however, after several months of treatment it increased again. Subsequently, he was treated with ibrutinib, which was recently approved for lymphoplasmocytic lymphoma. After a short period, he developed atrial fibrillation, a known side effect of ibrutinib, and therefore the treatment was stopped. He suffered from progressive heart failure and died a few months later at the age of 72 years. The appearance of his nails had never improved during treatment.

AL amyloidosis is a rare proliferative clonal plasma cell disorder in which fibrils of monoclonal light chains are deposited in extracellular tissue, such as the heart, liver, kidney or intestines. It is often overlooked at first and diagnosed at a late, irreversible stage. Nail dystrophy is a known but rare clinical finding in AL amyloidosis that is caused by amyloid deposition in the nail bed and nail fold. Early detection of AL amyloidosis, using clinical clues such as nail dystrophy, may enhance treatment options and thereby increase survival in this rare but severe disease.

PHOTO QUIZ

A patient with fever and skin lesions after vacation in South Africa

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CASE REPORT

A 61-year-old patient presented with fever to the emergency department. The fever started six days after she returned from a four-week vacation in South Africa and persisted throughout the day. She had been travelling from Cape Town, via Johannesburg to the northern border of Botswana. She had not taken any malaria prophylaxis nor had she had any vaccinations. During her vacation she had no symptoms. At the emergency department the patient complained of mild headache and localised myalgia in her lower back. Furthermore, she had a fever (38°C) and multiple skin lesions. There were no signs of lymphadenopathy. A vesicular (*figure 1*) and maculopapular rash was seen on both legs. One skin lesion presented with a central necrotic core (*figure 2+3*). The laboratory showed an elevated CRP (40 mg/l), the other laboratory results were unremarkable with normal haemoglobin, leukocytes and platelet count.

WHAT IS YOUR DIAGNOSIS?

See page 135 for the answer to this photo quiz.

Figure 1. *Vesicular skin lesion located on the right upper leg*

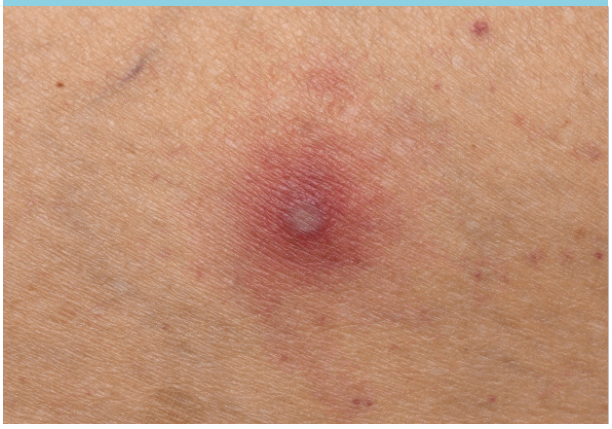


Figure 2. *Maculopapular skin lesion with central necrotic core*

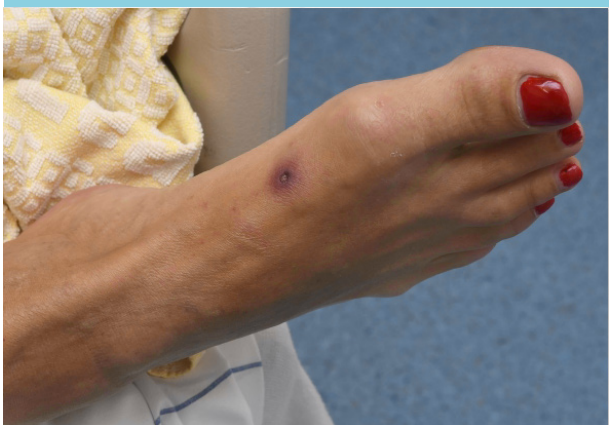
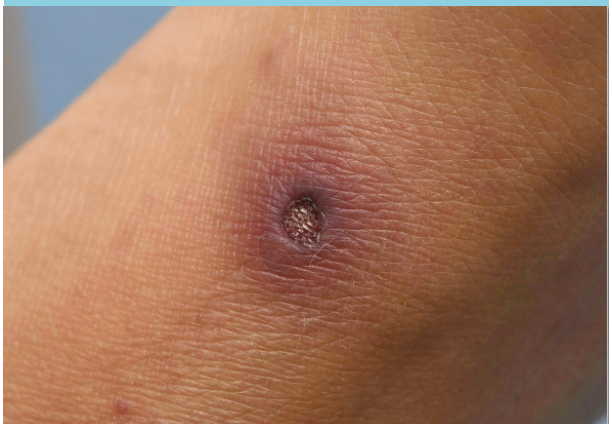


Figure 3. *In detail: Maculopapular skin lesion with central necrotic core*



ANSWER TO PHOTO QUIZ (PAGE 134)

A PATIENT WITH FEVER AND SKIN LESIONS AFTER VACATION IN SOUTH AFRICA

DIAGNOSIS

Eschar lesion due to African tick bite fever.

The diagnosis of African tick bite fever was made because of the specific skin lesion, also known as an eschar. We prescribed doxycycline 100 mg 2dd for 7 days and serological testing for Rickettsial infection was performed. The fever disappeared 48 hours after starting treatment with doxycycline and the skin lesions improved and eventually disappeared. The early phase indirect immunofluorescent assay was negative. Repeat serology after 10 days showed a clear serum conversion, confirming the diagnosis of a Rickettsial infection most probably due to African tick bite fever considering her travel history. A thick blood smear for malaria parasites was repeatedly negative. *Rickettsiae* are gram-negative bacteria divided into several bio-groups. African tick bite fever of the spotted fever group is caused by *R. africae* and generally transmitted by ticks. Serology typically shows an elevated IgG/IgM antibody titre. An elevated IgG ≥ 1:64 or IgM 1:32 suggests the presence of a Rickettsial infection. African tick bite fever is quite common and represents 87% of all Rickettsial infections. With an incubation period of 5-10 days African tick bite fever is often seen in travellers from South Africa with an estimated rate of infection of 4-5% in travellers to rural sub-equatorial Africa. The symptoms are self-limiting within 10 days in most patients. Rash due to Rickettsial infections is quite common and may present as a macular or maculopapular rash and even with a single or multiple eschar(s). Lymphangitis, aphthous stomatitis and arthralgias are known complications of Rickettsial infection. So far no fatal cases have been described. Doxycycline is the treatment of choice for mild disease whereas azithromycin can be used as an alternative prescription.[1-5]

Clinicians should be aware of Rickettsial infection when there are typical symptoms (fever, myalgia, headache, eschar) in combination with a history of travel. Start early antibiotic treatment to reduce the duration of symptoms.

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PHOTO QUIZ

Abdominal pain: diagnosis based on specific CT findings

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CASE REPORT

A 43-year-old man presented to our emergency department for the second time in three days because of abdominal pain, vomiting and lack of defecation. His medical history revealed a sliding hiatal hernia and reflux oesophagitis for which he took pantoprazole 40 mg twice daily. The abdominal pain started in the left lower quadrant four days before the second presentation, but had now spread through the entire abdomen with maximal intensity in the right lower quadrant. Paracetamol and laxatives did not reduce the pain sufficiently. Physical examination did not reveal any abnormalities and he was afebrile. Laboratory tests including liver enzymes, renal function and inflammation parameters were within the normal ranges. Abdominal X-ray showed a normal bowel gas pattern and faecal material. Additionally, an abdominal computed tomography scan was performed (*figures 1 and 2*).

Figure 1. *Abdominal CT-scan – transverse view*

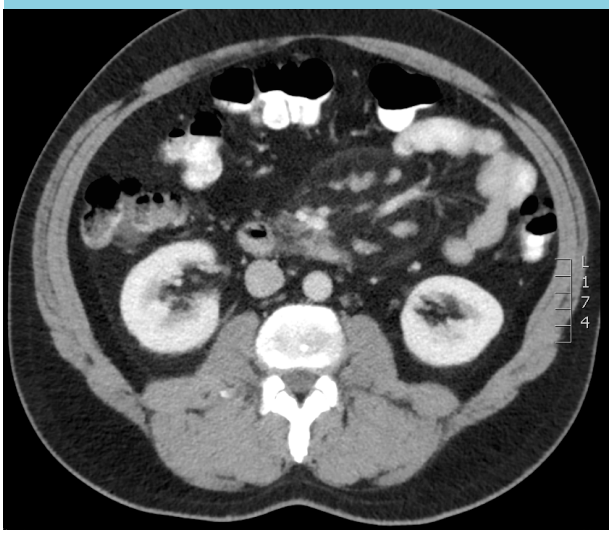
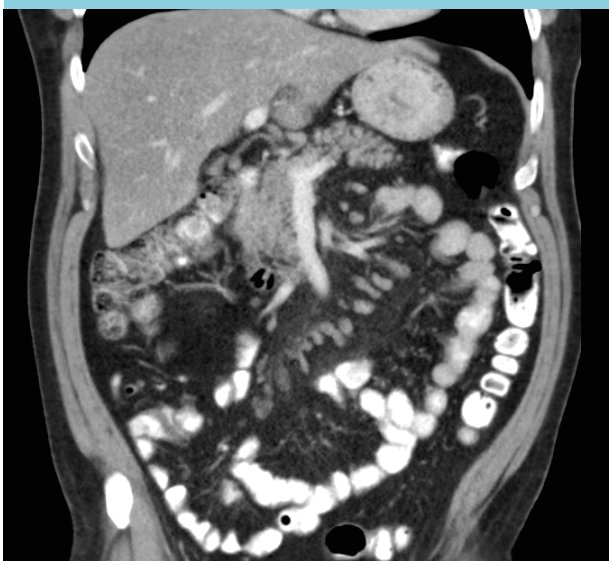


Figure 2. *Abdominal CT-scan – coronal view*



WHAT IS YOUR DIAGNOSIS?

See page 137 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 136)

ABDOMINAL PAIN: DIAGNOSIS BASED ON SPECIFIC CT FINDINGS

DISCUSSION

The abdominal computed tomography (CT) showed increased attenuation of the mesenteric fat – called misty mesentery – with some soft tissue nodules. A misty mesentery is a sign of mesenteric infiltration. This is seen in mesenteric panniculitis, a non-specific inflammatory disorder of the mesenteric fat, which can be either acute or chronic. Mesenteric panniculitis can lead to fat necrosis, fibrosis and retraction of the mesentery. Sclerosing mesenteritis and mesenteric lipodystrophy are synonyms of mesenteric panniculitis.[1,2]

The prevalence of mesenteric panniculitis is 0.6-2.5%, with a male predominance and increasing incidence in the 6th and 7th decade of life.[1-3] Aetiology and pathogenesis are unknown. It may occur independently, but an association with malignancy, autoimmune disease, abdominal surgery or trauma has been suggested.[2,3] Most patients present with aspecific abdominal pain (78%). Other presenting symptoms are fever (26%), weight loss (23%), diarrhoea (19%) or vomiting (18%).[1] It can also be asymptomatic (10%).[1] On physical examination abdominal tenderness (38%) or an abdominal mass (34%) may be present.[1] Laboratory tests may show slightly elevated CRP, leucocytosis or anaemia, but in most cases laboratory tests are unremarkable.[1] Differential diagnosis can include abdominal malignancies such as lymphoma or colorectal carcinoma, or inflammatory processes such as appendicitis, diverticulitis, cholecystitis or pancreatitis.[3]

In most cases, diagnosis is based on abdominal CT. In addition to the misty mesentery, there are two more characteristic abnormalities in mesenteric panniculitis. CT can show a fat ring sign (75-85%), a halo of fat surrounding the mesenteric vessels and nodules, or tumoral pseudocapsule (50-59%), a dense stripe of soft tissue attenuation separating the inflamed mesenteric mass from surrounding normal folds (*figures 1 and 2*).[1,2] However, these findings are not pathognomonic for mesenteric panniculitis. Histopathology is still considered to be the gold standard, but in patients with mild symptoms and a strong suspicion based on clinical presentation and CT findings, a biopsy should be avoided.[4]

Mesenteric panniculitis is mostly self-limiting and the mainstay of treatment is supportive. A wide range of medicines including steroids, colchicine, tamoxifen and antibiotics have been tried, but none have been scientifically proven.[1,2,4] Surgery is indicated in cases with extensive fibrosis and bowel obstruction.[2]

Complications occur in approximately one in five patients. The most common are bowel obstruction, ileus and ischaemia.[1] Approximately 80% of patients have complete resolution of symptoms and CT findings within one year.[1]

The abdominal pain of our patient decreased during his two day stay in hospital. Follow-up abdominal CT after three months still showed mesenteric panniculitis, but the size of the soft tissue nodules had decreased. The patient did not have any symptoms and his weight was stable.

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LETTER

BeCaf study: caffeine and behaviour in nursing homes, a study protocol and EBM training program

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To the Editor,

Medical care in Dutch nursing homes is provided by elderly care physicians (ECPs). The three-year specialist training program for ECPs consists of three training periods in an educational nursing home, three internships, and a theoretical course lasting 100-130 days. Evidence-based medicine (EBM) is taught during the theoretical course. Currently, the EBM training in the ECP program at Leiden University Medical Centre comprises: 1) several lectures on the basics of research and critical reading, 2) the writing of three critically appraised topics (CATs)[1,2] with questions initiated by the trainees themselves, and 3) participation in a group of ECP trainees to analyse an existing dataset and present the results to their peers. Teaching EBM is essential to create lifelong learners who can critically appraise information and assess the applicability of this information for the individual patient.[3] This applies, in particular, to elderly care medicine, due to the underrepresentation of frail elderly persons and nursing home residents in medical research. Although classroom teaching of EBM improves knowledge, clinically integrated teaching improves not only knowledge but also related skills, attitude and behaviour.[4] Compared with traditional teaching, a blended learning approach is more effective in improving the attitude towards EBM and results in a higher self-reported use of EBM in clinical practice.[5] The EBM training is regularly evaluated and updated to maintain a state-of-the-art program. Our latest innovation is the integration of a prospective cohort study assessing the relation between caffeine and behavioural symptoms, and the EBM training program.

Of all patients admitted to Dutch nursing homes, ≥ 50% are diagnosed with cognitive disorders or dementia. In patients with dementia behavioural symptoms are often the main reason for nursing home admission, often due to the heavy burden placed on the caregivers,[6] resulting in a high demand for care. In addition, behavioural symptoms lower the patient's quality of life.[7] Behavioural symptoms are present in ≥ 80% of patients with dementia in a nursing home.[8,9] In patients with dementia the aetiology of behavioural symptoms is complex and thought to be multifactorial.[10] To manage these symptoms, national guidelines recommend a detailed analysis of the patient, including contributing physical, psychological, social and environmental factors.[10] Despite the fact that many pharmacological[11,12] and psychosocial interventions have been studied,[13,14] no standardised solution is available and all interventions targeting behavioural symptoms must be tailored.[13,15]

The Dutch national guideline on behavioural symptoms in patients with dementia mentions caffeine consumption as a possible contributing factor.[10] However, this conclusion is not based on research in patients with dementia or in patients in nursing homes. To date, the only study available on caffeine and behavioural symptoms in older patients with dementia in nursing homes is a small observational study showing an association with apathy, and an inverse association with aberrant motor behaviour and caffeine consumption.[16] On the other hand, the effect of caffeine on behaviour in adults has been widely investigated but the effects differ between individuals, and people normally adjust their consumption of caffeine based on their own experienced (non-)beneficial side effects.[17,18] However, institutionalisation and cognitive disorders tend to impair the ability to self-adjust caffeine consumption. Based on research among healthy adults, both a positive and a negative influence of caffeine consumption on behavioural symptoms can be expected in older patients with dementia in nursing homes. Additional research in larger study populations is needed to gain more insight into the effects of caffeine consumption in older people.

The purpose of the BeCaf study is twofold. The primary aim is to assess the relation between caffeine and

behavioural symptoms (e.g. apathy and agitation) in older patients in nursing homes and to assess factors contributing to this relation. The second aim is to create an educational innovation of EBM training for ECPs, leading to a new EBM curriculum which stimulates trainees' interest in research and integrates research into clinical practice.

In the new EBM program several improvements will be made. First, the basics of research and critical reading will be taught using classroom activities (lectures and part-task practice) and online learning. Second, each trainee will participate in a complete medical study and this study will be embedded in their clinical practice. Writing three critically appraised topics (CATs) remains part of the program. The result is a complete EBM curriculum with research skills introduced in manageable parts, a blended learning approach, and integration of the EBM program in clinical practice.

The BeCaf study is a prospective multicentre cohort study, embedded in the ECP training program during the theoretical course. All trainees are asked to collect data from their own patients, thereby making every educational nursing home a possible centre of study. As the population in nursing homes is highly diverse, a more homogeneous study population was desired, but without limiting the study population to a specific ward or unit; this would allow every trainee, irrespective of their training period, to participate. Therefore, to create a more homogeneous study population, a 'ward transcending' factor was chosen, i.e. diabetes mellitus type 1 and 2. In European nursing homes, 21.8% of patients are diagnosed with diabetes mellitus.[19] A trainee on a full-time contract is supposed to provide medical care for 50-80 patients. For this study, trainees were asked to include all patients under their care who had a diagnosis of diabetes (type 1 or 2); no other inclusion criteria were applied. All participants and educational nursing homes received adequate oral and written information about the study. The study protocol was approved by the Medical Ethics Committee of the Leiden University Medical Centre.

Trainees identify all patients under their care who have diabetes. Data of these patients are collected by the trainees, based on medical records and interviews with the nursing staff. The data are gathered according to the Somatic, Activities of daily living, Social, Psychological and Communication (SASPC) system, a problem-oriented system for multidisciplinary care,[31] which creates a complete overview of the patient. Only reliable and validated instruments are used to collect the data. None of the instruments burdens or bothers the patient in any way. The instruments used are described in *table 1*. After assessment, the anonymised data are entered in a secure online platform (NetQ Healthcare) by the trainees. If any data are missing, the senior researcher contacts the trainee to complete the data. After trainees have formulated a research question, they are only provided with data required to answer their question.

Table 1. *The assessment instruments used*

	Instrument	T0*	T1*	T2*
Somatic	Patient characteristics (incl. advance care planning, blood pressure, heart rate, serum haemoglobin, serum glycated haemoglobin and kidney function)	X	X	X
	Height, weight and body mass index	X	X	X
	Functional comorbidity index[20]	X	X	X
	Medication	X	X	X
	Nutritional data (incl. caffeine consumption, food consistency, and energy-enriched diets)	X	X	X
	Minimum Data Set Resident Assessment Instrument – subscale pain[21]	X	X	X
	Presence of a urinary tract infection in the last 7 days	X	X	X
Functional status/ activities of daily living	Barthel index[22]	X	X	X
	Functional ambulation categories[23]	X	X	X
Social	Date of admission to nursing home	X	X	X
	Marital status	X	X	X
Psychological	Global deterioration scale[24]	X	X	X
	Neuropsychiatric Inventory – Nursing Home edition[25-27]	X	X	X
	Minimum Data Set Depression Rating Scale[28]	X	X	X
	Apathy evaluation scale[29,30]	X	X	X
Communication	Vision	X	X	X

*T0 = baseline; T1 = 2 months post-baseline; T2 = 4 months post-baseline (although not currently part of the study, this measurement will soon be added).

Only a few studies have examined the effects of caffeine among older patients. To our knowledge, our study will potentially include the largest group of older patients with data on their behaviour, cognition and caffeine consumption.

Although EBM is considered essential in practising medicine, obstacles in teaching EBM include: insufficient interest and/or limited time of trainees and faculty, lack of trainee research skills, absence of a research curriculum, and inadequate funding.[32] As this study is embedded in the EBM training program, the above obstacles related to teaching EBM have been tackled. Integration with clinical practice is beneficial for the trainees[4,33] and might also improve the knowledge and attitude of current ECPs.[34]

In conclusion, this is the first large study to focus on caffeine and behavioural symptoms in older patients in nursing homes. If caffeine proves to be related to several types of behavioural symptoms, a relatively simple intervention (such as adjusting caffeine consumption) might prove beneficial and improve the patient's quality of life. Embodiment of this study in the ECP training program serves to update the medical research training program and facilitates a continuous link between education and research.

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LETTER

Much work remains to be done in the intensive care of patients with malignant haemopathies

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To the Editor,

As intensivists of the Groupe de recherche respiratoire en Onco-Hématologie (http://www.grrroh.com/), we have read the review by Kusadasi et al.[1] First of all, we must congratulate the authors on the quality of their work covering a wide range of topics in the management of patients with haematological malignancy (HM) admitted to the intensive care unit (ICU). However, some aspects in the review require clarification or discussion. First, the differentiation between oncology and HM patients seems fundamental. Indeed, the reasons for admission to the ICU, the pathology, the existence of neutropenia, and the prognosis (short and medium term) are not the same.[2] Another major aspect differentiating these patient populations is that administration of chemotherapy in the ICU seems quite reasonable for HM patients, whereas it provides very poor results in patients with solid tumours.[3,4] The terms 'cancer patients' or 'oncological patients,' which are frequently used even in recent studies or reviews, must be banned. This aspect remains unclear in Kusadasi's review, which cites an old study on the reasons for non-admission to the ICU, concerning only patients with metastatic solid tumours (Garrouste-Orgeas et al., 2005, as cited by Kusadasi).[1] The frequent mention of allogeneic bone marrow or stem cell recipients in the review is another aspect that is unclear. In these patients, the policy and the reasons for admission to the ICU, the type of immunosuppression, the pathologies encountered (hepatic sinusoidal obstruction syndrome, graft-versus host disease, thrombotic microangiopathy, etc.), and the prognosis are also probably different from those in other HM patients. Regarding acute respiratory failure (ARF), the leading cause of admission of HM patients to the ICU, we think that more than the ventilatory mode, which is certainly important, the research and the determination of an aetiology seems to be the main prognostic factor of short- or medium-term survival. This was not discussed by the authors but has been demonstrated by Contejean et al.[5] Using multivariable analysis in 604 HM patients with ARF admitted in the ICU, one on the main factors associated with in-hospital mortality was an undetermined ARF aetiology (odds ratio: 2.92 [95% confidence interval: 1.71–5.07]; $p < 0.005$). In this sense, intensivists must not only be organ-support technicians but also be able to make a diagnosis with the help of other specialists (radiologists, pulmonologists, and haematologists). This recommendation is also of value for understudied pathologies, such as digestive or neurological ones, in critically ill HM patients. Further studies should be conducted for critically ill HM patients.

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