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Nephrocalcinosis in Bartter syndrome
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Outcomes of hematological patients on the ICU

“Swelling of the eyelid, what is your diagnosis?”
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Patients with cancer on the ICU:
Time for optimism

E. de Jonge

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Severely ill patients with solid cancers or haematological malignancies are often considered poor candidates for intensive care treatments. Not so long ago, in guidelines for ICU admission, a taskforce of the American College of Critical Care Medicine concluded that patients with haematological or metastasised solid malignancies were poor candidates for ICU admission.¹ In a Dutch study from Nijmegen, published in 1992, it was reported that of 13 patients admitted to the ICU after bone marrow transplant, only one patient survived. The authors argued that physicians should be reluctant to admit these patients to an ICU.²

In this issue of the Netherlands Journal of Medicine, Van Vliet and coworkers, again from the Nijmegen University Medical Center, report a marked improvement of 100-day post-transplant survival in patients admitted to the ICU after haematopoietic stem cell transplantation (HSCT) from 22% in 2004/2005 to 65% in 2008/2009.³ Although these results are from a single-centre study, it is likely that outcomes after ICU admission in haematology patients have also been improving in many hospitals worldwide over the last years. Indeed, in a review of the literature, it was shown that survival of patients after HSCT who received mechanical ventilation improved from lower than 10% in the period before 1990 to 25-50% in the period 1994-2000.⁴

It is possible that the improved survival of critically ill haematology patients is a reflection of an improvement in the quality of intensive care in general. In accordance, the standardised mortality ratio for all non-surgical ICU patients in the Netherlands, adjusted for reason for ICU admission and severity of illness using the APACHE IV model, decreased from 0.94 in 2007 to 0.77 in 2012 [NICE-online, Stichting Nationale Intensive Care Evaluatie; unpublished data]. However, the magnitude of the improvement in survival in patients after HSCT makes it unlikely that improved quality of ICU care can fully explain these findings. Alternatively, the characteristics of patients may have changed with lower severity of illness in patients admitted to the ICU in recent years. Although APACHE II scores were comparable over the years, the mean European Society for Blood and Marrow Transplantation (EBMT) risk scores of patients decreased from 4.0 to 2.8 in most recent years. Moreover, the proportion of patients treated with myeloablative conditioning, which is an established risk factor for mortality, decreased from 78% to 36%.

In patients with solid cancers in need of intensive care, a similar improvement in outcome has been reported in recent years. In a large study in 198 European ICUs, 15% of patients had a malignancy. In ICU patients with solid cancers, hospital mortality was 27%.¹ It should be noted that the prognosis of ICU patients with cancer strongly differs between patients admitted after surgery or for medical reasons. In the Netherlands, hospital mortality was shown to be 45% if patients were admitted to the ICU for non-surgical reasons, compared with 18% for unplanned ICU admission after surgery⁵ and 4.7% in patients admitted to the ICU after elective surgery.⁶ Van Vliet and coworkers clearly demonstrate that prognosis of critically ill patients after HSCT may be good enough to allow admission to an ICU. The most recent survival rate, 65%, is similar to the survival of patients admitted to the ICU for pneumonia.⁷ This, however, strongly depends on the selection of patients who are actually offered ICU treatment. In a recent study in patients with different haematological malignancies, only a minority of which were treated with HSCT, performed in two university hospitals and two general hospitals in the Netherlands, 6.2% of 4275 patients were admitted to an ICU within two years after making the diagnosis. Of these ICU patients, almost 50% died within 30 days and 67% died within 365 days after ICU admission [M.M. Bos, Intensive Care Admission of Cancer Patients: A Comparative Analysis; manuscript submitted]. Selectively offering ICU treatment only to patients with a relatively good prognosis is a two-edged sword. It is
clearly beneficial in terms of cost-effectiveness and may also avoid prolonged treatment in the ICU, with its many discomforts to both patients and relatives, in patients who will not survive this treatment. On the other hand, also in patients with a high risk of mortality, some of them could survive if offered ICU. Selection of patients will inevitably lead to undertreatment and unnecessary deaths in a minority of patients. Optimal selection of patients is hampered by the fact that we do not know how to objectively assess prognosis. We do know that some factors, such as APACHE IV score, mechanical ventilation, and myeloablative conditioning, are associated with a poor prognosis, but we cannot translate this into a quantitative and individual chance of survival. Furthermore, we do not know at what risk of death a treatment should be considered futile. Is that 85%, 95%, 99%? Future research should focus on understanding individual preferences towards life-sustaining treatments related to the likelihood of a favourable outcome as well as on making reliable individual prognosis. For now, we can only conclude that with the present implicit selection criteria that we use, prognosis for patients after HSCT who need ICU has greatly improved over the last years.

REFERENCES

Steroid diabetes: from mechanism to treatment?

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ABSTRACT

Glucocorticoids (GCs) are frequently prescribed anti-inflammatory and immunosuppressive drugs. In addition to their beneficial effects on disease activity, GCs have an extensive side effect profile, including adverse effects on metabolism resulting in the development of glucose intolerance and overt diabetes. Recent developments have led to renewed interest in the mechanisms underlying these diabetogenic effects of GCs. First, dissociated glucocorticoid receptor (GR) agonists were developed which are designed to segregate the anti-inflammatory and metabolic actions of GCs, potentially rendering compounds with a higher therapeutic index. Second, at present, 11-beta hydroxysteroid dehydrogenase type-1 inhibitors are under development. These compounds may lower tissue GC concentrations by inhibiting cortisone to cortisol conversion and are being evaluated in clinical trials as a novel treatment modality for the metabolic syndrome. Here, we provide an up-to-date overview of the current insights regarding the mechanisms responsible for the adverse metabolic effects of GCs that may lead to steroid diabetes. Particularly, we will focus on GC-related induction of insulin resistance and pancreatic islet-cell dysfunction. Finally, we will discuss how increased knowledge concerning the pathophysiology of steroid diabetes may result in improved treatment strategies.

KEYWORDS

Pancreatic islet-cell dysfunction, glucocorticoids, insulin resistance, steroid diabetes

INTRODUCTION

Glucocorticoid (GC) hormones are secreted by the cortex of the adrenal gland, under control of the hypothalamic-pituitary-adrenal axis. GCs are stress hormones that facilitate a flight or fight reaction by providing substrate for oxidative metabolism by increasing hepatic glucose production, adipose tissue lipolysis and proteolysis, and by maintaining adequate blood pressure. In the clinic, synthetic GCs are extensively used in the treatment of numerous disease entities due to their potent anti-inflammatory and immunosuppressive actions when administered at pharmacological dosages. GCs affect both the innate and the acquired immune system. As such, GCs impair the ability of leukocytes to exit the bloodstream and enter sites of infection and tissue injury, resulting in suppression of the inflammatory response. In addition, GCs impair the phagocytic function of macrophages and reduce the production of inflammatory cytokines required for inflammatory responses. Moreover, GCs reduce the activity of the acquired immune system by inducing T-cell depletion, while B-cell function is mostly minimally altered by GC treatment.

GLUCOCORTICOIDS: A BRIEF HISTORY

In 1908, it was first established that ‘substances’ secreted by the adrenal gland were involved in glucose metabolism following studies in adrenalectomised dogs that developed hypoglycaemia. In the following decades, the critical role of the adrenal cortex in intermediary metabolism and energy homeostasis was further characterised. A major advance was made in 1936 with the simultaneous isolation of the inactive form of the adrenal hormone cortisol, known as cortisone, by the Polish-born, Swiss chemist Tadeusz Reichstein and the American chemist Edward Calvin Kendall. This breakthrough enabled further experiments into the various physiological roles of adrenal cortex hormones. The amount of cortisone that could be isolated from bovine adrenal glands, however, was small and the need to produce adrenocorticosteroids through synthetic methods
soon became apparent. This process was fuelled by the US entry into the Second World War, when rumours circulated that Luftwaffe pilots were taking adrenal extracts to increase their resistance to oxygen deprivation at high altitudes. Although this rumour was never confirmed, it induced an all-out quest for large-scale synthesis of active adrenal hormone. In 1946, Lewis Hastings Sarett of Merck Research Laboratories succeeded in synthetically producing cortisone from desoxycholic acid. By the summer of 1948, sufficient material was produced to initiate the first studies in humans. The newly produced cortisone indeed improved the symptoms of Addison’s disease. In addition, rheumatologist Philip Showalter Hench, a friend and collaborator of Kendall, tested cortisone in patients with rheumatoid arthritis. This was driven by observations that joint complaints were reduced by jaundice and that the newly discovered steroid cortisone seemed structurally related to bile acids. Indeed, cortisone treatment induced a spectacular reduction in joint tenderness and swelling in chronic rheumatoid arthritis patients. In the following year, the use of cortisone was successfully introduced in the treatment of other autoimmune diseases. In 1950, the ‘wonder drug’ cortisone was officially launched as a pharmacological agent. In the same year Tadeusz Reichstein, Philip Showalter Hench and Edward Calvin Kendall shared the Nobel Prize for Physiology or Medicine ‘for research on the structure and biological effects of adrenal cortex hormones’. Currently, over six decades later, GCs remain the cornerstone in the treatment of numerous diseases that cover the entire spectrum of internal medicine (table 1).

| Table 1. Common indications for systemic glucocorticoid therapy within the field of internal medicine |
|---------------------------------|------------------|
| Subspeciality                   | Indication       |
| Rheumatology                    | RA*, SLE*, GCA*, PMR*, sarcoidosis* |
| Nephrology                      | Vasculitis/glomerulonephritis* |
| Gastroenterology                | IBD*, autoimmune hepatitis* |
| Haematology- Oncology           | Lymphoma*, multiple myeloma* |
| Infectious diseases             | Meningitis* |
| Pulmonology                     | COPD* |
| Emergency medicine              | Anaphylactic/allergic reactions* |

COPD = chronic obstructive pulmonary disease; GCA = giant cell arteritis; IBD = inflammatory bowel disease; PMR = polymyalgia rheumatica; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

GLUCOCORTICOIDS: ESTIMATION OF DIABETES RISK

The GC-associated risk to develop diabetes is difficult to estimate for a number of reasons. First, patients are often treated with different GC formulations, during widely differing time periods and importantly, at different dosing regimens. Also, patient populations have a large variety of susceptibility to develop hyperglycaemia in part due to the varying indications for GC treatment, different age groups, comorbidities and genetic factors. Finally, since most studies measured only fasting glucose levels, steroid diabetes may go underreported in current literature. In a case control study, a 36% (OR 1.36; 95% CI 1.10-1.69) increased diabetes risk was reported. In an older population (aged >65 years), higher risks were observed (OR 2.31; 95% CI 2.11-2.54). In patients using oral GCs, a dose-dependent increase in the risk to develop diabetes requiring antihyperglycaemic therapy was described, with ORs of 1.36 (95% CI 1.10-1.69) and 5.82 (95% CI 2.74-12.35) for lower (defined as <10 mg prednisolone equivalent) and higher (defined as >25 mg prednisolone equivalent) GC dosages, respectively. In GC-treated rheumatoid arthritis patients and primary renal disease patients, diabetes prevalence ranging between 20-40% was reported, although in the non-GC treated groups, diabetes prevalence was usually also high due to the adverse effect of systemic inflammation on glucose tolerance.

The mechanisms underlying these so-called diabetogenic effects of GCs regarding glucose, lipid and protein metabolism were studied in the 1960-1970s and were mainly attributed to GC-induced insulin resistance at the level of liver, skeletal muscle and adipose tissue. After this period of intensive research on the adverse metabolic effects of GCs, a temporary decline in research on this topic was observed (figure 1).
In recent decades, there has been a renewed interest in the diabetogenic effects of GCs (Figure 1). This has two important reasons. First, there is increasing evidence that endogenous hypercortisolism, whether resulting from chronic stress or excessive production in adipose tissue, may play a role in the development of (visceral) obesity, metabolic syndrome, type 2 diabetes (T2DM) and cardiovascular disease, as postulated by Bjorntorp. This was partly encouraged by the striking resemblance between several features of obesity and the metabolic syndrome and the phenotype of chronic GC excess (Cushing’s syndrome). Indeed, in a number of studies, elevated cortisol levels were demonstrated in T2DM patients and in individuals with cardiovascular risk factors as compared with healthy controls, and were shown to correlate with body mass index and waist circumference. Interestingly, in addition to these subtle changes in plasma cortisol levels, other groups have shown that disturbed tissue GC metabolism, especially in liver and adipose tissue, may also contribute to the current obesity/metabolic syndrome pandemic (as detailed below). Second, increased knowledge regarding tissue GC metabolism and the genomic actions of GCs has led to the development of two novel, distinct classes of therapeutic agents which currently fuel research into the metabolic effects of GCs (see below).

**Pharmacological modulation of glucocorticoid action: dissociated glucocorticoid receptor agonists**

Improved understanding of the genomic actions of GCs has led to the development of novel agents which are devoid of the metabolic side effects, while their anti-inflammatory action is preserved. These compounds are named dissociated glucocorticoid receptor (GR) agonists. In 1985, the GR was discovered. Subsequently, it was shown that GCs exert most of their actions by binding to this intracellular receptor after which the formed hormone-receptor complex migrates to the nucleus to regulate target gene expression. More recently, it became evident that the anti-inflammatory actions of GC drugs are largely mediated by transrepression of target genes, whereas the metabolic effects are mostly mediated by transactivation of genes. Since these genomic actions of GCs have different molecular mechanisms (Figure 2), they may potentially be separated. These findings are at the basis of the novel dissociated GR agonists. Several compounds with a dissociated profile are currently under development by different pharmaceutical companies and have shown promising results in animal models.
Glucocorticoid-induced insulin resistance

Liver

The liver is a key regulator of metabolism, within a complex regulatory network of hormonal, autonomic nervous and metabolic stimuli. Under fasting conditions, the liver maintains euglycaemia by producing glucose through both gluconeogenesis and glycogenolysis. Insulin, which is secreted in response to a meal or carbohydrate load, is the most important hormone that suppresses endogenous glucose production (EGP). On the other hand, the contra-regulatory hormones cortisol and glucagon increase EGP under fasting or hypoglycaemic conditions.55

Pharmacological dosages of GCs administered in the short term to healthy volunteers increased EGP in the fasted state in a number35,39 but not in all studies.50-53 This increase in EGP is driven by GC-induced increment in gluconeogenesis rather than glycogenolysis.35 GCs mainly stimulate gluconeogenesis by promoting the expression and activity of key enzymes of gluconeogenesis including phosphoenolpyruvate carboxykinase (PEPCK)35 and glucose-6-phosphatase. 16 Indeed, the PEPCK gene contains a glucocorticoid response element (GRE) in its promoter region and is considered a key player in GC-induced hyperglycaemia.37 Other mechanisms by which GCs may enhance gluconeogenesis include increased delivery of substrate for gluconeogenesis to the liver through breakdown of peripheral protein and fat stores55 and potentiation of the effects of other glucoregulatory hormones such as glucagon and epinephrine. The most prominent effects of GCs on liver glucose metabolism are evident during hyperinsulinaemic conditions. Both acute and more prolonged GC treatment were shown to blunt the suppressive effects of insulin on EGP by up to 50%.46-47,61 The mechanisms underlying this GC-induced liver insulin resistance are currently not clarified. In rats, dexamethasone was shown to impair the insulin-signalling cascade, leading to reduced activation of insulin target proteins and genes in liver cells.60

Thus, the liver is an important player in the diabetogenic effects induced by GC treatment. This is further illustrated by a study in rats where treatment with a liver-selective GR antagonist resulted in reduced fasting plasma glucose levels and decreased EGP during a hyperinsulinaemic-euglycaemic clamp.62 Of note, GCs also affect hepatic lipid metabolism by increasing very-low-density lipoprotein production and stimulating de novo lipogenesis; however, this topic is beyond the scope of this review and is discussed in detail elsewhere.62

Skeletal muscle

Skeletal muscle tissue is the most important site for insulin-stimulated glucose disposal in the postprandial state and thus plays a crucial role in glucose metabolism.63 Following binding to its membrane-bound receptor, insulin stimulates glucose uptake, glucose oxidation and glycogen synthesis by phosphorylation of several proteins, usually referred to as the insulin-signalling cascade.64

Figure 2. Novel compounds related to glucocorticoid metabolism (simplified scheme)

- Figure 2 shows a simplified scheme of glucocorticoid metabolism and the effects of novel GR agonists on the glucocorticoid receptor (GR) and glucocorticoid response element (GRE).

- The scheme illustrates the interaction of Gr monomers with other transcription factors, leading to gene transcription and the regulation of target genes.

- The transactivation pathway is thought to primarily induce transactivation pathways, whereas the transrepression pathway seems mainly responsible for GC-induced side effects.

- Figure 2 also highlights the mechanisms underlying the classical GC-induced side effects, including cortisol regeneration in tissues and the role of 11-beta hydroxysteroid dehydrogenase type 1 (11-beta HSD1).

- The figure further discusses the potential of novel GR agonists in reducing inflammation without altering glucose levels, along with the need for further development of these compounds for use in humans.

- The mechanisms underlying this GC-induced liver insulin resistance are currently not clarified. In rats, dexamethasone was shown to impair the insulin-signalling cascade, leading to reduced activation of insulin target proteins and genes in liver cells.
Decades ago, cortisol was shown to reduce insulin-stimulated glucose disposal in a dose-dependent manner, a finding that was confirmed in several subsequent studies. GCs particularly impair nonoxidative glucose disposal (reflecting glycogen synthesis), whereas glucose oxidation rates remain intact. Despite the fact that GC-induced skeletal muscle insulin resistance is a well-known phenomenon, the mechanisms involved remain currently incompletely understood.

GCs may reduce skeletal muscle glucose uptake by reducing total skeletal muscle mass through GC-induced atrophy. However, since GCs reduce insulin-stimulated glucose uptake already after short-term treatment in the absence of significant decrements in skeletal muscle mass, direct effects of GCs on insulin-regulated metabolic pathways in skeletal muscle may be more important. Indeed, GCs were shown to disturb the insulin-signalling cascade in rats, resulting in impaired glucose uptake and glycogen synthesis. The mechanisms by which GCs interfere with insulin signalling in skeletal muscle are yet to be elucidated. GCs could directly affect the phosphorylation of proteins involved in the insulin-signalling cascade, or indirectly through changes in lipid and protein metabolism. As such, GCs increase plasma levels of nonesterified fatty acids (NEFA) by impairing the insulin-mediated suppression of adipose tissue lipolysis (detailed below) and increase plasma levels of amino acids due to enhanced proteolysis. Both elevated NEFA and amino acids concentrations are strong inhibitors of insulin-stimulated glucose uptake.

In addition to changes in skeletal muscle cells, GCs may also impair glucose uptake by disturbing the insulin-induced recruitment of capillaries in skeletal muscle tissue. In the last decade, it has become progressively evident that vascular tissue, and particularly endothelial cells, represent an important physiological target for insulin. Insulin exerts a vasodilatory action by promoting nitric oxide (NO) release from the endothelial cells. By recruiting capillaries to expand the endothelial transporting surface available for nutrient exchange, the vascular actions of insulin significantly contribute to overall insulin-stimulated glucose uptake. In our study, a two-week treatment with low-dose (7.5 mg daily) and high-dose (30 mg daily) prednisolone dose-dependently impaired insulin-stimulated capillary recruitment in healthy individuals as assessed by capillary microscopy. Moreover, prednisolone-induced impairment in insulin-stimulated capillary recruitment was related to changes in fasting and postprandial glucose levels as well as insulin sensitivity as measured by a hyperinsulinaemic clamp and standardised meal test.

Thus, GC-induced skeletal muscle insulin resistance is a hallmark of GC-induced hyperglycaemia; however, the alterations within skeletal muscle tissue that induce this effect are unknown. In addition, GC-induced impairment in insulin-related capillary recruitment may also partly account for the reduction in glucose uptake by skeletal muscle.

**Adipose tissue**

Although the adverse metabolic effects of elevated GC levels on glucose and protein metabolism are reasonably well defined, the effects on lipid metabolism and in particular the role of adipose tissue herein are less clear. However, several observations indicate that GCs exert unfavourable effects on adipose tissue.

As such, chronic GC excess in Cushing’s syndrome or during prolonged GC treatment increases fat deposition in the visceral compartment and promotes liver fat accumulation, at the cost of subcutaneous fat deposition which, together with peripheral muscle wasting, causes the well-known Cushingoid phenotype. The GC-induced reduction in subcutaneous adipose tissue (SAT) with concomitant increase in visceral adipose tissue (VAT) is clinically relevant since VAT is well known to be associated with an untoward metabolic profile as opposed to SAT, is metabolically more active and is associated with increased cardiovascular risk. Mechanisms involved in this GC-induced specific alteration in adipose tissue distribution are yet to be clarified.

In addition to altering adipose tissue distribution, GCs may also affect adipose tissue function. Although GCs display lipogenic actions in VAT, they acutely increase fasting lipolysis rates in vitro and in vivo. GC-induced induction of whole-body lipolysis could be explained by increased activity of the key lipolytic enzymes adipose triglyceride lipase (ATGL) and hormone sensitive lipase (HSL) and possibly by augmented beta-adrenergic signalling and results in increased plasma NEFA levels. As mentioned earlier, increased NEFA levels contribute to hyperglycaemia by impairing muscle and liver insulin sensitivity.

In analogy to liver and skeletal muscle, GCs were shown to impair insulin signalling in 3T3-L1 adipocytes in vitro and in human adipose tissue in vivo (Van Raalte et al.; unpublished observations). At the level of adipose tissue, insulin inhibits adipose tissue lipolysis and stimulates triglyceride uptake. We observed that prednisolone treatment dose-dependently impaired insulin-stimulated suppression of lipolysis resulting in elevated plasma NEFA levels during hyperinsulinaemia.

In addition to regulating adipose tissue lipid metabolism, insulin also stimulates adipose tissue glucose uptake. Although the overall contribution of glucose uptake by adipose tissue in the postprandial state is thought to be relatively modest, fat cells contribute to overall glucose tolerance by a cross-talk with liver and skeletal muscle. This is most likely mediated by metabolically active...
factors and hormones that are secreted by adipose tissue, collectively known as adipocytokines. As such, GCs have been shown to alter levels of various adipocytokines both in vitro\(^6\) and in vivo (Van Raalte, et al.; unpublished observations) towards a more diabetogenic profile. Thus, plasma concentrations of adiponectin, which are generally positively associated with insulin sensitivity,\(^5\) were reduced following high-dose prednisolone treatment. The pro-inflammatory adipocytokines resistin and leptin, which are usually negatively associated with insulin sensitivity,\(^5,6\) were both increased by high-dose prednisolone treatment.

In conclusion, GCs diabetogenic effects also involve actions on adipose tissue, i.e. unfavourable changes in adipose tissue distribution and induction of adipose tissue insulin resistance, which result in increased lipolysis, hyperlipidaemia and altered adipocytokine secretion by fat cells.

**Glucocorticoid-induced islet-cell dysfunction**

_**Pancreatic beta cells**_

The pancreatic beta cell plays a crucial role in glucose metabolism and in the past decades, beta-cell dysfunction has been acknowledged as the key defect underlying the development of T2DM.\(^8\) Under physiological conditions, insulin secretion is directly related to insulin sensitivity through a hyperbolic relation. The product of these parameters, known as the disposition index, remains constant.\(^5\) Thus, when the workload on the beta cell increases (by factors such as obesity, insulin resistance or low-grade inflammation), healthy beta cells can adapt by augmenting insulin secretion to meet this increased demand, thus maintaining euglycaemia.\(^6\) Failure of the beta cells to sufficiently secrete insulin to meet insulin demands results in glucose intolerance and T2DM.

**Direct effects of glucocorticoids on beta-cell function: in vitro studies**

GCs were extensively shown to impair insulin secretion in vitro in insulinoma cell lines and in rodent-derived islets. Various aspects of the insulin secretory machinery were inhibited by GCs including glucose uptake and oxidation, membrane depolarisation and calcium-triggered insulin exocytosis. By these combined actions, GCs reduced glucose-stimulated insulin secretion (GSIS), but also inhibited the effects of numerous other insulin secretagogues.\(^1\) In addition to attenuating insulin secretion, GCs impaired insulin biosynthesis and induced beta-cell apoptosis following more prolonged incubation.\(^9\)

GC-induced impairment in the function of the endoplasmic reticulum (ER), a cell organelle responsible for the synthesis of all secreted proteins, most notably insulin, may be critically involved in these conditions. GCs induce ‘ER stress’ which is characterised by an accumulation of misfolded proteins inside the organelle. This ER stress may result in reduced insulin production, but may also trigger beta-cell apoptosis.\(^9\) The detrimental effects of GCs on beta-cell function were further emphasised in mice that developed diabetes through impaired insulin secretion after specific overexpression of the GR in beta cells.\(^9\)

**Effects of glucocorticoids on beta-cell function in humans**

Also in vivo in humans, GCs acutely impair insulin secretion.\(^4\) High-dose prednisolone impaired first-phase glucose-stimulated insulin secretion as well insulin secretion induced by the amino acid and beta-cell membrane depolariser arginine following a single gift as measured by a hyperglycaemic clamp study.\(^9\) At the same GC dose, impairment of beta-cell function during a standardised meal test was also noted, in particular, a reduction in glucose-adjusted insulin secretion (beta-cell glucose sensitivity).\(^6\)

More prolonged administration (maximally up to two weeks) of GCs to healthy volunteers has shown somewhat different results. Due to the induction of insulin resistance, GCs were shown to increase fasting insulin levels and insulin secretion following oral or intravenous stimulation tests.\(^6,5,9,6,8\) This increased beta-cell response, however, does not indicate improved beta-cell function, but rather compensation for GC-induced insulin resistance, which was evident after correction for insulin sensitivity by regression methods or by calculating a disposition index. In many studies in healthy volunteers, unchanged disposition index indicated adequate compensation for GC-induced insulin resistance. However, in susceptible populations, including obese and normoglycaemic insulin-resistant individuals\(^6\) or those with low glucose-stimulated insulin secretion (GSIS)\(^6\) prior to treatment with GCs, GSIS was not enhanced to such an extent to compensate for GC-induced impairment of insulin sensitivity. Thus, in normoglycaemic first-degree relatives of patients with T2DM\(^9\) and obese women,\(^9\) the disposition index decreased following GC treatment.

In addition to glucose-stimulated insulin secretion, we studied the effects of GCs on arginine-induced insulin secretion, which may be a proxy for maximal insulin secretory capacity at a given level of hyperglycaemia.\(^6\) Interestingly, prednisolone dose-dependently decreased arginine-induced insulin secretion.\(^9\) In addition, prednisolone reduced glucose-independent insulin secretion during standardised meal tests\(^9,6\) and impaired insulin secretion induced by the incretin hormones (detailed below).\(^9\)

Thus, GC-induced beta-cell dysfunction is a hallmark of GC-induced hyperglycaemia; however, the effects are dependent on the duration of treatment, population exposed and the specific beta-cell parameters that are
investigated. Finally, additional evidence for a role of beta-cell function in GC-induced diabetes comes from a study where functional single nucleotide polymorphisms in the GR gene with increased GC sensitivity were shown to be related to reduced insulin secretion during a hyperglycaemic clamp.

Pancreatic alpha cells
By secreting glucagon, the pancreatic alpha cell has an important role in glucose metabolism. As previously mentioned, glucagon stimulates hepatic glucose production by promoting glycogenolysis and gluconeogenesis. In many patients with T2DM, glucagon levels are increased in the fasted state and are incompletely suppressed in the postprandial state. Thus, elevated glucagon levels were shown to contribute importantly to both fasting and postprandial hyperglycaemia. Already in 1971, GCs were shown to augment glucagon levels. This was demonstrated both in healthy individuals treated with dexamethasone and in patients with Cushing’s syndrome. In both groups, fasting glucagon levels were increased and glucagon concentrations were incompletely suppressed following ingestion of a protein meal or following alanine infusion. We demonstrated that the effects of GCs on glucagon levels are dose-dependent: only high-dose (30 mg prednisolone daily), but not low-dose (7.5 mg prednisolone daily) GC treatment increased fasting and postprandial glucagon levels following a two-week treatment in healthy men. Interestingly, this effect of high-dose GCs on glucagon levels was already evident after a single gift. Thus, both fasting and postprandial hyperglucagonaemia are present in GC-induced hyperglycaemia.

The gut-islet axis
The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are hormones secreted by the gut that are released following nutrient ingestion. GLP-1 lowers (postprandial) blood glucose through several mechanisms, including stimulation of meal-related insulin response and suppression of glucagon secretion in a glucose-dependent manner. In addition, GLP-1 slows down gastric emptying, promotes satiety, decreases appetite and reduces body weight. In human beta cells and in vivo in animals and in humans, exogenous GLP-1 administration, in the presence of elevated glucose, acutely induces insulin secretion while prolonged GLP-1 exposure may result in increased insulin production. GLP-1 has a short half-life (1-2 minutes) since it is cleaved by the ubiquitous enzyme dipeptidyl peptidase (DPP)-4. Due to the above-mentioned beneficial effects of GLP-1 on glucose metabolism, treatment with DPP-4 resistant GLP-1, GLP-1 receptor agonists and DPP-4 inhibitors has been developed in T2DM patients, in whom the insulinotropic effects of GLP-1 are still intact, albeit to a lesser extent than in non-diabetic subjects.

Up to recently, the effects of GC treatment on GLP-1 secretion and its insulinotropic actions had been little addressed. In rodents, GC treatment resulted in decreased mRNA stability of the proglucagon gene, a precursor of GLP-1, resulting in reduced GLP-1 levels. In our study in healthy volunteers, a two-week treatment with prednisolone did not affect circulating GLP-1 concentrations during standardised meal tests, which was confirmed by others. Interestingly, however, the insulinotropic effects of GLP-1 were reduced by GC treatment, as demonstrated by reduced potentiation of glucose-stimulated insulin secretion when GLP-1 was co-infused. It is unclear whether this impaired incretin effect is a specific beta-cell defect induced by GC treatment or whether it may be secondary to general GC-induced beta-cell dysfunction. Thus, an impaired gut-islet axis characterised by impaired insulinotropic effects of GLP-1 is present in GC-induced hyperglycaemia. The mechanisms by which GCs are thought to induce hyperglycaemia are summarised in figure 3.

STEROID DIABETES: FROM MECHANISM TO TREATMENT?
Due to these combined effects of GCs on both insulin sensitivity and islet-cell function, and due to their specific PK/PD profile, it has become clear that synthetic GCs
particularly increase postprandial glucose levels,\(^{109}\) without affecting fasting glucose levels,\(^{105}\) similarly as has been observed in patients with Cushing’s syndrome.\(^{106}\) This observation has important consequences. First, the incidence of steroid diabetes may be underestimated due to the fact that usually only fasting glucose levels are monitored during therapy. As such, low-dose prednisolone treatment is reported to have few side effects,\(^{109}\) while in our studies we observed various metabolic processes, particularly in the postprandial and hyperinsulinaemic state, to be disturbed by low-dose prednisolone treatment (table 2). Second, the described specific pattern of GC-induced hyperglycaemia may provide directions for the development of the dissociated GR agonists. Finally, increased insight into the mechanisms by which GCs induce hyperglycaemia may also be used for the management of steroid diabetes in clinical practice. It is remarkable that despite the fact that GCs are well known to induce diabetes, there are very few studies that have investigated how GC-induced diabetes may best be treated, or preferentially, be prevented. Guidelines are currently solely based on expert opinions.\(^{111,114}\)

‘Classic’ hypoglycaemic agents
A few intervention studies that aimed to treat or prevent GC-induced hyperglycaemia have been performed in healthy individuals. In a crossover study carried out in five volunteers, a 14-day pre-treatment with the thiazolidinedione (TZD) troglitazone, but not metformin or pioglitazone, reduced hyperglycaemia during an oral glucose tolerance test after three days of dexamethasone treatment at 4 mg daily.\(^{115}\) Another small-sized uncontrolled study also showed effectiveness of troglitazone in preventing GC-induced glucose intolerance in healthy participants treated with dexamethasone for four days.\(^{116}\) However, participants gained 1.7 kg of weight during the four weeks of pre-treatment with troglitazone.

In addition to weight gain, thiazolidinediones cause oedema, heart failure and bone fractures,\(^{117,118}\) all of which are particularly unfavourable given the side effect profile of GCs, which shares similar features. Meanwhile, the market authorisation of troglitazone (2000) and rosiglitazone (2010) was suspended in Europe due to liver toxicity and cardiovascular disease risk, respectively.

Given the GC-induced increment in postprandial glucose levels, short-acting prandial insulin is currently recommended.\(^{111}\) However, choosing the right dosage of insulin may be challenging due to the fact that GC dosage is often tapered over time making insulin demand variable. Furthermore, insulin therapy may increase the risk of hypoglycaemia and induce weight gain, both of which are undesired side effects.

Incretin-based therapies
In recent years, incretin-based therapies have become available for the treatment of T2DM. These include the injectable DPP-4 resistant GLP-1 receptor agonists and the class of oral DPP-4 inhibitors. Since GLP-1 receptor agonist treatment decreases gastric emptying,\(^{119}\) stimulates meal-related insulin secretion\(^{120}\) and reduces glucagon secretion,\(^{121}\) it addresses at least two important pathophysiological features of GC-induced hyperglycaemia. In addition, incretin-based therapies mainly target postprandial hyperglycaemia and, due to their glucose-dependent mechanism of action, have low hypoglycaemia risk. Given these properties, incretin-based therapies may particularly be suited to treat GC-induced hyperglycaemia. The potential use of GLP-1 receptor agonists for the treatment of GC-induced hyperglycaemia was first proposed in 2007 when Ritzel and colleagues infused GLP-1 in ten patients with T2DM of whom one patient was only later found to have diabetes due to Cushing’s disease.\(^{122}\) By comparing the one patient with Cushing’s disease with the nine T2DM patients, the investigators studied whether the effects of GLP-1 on glucose metabolism were preserved in hypercortisolism. In another paper, four cases of patients who were previously diagnosed with T2DM, but whose glycaemic control worsened under GC therapy, were successfully treated with exenatide twice daily\(^{123,124}\)

We explored the potential of GLP-1 receptor agonists to prevent GC-induced hyperglycaemia in a randomised, proof-of-concept study in eight healthy volunteers. We could show that intravenous infusion of the GLP-1 receptor agonist exenatide prevented the rise in postprandial glucose levels induced by acute treatment with high-dose prednisolone. This was achieved by preventing GC-induced hyperglucagonaemia and GC-induced beta-cell dysfunction, and by reducing gastric emptying rates.\(^{124}\) Currently, other proof-of-concept studies are ongoing in which the effects of more prolonged treatment with

\[
\text{Table 2. Adverse metabolic effects of low-dose glucocorticoid therapy (7.5 mg prednisolone equivalent)}
\]

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Postprandial hyperglycaemia(^{17})</th>
<th>Liver</th>
<th>Skeletal muscle</th>
<th>Adipose tissue</th>
<th>Adipose tissue</th>
<th>Beta cells</th>
<th>Beta cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired suppression of glucose production by insulin(^{17})</td>
<td>(\text{Impaired suppression of glucose production by insulin})</td>
<td>(\text{Reduced insulin-stimulated glucose uptake}) (^{17})</td>
<td>(\text{Reduced insulin-stimulated glucose uptake}) (^{17})</td>
<td>(\text{Increased NEFA levels during hyperinsulinaemia}) (^{17})</td>
<td>(\text{Reduced glucose-adjusted basal insulin secretion}) (^{17})</td>
<td>(\text{Reduced potentiation of glucose-stimulated insulin secretion}) (^{17})</td>
<td></td>
</tr>
</tbody>
</table>

\(p=0.07; \#p=0.09; ‡p=0.06.\)
the DPP-4 inhibitor sitagliptin on glucose metabolism are assessed in men with the metabolic syndrome concomitantly treated with high-dose prednisolone. It will be interesting to see whether also in this population, incretin-based therapies may be useful in the treatment of GC-induced hyperglycaemia.

Future, real-life studies need to be conducted in relevant patient populations, i.e. patients taking GCs in clinical practice for inflammatory conditions. Since inflammation also negatively affects insulin secretion and sensitivity, the interactions among GCs, systemic inflammation and incretin-based drugs may yield unexpected findings.

**CONCLUSION**

Knowledge regarding the diabetogenic effects of GCs has significantly been expanded in recent years, which will help the development of novel GR agonists with a more favourable therapeutic index. In addition, the increased insight into the pathophysiology of the diabetogenic effects of GC treatment should in due time result in a more tailored therapy to treat the associated hyperglycaemia.

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Ethylene glycol or methanol intoxication: which antidote should be used, fomepizole or ethanol?

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ABSTRACT

Ethylene glycol (EG) and methanol poisoning can cause life-threatening complications. Toxicity of EG and methanol is related to the production of toxic metabolites by the enzyme alcohol dehydrogenase (ADH), which can lead to metabolic acidosis, renal failure (in EG poisoning), blindness (in methanol poisoning) and death. Therapy consists of general supportive care (e.g. intravenous fluids, correction of electrolytes and acidemia), the use of antidotes and haemodialysis. Haemodialysis is considered a key element in the treatment of severe EG and methanol intoxication and is aimed at removing both the parent compound and its toxic metabolites, reducing the duration of antidotal treatment and shortening the hospital observation period. Currently, there are two antidotes used to block ADH-mediated metabolism of EG and methanol: ethanol and fomepizole. In this review, the advantages and disadvantages of both antidotes in terms of efficacy, safety and costs are discussed in order to help the physician to decide which antidote is appropriate in a specific clinical setting.

KEYWORDS

Haemodialysis, 4-methylpyrazole, poisoning, toxicity

INTRODUCTION

Ethylene glycol (EG) and methanol poisoning are associated with significant morbidity and mortality if left untreated. Poisoning may occur through attempted inebriation, unintentional ingestion, or intentional self-harm. EG is a common component of antifreeze and de-icing solutions. The majority of the information requests to the Dutch Poisons Information Centre (DPIC) regarding EG involve exposure to EG-containing antifreeze or de-icing solutions (~900 exposures reported from 2005 until 2012).

Methanol is present as a solvent in many household products, such as antifreeze, cleaning solutions, dyes, and paint removers. The consumption of illegally produced or homemade alcoholic beverages containing relatively high levels of methanol entails another risk. Several large outbreaks of methanol poisoning have occurred in the past decades, which have resulted in numerous deaths.1 For example, in a large methanol outbreak in Norway, 17 patients died after consumption of illegally produced liquor containing -20% methanol.2 From 2005 until 2012, the DPIC was consulted about ~800 methanol exposures, mainly by ingestion of methylated spirits (containing -3% methanol), formaldehyde solutions (-15% methanol) or pure methanol.

CLINICAL FINDINGS IN ETHYLENE GLYCOL POISONING

Acute EG intoxication can proceed through three distinct stages: central nervous system (CNS) depression, followed by cardiopulmonary dysfunction, and finally renal dysfunction (0.5-12 hours, 12-24 hours and 24-72 hours, respectively, after ingestion). However, the onset and progression of the clinical course is often not consistent or predictable.3
Toxicity of EG is related to the production of toxic metabolites by the hepatic enzyme alcohol dehydrogenase (ADH). EG is oxidised to glycolaldehyde by ADH, and subsequently converted to glycolic acid, glyoxylic acid and oxalic acid (figure 1). Oxalic acid binds to calcium, leading to the formation of insoluble calcium oxalate crystals, sometimes leading to hypocalcaemia. These calcium oxalate crystals deposit in several organs, causing acute renal failure and myocardial, neurological and pulmonary dysfunction.

Initially, only mild confusion or stupor is present, and patients may experience nausea and vomiting. As the intoxication progresses, neurological symptoms can become more profound. EG may cause severe neurological deficits, and even mimic a clinical state of brain death. Metabolic acidosis arises from accumulation of glycolic acid and oxalic acid. To compensate for metabolic acidosis, patients develop hyperventilation (Kussmaul breathing). Hypocalcaemia can lead to hyperreflexia and cardiovascular complications. After 24-72 hours, acute renal failure may become manifest. In severe intoxication, renal failure appears early and progresses to anuria. In severe cases, multiorgan failure and death occur. Some analysers falsely measure increased levels of lactic acid when glycolic acid is present, because glycolic acid has almost the same chemical structure as lactic acid. This can lead to misdiagnosis and a delay in the treatment of EG poisoning.

Although the lethal dose of EG in humans has been reported to be ~1.5 ml/kg bodyweight, death has been associated with lower amounts, and survival has been reported with much greater amounts. This could indicate individual susceptibility to the adverse effects of EG.

**CLINICAL FINDINGS IN METHANOL POISONING**

Toxicity of methanol is also related to the production of toxic metabolites by ADH. Methanol is oxidised to formaldehyde by ADH, which can be subsequently oxidised to formic acid, which is the major toxic metabolite of methanol (figure 1). Depending on the co-ingestion of ethanol, onset of symptoms ranges from 40 minutes to 72 hours with an average of 24 hours. Early stages of methanol poisoning are mild and transient, manifesting as mild euphoria or inebriation, followed by a latent phase lasting from 6 to 30 hours during which toxic methanol metabolites are formed. The toxic metabolite formic acid is primarily responsible for the retinal and optic nerve damage, probably caused by disruption of mitochondrial electron transport. This damage results in visual disturbances, which are reversible in most patients. However, permanent visual sequelae have been described following severe intoxication. CNS manifestations include headache, lethargy and confusion in mild-to-moderate intoxication and Parkinson-like extrapyramidal symptoms in severe intoxication. Poor prognostic signs include severe metabolic acidosis, cardiovascular shock, seizures or coma. Respiratory failure or sudden respiratory arrest is the most common cause of death in methanol poisoning. The lethal dose of pure methanol is generally estimated to be 1-2 ml/kg bodyweight. However, permanent blindness and deaths have been reported with 0.1 ml/kg bodyweight.

**LABORATORY FINDINGS IN ETHYLENE GLYCOL AND METHANOL POISONING**

In many hospital laboratories, no direct measurement of EG or methanol concentrations, or their toxic metabolites, is available on a 24-hour basis. The measurement of osmolal (OG) and anion gap (AG) can be useful in the diagnosis of EG and methanol intoxication. Early in the intoxication, serum osmolality can be increased, which is caused by increased EG or methanol concentrations. As methanol and EG metabolism proceeds, the OG decreases and, because of accumulation of toxic metabolites, the AG increases (figure 1). Later on, the osmolality might not be increased anymore, while AG is still increased by the toxic metabolites. In EG intoxication, AG can also
be increased by EG-induced kidney failure. In EG poisoning, envelop-shaped and needle-shaped oxalate crystals may be present in urine.

TREATMENT OF ETHYLENE GLYCOL AND METHANOL POISONING

In case of EG or methanol exposure, immediate consultation with a poison control centre is strongly recommended. Patients with moderate-to-severe EG or methanol poisoning should be admitted to a medical ward, and in case of life-threatening symptoms, to an intensive care unit. Because EG and methanol are rapidly absorbed, gastrointestinal decontamination using gastric lavage or activated charcoal is not recommended. However, the induction of vomiting directly after ingestion of massive amounts of EG or methanol may be useful.

General supportive care, i.e. mechanical ventilation, intravenous fluids, and vasopressors, may be indicated in severe intoxication. To correct severe acidemia (pH <7.3), the administration of sodium bicarbonate is recommended. Calcium suppletion is indicated in EG intoxication if hypocalcaemia, due to formation of calcium oxalate crystals, significantly contributes to symptoms such as muscle spasms or seizures.

Currently, there are two antidotes used to block ADH-mediated metabolism of EG and methanol in order to reduce formation of toxic metabolites: ethanol, a competitive ADH substrate, and fomepizole (4-methylpyrazole), an ADH inhibitor (figure 1). Today, in North-American and Western-European countries, fomepizole is considered by some authors to be the first-line antidote for EG and methanol poisoning. Fomepizole was approved in the United States for the treatment of EG and methanol poisoning in 1997 and 2000, respectively. Fomepizole and ethanol are most effective when given in the early phase of the intoxication, before significant levels of the toxic metabolites are formed.

Criteria for the initiation of antidote administration in EG and methanol poisoning are shown in table 1. Antidotal treatment considerably increases the half-life of EG and methanol (table 2). Haemodialysis is considered an integral part of the treatment of severe EG and methanol poisoning and is aimed at removing both the parent compound and its toxic metabolites, to correct metabolic acidosis and electrolyte disturbances, thereby reducing the duration of antidotal treatment and, in most cases, the duration of hospitalisation.

Current criteria for haemodialysis in EG and methanol poisoning, which are based more on clinical experience rather than on research data, include an initial plasma methanol or EG concentration ≥500 mg/l (8.1 mmol EG/l or 15.6 mmol methanol/l). Other criteria are severe metabolic acidosis, renal failure, electrolyte imbalances unresponsive to conventional therapy, deterioration of vital signs despite intensive supportive care or visual disturbances (in methanol poisoning). However, haemodialysis carries a low risk of bleeding, air embolism, thrombosis, hypovolaemia, hypotension, electrolyte abnormalities and infections.

Several adjunctive therapies with limited demonstration of efficacy have been suggested. In EG poisoning, pyridoxine and thiamine could prevent the formation of oxalic acid by facilitating the conversion of glyoxylic acid to non-toxic metabolites. In methanol poisoning, the administration of folic acid might theoretically be beneficial, as formic acid is converted to carbon dioxide and water by tetrahydrofolate synthetase, an enzyme that is dependent on folic acid.

ETHANOL VS FOMEPIZOLE

There are a number of reasons to prefer fomepizole as an antidote instead of ethanol (table 3). Fomepizole has a higher potency to inhibit ADH, with a longer duration of action. The administration regimen is easy, including a fixed loading dose followed by intermittent bolus doses.
every 12 hours, and there is no need for fomepizole blood concentration monitoring (table 4).

The fomepizole dose should be increased after 48 hours to account for an enhanced fomepizole clearance due to fomepizole-induced cytochrome P450 (CYP2E1) induction.21 Haemodialysis efficiently removes fomepizole. Two different protocols are proposed to compensate for fomepizole loss in the dialysate (table 4).9,10 Fomepizole is generally well tolerated, although sometimes injection site irritation, nausea, dizziness, tachycardia, headache, eosinophilia, slight increases in hepatic transaminase, agitation and seizures were reported.9,22-25 However, it is unknown whether most of these effects were due to the fomepizole treatment itself or to the EG or methanol poisoning.26

During ethanol therapy, regular ethanol blood concentration monitoring is necessary (every 1-2 hours), requiring frequent ethanol infusion adjustments. First, a loading dose of 600-1000 mg/kg should be administered, followed by a maintenance dose to maintain the target ethanol level (1000-1500 mg/l).26 This ethanol level leads to sufficient saturation of ADH, thereby inhibiting further metabolism of EG and methanol to their toxic metabolites. Individual variability, e.g. chronic alcohol abuse, influences the rate of ethanol metabolism. Therefore, the maintenance dose of ethanol should be increased in chronic alcohol abusers (table 5).26 Like fomepizole, ethanol is also removed during haemodialysis. Therefore, the ethanol dose must be increased in patients undergoing haemodialysis, representing an additional difficulty. During ethanol therapy, significant mental status changes, hypoglycaemia (especially in paediatric and malnourished patients), liver toxicity or pancreatitis can occur. Ethanol therapy may therefore confuse the interpretation of the already complex clinical course of EG and methanol poisoning. Despite these disadvantages, ethanol is used as a first-line antidote for EG and methanol intoxication in some medical centres, especially due to its low costs, physician experience and the fact that it is readily available.27

In the Netherlands, the cost of fomepizole is ~150 € per 100 mg. In two prospective clinical trials,10,22-23 EG- and methanol-intoxicated patients received a median of 3.5-4 doses of fomepizole (total fomepizole costs ~4500 € per treated patient weighing 70 kg). Ethanol itself is inexpensive. However, ethanol therapy requires ICU or high-care admission and regular determination of serum ethanol and blood glucose levels, which increases total treatment costs. Table 3 summarises the advantages and disadvantages of fomepizole and ethanol in the treatment of EG and methanol intoxication.
Several authors suggest that the introduction of fomepizole has obviated the need for haemodialysis in specific patient groups, i.e. in patients without signs of renal or optical injury and with normal acid-base status. Given the effectiveness in removing both the alcohols and the toxic metabolites, and the difficulty of rapid determination of EG and methanol levels, haemodialysis (in concert with fomepizole or ethanol) should always be considered in suspected cases and in patients with, for example, severe metabolic acidosis, electrolyte disturbances, renal failure or visual disturbances, or deterioration of vital signs despite intensive supportive care. Fomepizole and ethanol treatment increases the half-life of EG and methanol and therefore prolongs the necessity of clinical observation. Haemodialysis considerably reduces the half-life of these compounds and consequently will reduce hospital stay (table 2). Controlled, prospective studies would be useful in developing evidence-based guidelines, and aid in the decision to initiate haemodialysis in addition to antidotal therapy. There has been no direct head-to-head comparison of ethanol and fomepizole in terms of efficacy, safety, or cost-effectiveness to provide evidence that fomepizole is superior to ethanol. Interestingly, by using a physiologically based pharmacokinetic (PBPK) model, it was demonstrated that fomepizole, if administered early during an EG intoxication, can be more effective than ethanol in preventing the metabolism of EG to toxic metabolites. Beatty et al. performed a systematic review to investigate the efficacy and safety of ethanol and fomepizole as an antidote in EG and methanol poisoning in adults. Mortality in patients treated with ethanol was ~22% for methanol and ~18% for EG. In patients administered fomepizole, mortality was lower: ~17% for methanol and ~4% for EG. However, because of the quality of the reported data it cannot be concluded that the mortality difference is due to the use of a specific antidote. In addition, the majority of case reports reported in this review from before the mid-1990s describe the use of ethanol, whereas fomepizole is much more commonly reported in recent years, when advances in general supportive care and haemodialysis have significantly improved patient outcomes. Lepik et al. investigated adverse drug events associated with ethanol and fomepizole in methanol or EG poisonings. Although

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**Table 4. Recommended doses of fomepizole for ethylene glycol (EG) and methanol poisoning**

<table>
<thead>
<tr>
<th>Fomepizole dosing scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients not undergoing haemodialysis</td>
</tr>
<tr>
<td>Loading dose (t=0 h): 15 mg/kg, followed by 10 mg/kg at t=12 h, t=24 h and t=36 h. After 48 h, fomepizole dose should be increased to 15 mg/kg every 12 h.</td>
</tr>
<tr>
<td>For patients undergoing haemodialysis: two proposed protocols</td>
</tr>
<tr>
<td>1. A reduction in time interval between fomepizole doses. Same doses administered to patients who are not undergoing haemodialysis, except that fomepizole is given 6 h after the first dose and every 4 h thereafter.</td>
</tr>
<tr>
<td>2. A continuous IV infusion of 1.5 mg/kg/h following the initial loading dose</td>
</tr>
</tbody>
</table>

*All doses are administered intravenously over a 30-minute period.

---

**Table 5. Recommended doses of ethanol for ethylene glycol (EG) and methanol poisoning**

<table>
<thead>
<tr>
<th>Ethanol dosing scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading dose</td>
</tr>
<tr>
<td>0.6-1.0 g/kg intravenously (7.5-12.5 ml ethanol 10% solution in glucose/kg)</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>2.5 ml/kg orally 40% ethanol solution</td>
</tr>
<tr>
<td>Maintenance dose (intravenously)</td>
</tr>
<tr>
<td>The maintenance dose can be calculated as follows:</td>
</tr>
<tr>
<td>Dose (g/h) = (target ethanol concentration x V_{\text{max}} x bodyweight in kg) / (K_m + target ethanol concentration)</td>
</tr>
<tr>
<td>V_{\text{max}} (maximum reaction rate): in children: 0.075 g/kg/h; in adults: 0.125 g/kg/h (occasional alcohol intake) and 0.175 g/kg/h (alcohol abusers)</td>
</tr>
<tr>
<td>K_m (Michaelis Menten constant): 0.138 g/l</td>
</tr>
<tr>
<td>Target ethanol concentration = 1000-1500 mg/l (1-1.5‰). Use for this calculation a target ethanol concentration of 1‰</td>
</tr>
<tr>
<td>Children: 0.8 ml ethanol 10% solution in glucose/kg/h</td>
</tr>
<tr>
<td>Adult (occasional alcohol intake): 1.4 ml ethanol 10% solution in glucose/kg/h</td>
</tr>
<tr>
<td>Alcohol abuser: 2.0 ml ethanol 10% solution in glucose/kg/h</td>
</tr>
<tr>
<td>Maintenance dose (intravenously) during haemodialysis</td>
</tr>
<tr>
<td>During haemodialysis, an additional dose of 1.9 ml ethanol 10% solution in glucose/kg/h should be administered intravenously (in addition to the calculated maintenance dose)</td>
</tr>
<tr>
<td>Children: 2.7 ml ethanol 10% solution in glucose/kg/h</td>
</tr>
<tr>
<td>Adult (occasional alcohol intake): 3.3 ml ethanol 10% solution in glucose/kg/h</td>
</tr>
<tr>
<td>Alcohol abuser: 3.9 ml ethanol 10% solution in glucose/kg/h</td>
</tr>
</tbody>
</table>

* The target ethanol concentration is 1000-1500 mg/l (1-1.5‰)
there are several observational study limitations, results suggest a lower occurrence of adverse drug events with fomepizole compared with ethanol.13

USE OF FOMEPIZOLE IN CHILDREN

Few data are available on the use of fomepizole in the treatment of EG and methanol poisoning in paediatric patients.14-40 Most of these case reports were evaluated by Brent et al.41 These data suggest that fomepizole is safe and effective in the paediatric population using the same dosage regimen as that used for adults (table 4).41 All patients recovered without sequelae. The only adverse reaction reported during fomepizole therapy in these children was transient nystagmus in a 6-year-old.13 However, it is unclear whether this effect was related to fomepizole.

CONCLUSION

There is no conclusive scientific evidence whether ethanol or fomepizole should be used as first-line treatment of EG and methanol intoxication, as there has been no direct comparison between the two antidotes in terms of efficacy, safety, or cost-effectiveness. The decision to use fomepizole or ethanol is dependent on the availability and costs of the antidote, haemodialysis facilities, patient characteristics and physician experience with the specific antidote. If the treating physician has no experience with either antidote, then the treatment with fomepizole is easier, especially in the paediatric population.

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Compression therapy in patients with orthostatic hypotension: a systematic review

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ABSTRACT

Aim: Orthostatic hypotension is common, especially in the elderly, and it is strongly associated with discomfort and falls. Physicians may sometimes prescribe compression therapy, but the beneficial effect of this treatment in orthostatic hypotension is unclear. The aim of this review was to summarise all available evidence on the effect of four different levels of compression therapy in the treatment of orthostatic hypotension: knee-length, thigh-length, full-length and abdominal compression only.

Methods: A systematic search was performed in PubMed, Embase and Cochrane databases.

Results: A literature search identified 1232 reports; 11 publications were selected for inclusion in this review. The quality of studies was heterogeneous and generally poor. Full length compression (lower limbs and abdomen) and compression of solely the abdomen were found to be superior to knee-length and thigh-length compression. Both significantly reduced the fall in systolic blood pressure after postural change. Symptoms of orthostatic hypotension experienced by patients were improved the most by full-length compression.

Conclusions: When other interventions fail to ameliorate symptoms, compression therapy can be considered. This review demonstrates that compression treatment should include the abdomen as this has the greatest beneficial effect. However, this review also displays the paucity of evidence for compression therapy for patients with orthostatic hypotension, and further investigation is certainly warranted.

KEYWORDS

Compression therapy, orthostatic hypotension, review

INTRODUCTION

Changing from a supine to an upright position causes pooling of blood in the lower extremities and abdomen. As a result, the venous flow to the heart is reduced, decreasing cardiac output. Baroreceptors are subsequently stimulated, activating the sympathetic nervous system and thereby inducing peripheral vasoconstriction, maintaining stroke volume and increasing the heart rate. If such compensatory mechanisms are inadequate, blood pressure may fall when shifting postural position. Formally, orthostatic hypotension (OH) was defined as a reduction in systolic blood pressure (SBP) of at least 20 mmHg or at least 10 mmHg decrease in diastolic blood pressure within three minutes of standing or after a head-up tilt of at least 60° on a tilt table. The extent of the orthostatic hypotension can be influenced by several factors such as age, temperature, hydration and medications. The prevalence of orthostatic hypotension is particularly high in the elderly, rising to as much as 50% in hospitalised geriatric patients and 70% of nursing homes residents.

Orthostatic hypotension can be a major issue for patients, leading to falls and subsequent fractures and immobility. Prevention or treatment of this disorder is therefore indicated. If possible, causative factors such as medication should be removed. Additional posture and exercise instructions can be given to help patients cope with this disorder. Multiple sources, such as the European Federation of Neurological Societies guideline on the management of orthostatic hypotension as well as a myriad of review articles on this topic, also suggest the option of lower limb compression therapy. The underlying rationale is that external pressure reduces venous pooling in the legs and improves venous return to heart, thus preventing a reduction in stroke volume and maintaining cardiac output.

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In the Netherlands approximately 360,000 patients wear elastic stockings. It is not known what percentage of those stockings is prescribed as treatment for orthostatic hypotension. However, in an Irish survey performed in 2011, 43 of 48 participating physicians working in geriatric medicine stated that they prescribed elastic compression stockings for patients suffering from orthostatic hypotension.9 Several types of compression garments are used in the management of orthostatic hypotension. Apart from knee-length compression stockings, thigh-length garments and abdominal bandages are also recommended for the reduction of symptoms of orthostatic hypotension.8,12 The aim of this systematic review was to collect all available evidence on the use of lower limb compression therapy in orthostatic hypotension and to determine the effectiveness of four different levels of compression: knee-length, thigh-length, full-length and abdominal compression only.

METHODS

Search strategy and selection criteria
An extended search was performed in PubMed, Embase and Cochrane on 26 November 2012, using the following syntax: (postural hypotension OR postural hypotensive OR orthostatic OR ortostatic); in title/abstract AND (stocking* OR band OR binding OR bands OR bindings OR hosiery OR tights OR counter-pressure OR (counter AND pressure) OR band OR binding OR bands OR bindings OR binders); in all fields. Studies with less than ten patients were excluded as these were considered to lack sufficient statistical power. In addition, studies focusing only on orthostatic hypotension in the context of spinal cord injury, anaesthesia, rare syndromes such as the Nutcracker syndrome or post-space flight were excluded. No limitations were applied to the language or year of publication. The titles and abstracts of all studies retrieved by the search were assessed by one author (HS) to determine which were eligible for further investigation. All potentially relevant articles were subsequently screened as full text by two authors (HS and MK). Selected studies were cross-referenced to retrieve any additional relevant citations. Data extraction
Data regarding study design and results were extracted from each included study. Extracted items were: methods of study (definition of OH, manner of postural change, timing of measurements, use of sham compression, site and strength of compression) and study population (age, gender, comorbidity, number of participants with OH at baseline). All data were extracted by one author (HS) and subsequently cross-checked by a second (MK). In case of insufficient data in the original publication, authors were contacted wherever possible to retrieve additional data.

Quality assessment
The methodological quality of the studies was independently assessed by two authors (HS and MK), using the Cochrane Collaboration’s tool for assessing risk of bias in clinical studies.19 A summary of this tool can be found in Appendix 1a in the Supporting Information on the journal’s website. In case of disagreement among the reviewers, the assistance of a third reviewer (MH) was enlisted.

Data synthesis and analysis
As a result of heterogeneity in patient populations and outcome measures, a formal meta-analysis was not possible. Therefore, the study results were summarised to describe the main outcomes of interest: i.e. change in standing systolic blood pressure, change in postural drop (which is calculated by subtracting the change in SBP when changing position with compression from the change in SBP without compression) and orthostatic symptoms as reported by the patient. If not reported in the publication, these outcomes were calculated from the available data wherever possible. A distinction was made between different levels of compression in the studies. The four categories were knee-length compression, thigh-length compression, abdominal compression only or full-length compression, which was defined as compression of both full length of the legs as well as the abdomen.

RESULTS

Search and selection
The literature search yielded 1531 citations (figure 1). After exclusion of 299 duplicates and 1221 publications for other reasons, a total of 11 publications were considered suitable for inclusion in this review (table 1). Although two additional studies did investigate the influence of compression stockings on blood pressure, one was excluded because it lacked a description of the study methods and the use of statistics,14 and the other because no relevant data could be extracted from the publication to allow its inclusion in this review.15 Cross-referencing of included studies yielded no additional results.

Quality assessment
The summarised results of the quality assessment can be found in figure 2; full details can be found in Appendix 1b in the Supporting Information on the journal’s website. Reviewer agreement was over 93% for all aspects. The
risk of bias due to patient selection was considered low, as all studies were self-controlled, thus rendering issues such as randomisation not applicable. Although three studies used some form of sham compression,\textsuperscript{9,16,17} it was unclear whether the placebo was sufficient to prevent a performance or detection bias. For this reason, those studies were scored as having an unclear risk of bias on these items. The remaining studies did not use sham compression, thus resulting in a high risk of a performance and detection bias. The risk of an attrition bias was low in most studies,\textsuperscript{16,18-23} but was considered high in four,\textsuperscript{9,17,24,25} mostly because of unexplained loss of participants. The risk of a reporting bias was considered to be high in two studies\textsuperscript{18,24} due to incomplete reporting.

Study characteristics

The characteristics of the 11 included studies are summarised in Table 1. Sample sizes were generally small, with a median size of 15 patients (range 10-61). Definitions of orthostatic hypotension varied somewhat between the studies (Table 1) and in three studies no definition was provided.\textsuperscript{11,22,45} In six studies all participants had a history of orthostatic hypotension at baseline,\textsuperscript{17-19,21,44,45} whereas in two studies all participants were free from OH.\textsuperscript{9,16} The remaining studies included a mixed population. Comorbid conditions were common, varying from chronic haemodialysis\textsuperscript{91} to neurological diseases such as multiple system atrophy (MSA) or progressive autonomic neuropathy (PAN).\textsuperscript{18,21,25}

Changing of postural position was carried out passively in six studies, mostly using a tilt table.\textsuperscript{9,17-24} In the other five studies, the patients changed their postural position themselves.\textsuperscript{16,21-23,25} Two studies investigated seating-induced orthostatic hypotension.\textsuperscript{20,24}

The effect of merely knee-length compression was investigated in two studies\textsuperscript{9,18} six studies addressed thigh-length compression\textsuperscript{17,18,20-22,24} and in four studies the effect of full length compression including the abdomen was studied.\textsuperscript{16-19} Three studies focused on the effect of abdominal pressure alone.\textsuperscript{18,23,25}

Evidence for the effectiveness of compression therapy

Table 2 provides an overview of the effects of compression therapy on systolic blood pressure and symptoms. Full details can be found in Appendix 2 in the Supporting Information on the journal’s website.

Neither of the two studies that investigated the effect of knee-length compression found a beneficial effect on SBP.\textsuperscript{9,18} Nevertheless, one of these studies did report a moderate improvement of symptoms in two out of 14 patients.\textsuperscript{16}

Two of the six studies using thigh-length compression found a significant improvement in the decline of SBP with postural change,\textsuperscript{22,24} while a third reported a significant improvement of standing SBP with compression, with a median of 15 mmHg.\textsuperscript{17} Five of these six studies also investigated the effect of compression on symptoms of orthostatic hypotension. Although all found some improvement of symptoms, rates varied widely from 14-86% of patients.\textsuperscript{17,18,20-22,24}

Of the four studies assessing full-length compression, two reported a significant positive effect on standing SBP\textsuperscript{25,18} and a third study showed a significant reduction in
Table 1. Study characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>OH definition</th>
<th>Postural change</th>
<th>Time of measurements (minutes after change in position)</th>
<th>Applied pressure (mmHg)</th>
<th>Compression site</th>
<th>Sham compression</th>
<th>N</th>
<th>% Male</th>
<th>Age in years, mean (SD)</th>
<th>Comorbidities</th>
<th>% with OH at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deng, 1997&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥3 min decline in SBP of ≥30 mmHg or mean BP ≥20 mmHg</td>
<td>Passive, 80° tilt</td>
<td>?</td>
<td>40</td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>None</td>
<td>OH due to MSA, PAF or PAN</td>
<td>100</td>
</tr>
<tr>
<td>Gorelik, 2004&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥20 mmHg decline in SBP or ≥10 mmHg decline in DBP</td>
<td>Passive, lying to seating</td>
<td>1-5</td>
<td>30</td>
<td>C+T+T</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>None</td>
<td>Conditions requiring bed rest</td>
<td>30</td>
</tr>
<tr>
<td>Gorelik, 2009&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥20 mmHg decline in SBP or ≥10 mmHg decline in DBP</td>
<td>Passive, lying to seating</td>
<td>5</td>
<td>40 (ankle)</td>
<td>C+T+T</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>None</td>
<td>Decompensated heart failure</td>
<td>100</td>
</tr>
<tr>
<td>Hasegawa, 2000&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Fall of ≥20 mmHg in SBP</td>
<td>Active, upright standing</td>
<td>10</td>
<td>?</td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>None</td>
<td>Autonomic neurological disease</td>
<td>100</td>
</tr>
<tr>
<td>Henry, 1999&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Fall of ≥20 mmHg in SBP</td>
<td>Passive, 90° tilt</td>
<td>3</td>
<td>20-30 (ankle)</td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>None</td>
<td>History of falls</td>
<td>100</td>
</tr>
<tr>
<td>Morrison, 2012&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥40 mmHg decline in SBP or ≥20 mmHg decline in DBP within first 15 sec</td>
<td>Active, upright standing</td>
<td>1</td>
<td>10-15</td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Placebo garments</td>
<td>None</td>
<td>40</td>
</tr>
<tr>
<td>Podoleanu, 2006&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Symptoms after 3 asymptomatic min or decline of SBP to ≤90 mmHg</td>
<td>Passive, 60° tilt</td>
<td>10</td>
<td>20-60 (from abdomen to ankle)</td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Elastic bandages; 5 mmHg</td>
<td>Various</td>
<td>100</td>
</tr>
<tr>
<td>Protheroe, 2011&lt;sup&gt;a&lt;/sup&gt;</td>
<td>SBP ≤80 mmHg, HR ≤50 or ≥180; or presyncope during symptoms</td>
<td>Passive, 60° tilt +</td>
<td>30</td>
<td>29 (knee) to 35 (ankle)</td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Calf placebo (no compression)</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Smit, 1997&lt;sup&gt;a&lt;/sup&gt;</td>
<td>?</td>
<td>Active, upright standing</td>
<td>3</td>
<td>40</td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>None</td>
<td>OH due to MSA, PAF, PAF or other</td>
<td>100</td>
</tr>
<tr>
<td>Tezuka, 1997&lt;sup&gt;a&lt;/sup&gt;</td>
<td>?</td>
<td>Active, upright standing</td>
<td>?</td>
<td>8 (thigh) to 20 (ankle)</td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>None</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Yamamoto, 2006&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;55 mmHg decline in SBP or symptoms</td>
<td>Active, upright standing</td>
<td>1</td>
<td>20</td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>None</td>
<td>Chronic haemodialysis</td>
<td>100</td>
</tr>
</tbody>
</table>

A = abdomen; BP = blood pressure; C = calves; DAN = diabetic autonomic neuropathy; DBP = diastolic blood pressure; HR = heart rate; LBNP = lower body negative pressure; MSA = multiple system atrophy; PAF = pure autonomic failure; PAN = progressive autonomic neuropathy; SBP = systolic blood pressure; T = thighs.
postural drop of 19.9 mmHg. The fourth study reported a deterioration in both standing SBP and postural drop when compression was used, but these findings were not significant. Three of four studies addressing symptoms when compression was used, but these findings were not a deterioration in both standing SBP and postural drop. Standing SBP increased by 12-21 mmHg of orthostatic hypotension when applying abdominal compression due to pre-syncope symptoms. In the fourth study, six patients reported symptoms in both the control and the compression setting, but four patients were unable to complete the protocol with compression.

Compression of the abdomen only was investigated in three studies, all of which demonstrated an improvement of orthostatic hypotension when applying abdominal pressure. Standing SBP increased by 12-21 mmHg when compression was used. In addition, one of these studies reported a reduction in postural drop of 17 mmHg. Two studies investigating the effect of compression on symptoms showed improvement, with rates of 30 and 36% of patients.

<table>
<thead>
<tr>
<th>Table 2. Effect of compression on systolic blood pressure (SBP) and symptoms of orthostatic hypotension. Full details can be found in Appendix 2 in the Supporting Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Knee-length compression (calves)</td>
</tr>
<tr>
<td>Deng 1997b</td>
</tr>
<tr>
<td>Protheroe 2013a</td>
</tr>
<tr>
<td>Thigh-length compression (calves +thighs)</td>
</tr>
<tr>
<td>Deng 1997a</td>
</tr>
<tr>
<td>Gorelik 2004a</td>
</tr>
<tr>
<td>Gorelik 2009b</td>
</tr>
<tr>
<td>Hasegawa 2000a</td>
</tr>
<tr>
<td>Podoleanu 2006c</td>
</tr>
<tr>
<td>Tetzuka 1999b</td>
</tr>
<tr>
<td>Abdominal compression only</td>
</tr>
<tr>
<td>Deng 1997a</td>
</tr>
<tr>
<td>Henry 1999a</td>
</tr>
<tr>
<td>Morrison 2012a</td>
</tr>
<tr>
<td>Podoleanu 2006c</td>
</tr>
<tr>
<td>Abdominal compression only</td>
</tr>
<tr>
<td>Deng 1997a</td>
</tr>
<tr>
<td>Smit 1997a</td>
</tr>
<tr>
<td>Yamamoto 2006b</td>
</tr>
</tbody>
</table>

1Difference in SBP in standing position, without and with compression (SBP_{standing} without compression; SBP_{standing} with compression); 2Difference in change in SBP when moving from supine to upright position without and with compression (SBP_{supine} without compression minus SBP_{supine} with compression); 3Difference in change in SBP when moving from supine to upright position without and with compression (SBP_{standing} without compression minus SBP_{standing} with compression); 4Significant improvement; 5No significant improvement; 6Significant improvement, no percentage extractable.

DISCUSSION

This systematic review demonstrates that the effect of lower limb compression therapy on orthostatic hypotension is poorly investigated. The available evidence, however, shows that full-length compression and compression of solely the abdomen are superior to knee-length and thigh-length compression. The first two significantly reduced the fall in SBP after postural change. Symptoms of orthostatic hypotension experienced by patients were most improved by full-length compression.

In this review, a comprehensive overview is given of all available evidence on the effect of compression therapy of the legs on orthostatic hypotension. A distinction was made between four different levels of compression, resulting in a fair comparison between the studies. Nevertheless, this review has some limitations. For instance, it was not possible to perform a formal meta-analysis, because the studies included in this review differed significantly in the type of compression, the pressure that was used, the method by which postural change was achieved and the timing of measurements. Furthermore, not all publications provided sufficient information on the study methodology.

The beneficial effect of compression of the abdomen on orthostatic hypotension found in this review is supported by bio-impedance studies, which report that the abdomen is by far the biggest fluid reservoir in the body, accounting for over 70% of orthostatic body fluid shifts. By contrast, the lower limbs account for less than a third of such fluid shifts, explaining why compression of only the legs appears to have a very limited effect on orthostatic hypotension. Consequently, there appears to be no place for solely lower limb compression in the treatment of orthostatic hypotension.

Although the evidence for full-length compression and abdominal compression only is more promising, the paucity of data and the heterogeneous and generally small study populations mean that these data should be interpreted with caution. Furthermore, although compression therapy is relatively harmless, it also has disadvantages. Some patients complain about cutting-off of circulation, stockings being too hot to wear, limb soreness, poor cosmetic appearance or itching. Stockings can also be difficult to put on, particularly for elderly patients who may require home care nurses to help them with it. In addition to the extra cost of such care, this decreases the

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patients’ independence, as they will have to wait each day for someone to help put the stockings on and take them off again in the evening. These drawbacks are important to take into account before prescribing compression stockings.

However, despite these facts, there does seem to be a place for compression therapy if it is not possible to take away the primary cause of orthostatic hypotension. Alternative therapeutic options, including a range of different medications, carry the potential for serious side effects. For example, midodrine – one of the most researched drugs for this condition – can cause urine retention, paresthesia and hypertension. Moreover, evidence for the use of such medication is also quite poor.

**CONCLUSION**

The paucity of evidence for the benefit of compression therapy in addition to the potential discomfort does not justify the routine prescription of lower limb compression therapy for patients with orthostatic hypotension. However, treatment with compression therapy including the abdomen can be considered if other interventions, such as evaluation of medication, treatment of supine hypertension and postural manoeuvres, do not adequately ameliorate symptoms of orthostatic hypotension. Definitive conclusions on the benefit of this type of treatment will require further evidence from well-powered and well-documented clinical trials.

**REFERENCES**


Smeenk et al. Compression therapy in orthostatic hypotension.
Proton pump inhibitors do not increase the risk of acute rejection


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ABSTRACT

Background: Mycophenolate mofetil (MMF) is the prodrug of mycophenolic acid (MPA). Proton pump inhibitors impair exposure to MPA due to incomplete conversion from MMF. Lower exposure to MPA could result in an increased risk of acute rejection. We investigated whether MMF-treated renal transplant patients who concomitantly used pantoprazole as ulcer prophylaxis had a higher risk of acute rejection within the first three months after transplantation than those who used ranitidine.

Methods: We performed a retrospective study in adult patients who underwent kidney transplantation between January 2007 and December 2011. Their immunosuppressive therapy consisted of steroids, tacrolimus and MMF and they used either pantoprazole or ranitidine as ulcer prophylaxis.

Results: 202 patients were included: 125 using pantoprazole and 77 using ranitidine. There was no difference in the number of patients with biopsy-proven acute rejection (BPAR): 13 (10.4%) in the pantoprazole group versus 7 (9.1%) in the ranitidine group (NS). Also after correction for inequalities between the two groups, there was no significant relationship between the risk of BPAR and the type of anti-ulcer agent.

Conclusion: There was no evidence for an increased incidence of BPAR in renal transplant patients who use pantoprazole in combination with MMF.

KEYWORDS

Acute rejection, kidney transplantation, mycophenolate mofetil, proton pump inhibitor

INTRODUCTION

Mycophenolate mofetil (MMF) is a commonly used immunosuppressive drug after solid organ transplantation and in autoimmune disease. After intake, MMF is rapidly absorbed and hydrolysed to its active metabolite, mycophenolic acid (MPA). MPA reversibly inhibits inosine monophosphate dehydrogenase, which is a key enzyme involved in the de novo purine synthesis in activated lymphocytes. Adequate exposure to MPA is associated with a decreased rate of acute rejection in kidney transplant patients.1-4 Proton pump inhibitors (PPI) are frequently prescribed post transplantation as prophylaxis for peptic ulcer disease, which is common and can cause significant morbidity and mortality.5 During the last years, a series of studies have reported that PPI therapy decreases MPA exposure in kidney transplant patients, heart transplant patients, patients with autoimmune disease, and healthy volunteers.6-10 Studies showed that concomitant use of pantoprazole 40 mg resulted in 34-37% lower exposure to MPA.10,11 PPIs can raise the gastric pH level above 4, which results in a decreased de-esterification of MMF,12 and thereby a reduction of the MPA plasma concentration. In our centre, peptic ulcer prophylaxis in recipients of a kidney transplant usually consists of either the PPI pantoprazole or the histamine 2 (H₂) receptor antagonist ranitidine. During the first day after administration, H₂ receptor antagonists usually elevate the gastric pH to a similar degree, or even more, than PPIs.13,14 However, due to tolerance induction, the effect of H₂ receptor antagonists on gastric pH rapidly wanes during subsequent days, while the effect of PPIs strengthens. Thus, it can be expected that the effect of continuous use of H₂ receptor antagonists on MPA levels is considerably smaller than of PPIs. Currently, it is unknown whether the lower MPA exposure in patients treated with PPI has any clinical implications.

The present study therefore aimed to investigate whether MMF-treated renal transplant patients who concomitantly used pantoprazole had a higher risk of acute rejection within the first three months after transplantation than those who used ranitidine.
METH ODS

Study design
We performed a retrospective cohort study to investigate whether MMF-treated kidney transplant patients, who concomitantly used pantoprazole \( n=125 \), had an increased rate of acute rejection within the first three months after renal transplantation, compared with those who used ranitidine \( n=77 \). The data were derived from medical records and a local database with transplant outcome data. According to Dutch law, Institutional Review Board approval was not required.

The primary outcome was the occurrence of biopsy-proven acute rejection (BPAR) within the first three months after transplantation. Histological examination and classification were done according to the Banff criteria. A clinical diagnosis of presumed acute rejection was made when serum creatinine levels increased without another explanation and a biopsy was not performed. The secondary outcomes were the incidence of acute rejection (BPAR and presumed acute rejection) within three months after transplantation, BPAR and acute rejection within six months after transplantation, serum creatinine level, estimated glomerular filtration rate (eGFR) calculated by using the MDRD formula and proteinuria at three months after transplantation.

Patients
We included all adult patients who underwent renal transplantation in our centre between January 2007 and December 2011 and used a standard immunosuppressive therapy consisting of tacrolimus, prednisone and MMF with either ranitidine or pantoprazole, as ulcer prophylaxis. The choice between ranitidine and pantoprazole was made by the treating physician and usually depended on pre-existing use of either drug and personal preference of the treating physician. Exclusion criteria were: graft loss or death within the first three months after transplantation, treatment with drugs known to have a pharmacokinetic interaction with MMF (e.g. phosphate binders, rifampicin or cholestyramine), intravenous administration of MMF, combined use of ranitidine and pantoprazole, and switch between both drugs. Patients with a history of bowel surgery were also excluded. A number of the patients \( n=54 \) received induction therapy which consisted of basiliximab \( n=6 \), daclizumab \( n=1 \), or rituximab \( n=47 \). Rituximab was given within the framework of a blinded, prospective, placebo-controlled trial (clinicaltrials.gov: NCT00565331). Patients were treated with prednisone 100 mg per day during the first three days after surgery and subsequently with prednisone 20-25 mg/day, which was gradually tapered to 0.1 mg/kg/day. On the first day after renal transplantation, tacrolimus was started in a dose of 0.2 mg/kg/day to target the trough level between 15-20 µg/l. During the first three months after transplantation, the dose of tacrolimus was gradually tapered to aim for a target range between 5-10 µg/l. The initial dose of MMF was 1000 mg twice daily and after two weeks this was decreased to 750 mg twice daily, except in patients who weighed more than 90 kg. If patients suffered from leucopenia or gastrointestinal symptoms, the dose of MMF was reduced. Acute rejections were initially treated with intravenous methylprednisolone 750-1000 mg for three consecutive days. If this treatment failed, patients received anti-thymocyte globulin (ATG, Thymoglobulin\textsuperscript{®}), muromonab (Orthoclone OKT3\textsuperscript{®}), or alemtuzumab (Campath\textsuperscript{®}). All patients started with either pantoprazole 40 mg/day (some patients accidentally started with pantoprazole 20 mg) or ranitidine 150 mg/day. These doses could be increased if patients had gastrointestinal complaints. Unless there were still symptoms, the ulcer prophylaxis was stopped after three months. All patients used co-trimoxazole as \textit{Pneumocystis jirovecii} prophylaxis and valganciclovir was prescribed as prophylaxis if the renal transplant recipient was seronegative for cytomegalovirus while the donor was seropositive.

Statistical analysis
A threefold increase in the incidence of acute rejection might occur if patients have a 35% lower exposure to MPA in consequence of the combined use of pantoprazole and MMF in the early period after transplantation.\textsuperscript{3,10,11} We expected a rejection rate of 15% in ranitidine-treated patients and made a conservative estimate of the rejection rate of 30% in the pantoprazole-treated patients. Based on these rejection rates, a power of 0.8 and a type I error probability of 0.05, a sample size of 120 patients was required.

Normally distributed data are presented as mean with standard deviation (SD). Before analysis, data with a skewed distribution such as cold ischaemia time, panel reactive antibodies (PRA) and proteinuria were logarithmically transformed. We analysed our data with \textit{χ}\textsuperscript{2} test and unpaired T-test where appropriate. A multiple logistic regression analysis was carried out to evaluate whether variables, which were not equally distributed over both groups, affected the risk of BPAR. All statistical analyses were performed by using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The characteristics of the 202 patients who met the inclusion and exclusion criteria are summarised in \textit{table 1}. The number of patients who received rituximab induction
therapy differed significantly between the two groups. Small inequalities were present regarding cold ischaemia time, retransplantations, donor type, and cumulative dose of MMF. The daily dose of pantoprazole varied between 20-80 mg and the mean cumulative dose in three months was 3.9 g (standard deviation 1.0). The ranitidine dose varied between 150-300 mg per day, with a mean cumulative dose in three months of 14.4 g (2.4).

The percentage of patients with BPAR within three months after transplantation did not differ significantly between the two groups (table 2). The cumulative dose of MMF in patients with BPAR was 133.1 gram (14.3) and in patients without BPAR, it was 144.5 gram (18.1) (p<0.01). Creatinine level, eGFR, and level of proteinuria at three months after transplantation did not differ significantly between the two groups (table 3). Graft and patient survival was 100% in both groups at six months after transplantation.

Multiple logistic regression analysis was performed with the following covariates: race, age of the recipient, rituximab induction therapy, retransplantation, donor type, cold ischaemia time, PRA, human leukocyte antigen (HLA) mismatches, delayed graft function, cumulative dose of MMF, and type of anti-ulcer agent. Using BPAR within three months as dependent variable, the only statistically significant covariates were cumulative dose of MMF (p<0.01), race (p<0.05) and retransplantation (p<0.05). The type of anti-ulcer agent had no effect on the risk of BPAR.

Since the dose of pantoprazole varied between patients, we evaluated the correlation between the cumulative dose of pantoprazole within the first three months after transplantation and the incidence of BPAR. There was no significant association between exposure to pantoprazole and risk of acute rejection.

---

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Pantoprazole (n=125)</th>
<th>Ranitidine (n=77)</th>
<th>Significance p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>61.6</td>
<td>66.2</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.7 (12.8)</td>
<td>46.7 (13.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>98.4</td>
<td>98.7</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.3 (13.5)</td>
<td>75.4 (13.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>173.9 (5.7)</td>
<td>175.1 (10.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Living donor (%)</td>
<td>66.4</td>
<td>77.9</td>
<td>NS</td>
</tr>
<tr>
<td>PRA (%)</td>
<td>7.4 (1.2)</td>
<td>7.1 (1.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Retransplantation (%)</td>
<td>15.2</td>
<td>7.8</td>
<td>NS</td>
</tr>
<tr>
<td>Cold ischaemia time in deceased don-</td>
<td>18.05 (5.43)</td>
<td>15.17 (5.16)</td>
<td>NS</td>
</tr>
<tr>
<td>HLA mismatches on A, B and DR</td>
<td>3.2 (1.5)</td>
<td>3.2 (1.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>51.5 (10.8)</td>
<td>51.7 (11.3)</td>
<td>NS</td>
</tr>
<tr>
<td>CMV status (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D+/R+</td>
<td>23.2</td>
<td>26.0</td>
<td>NS</td>
</tr>
<tr>
<td>D+/R+</td>
<td>18.4</td>
<td>23.4</td>
<td>NS</td>
</tr>
<tr>
<td>D+/R-</td>
<td>27.2</td>
<td>22.1</td>
<td>NS</td>
</tr>
<tr>
<td>D-/R-</td>
<td>30.4</td>
<td>27.3</td>
<td>NS</td>
</tr>
<tr>
<td>Induction therapy (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>17.6</td>
<td>32.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>3.2</td>
<td>2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>0.8</td>
<td>0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Delayed graft function (%)</td>
<td>2.4</td>
<td>3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Cumulative dose of MMF in 3 months (g)</td>
<td>142.8 (18.0)</td>
<td>144.3 (18.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Daily dose of prednisone at 3 months (mg)</td>
<td>10.1 (4.0)</td>
<td>10.8 (3.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Daily dose of tacrolimus at 3 months (mg)</td>
<td>7.5 (4.2)</td>
<td>7.3 (4.0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are shown as mean (standard deviation) or percentage. CMV = cytomegalovirus; D = donor; HLA = human leucocyte antigen; MMF = mycophenolate mofetil; NS = not significant; PRA = panel reactive antigens; R = recipient; - = seronegative + = seropositive.

### Table 2. Percentage of patients with acute rejections within 3 or 6 months after transplantation

<table>
<thead>
<tr>
<th></th>
<th>Pantoprazole (n=125)</th>
<th>Ranitidine (n=77)</th>
<th>Significance p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAR within 3 months</td>
<td>10.4%</td>
<td>9.1%</td>
<td>NS</td>
</tr>
<tr>
<td>BPAR or presumed acute rejection within 3 months</td>
<td>20.0%</td>
<td>19.5%</td>
<td>NS</td>
</tr>
<tr>
<td>BPAR within 6 months</td>
<td>12.0%</td>
<td>10.4%</td>
<td>NS</td>
</tr>
<tr>
<td>BPAR or presumed acute rejection within 6 months</td>
<td>21.6%</td>
<td>20.8%</td>
<td>NS</td>
</tr>
</tbody>
</table>

BPAR = biopsy-proven acute rejection; NS = not significant.

### Table 3. Creatinine, eGFR and proteinuria at 3 months after transplantation in both groups

<table>
<thead>
<tr>
<th></th>
<th>Pantoprazole (n=125)</th>
<th>Ranitidine (n=77)</th>
<th>Significance p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.5 (0.4)</td>
<td>1.5 (0.4)</td>
<td>NS</td>
</tr>
<tr>
<td>eGFR (ml/ min/1.73m2)</td>
<td>49.5 (12.3)</td>
<td>50.7 (12.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Proteinuria (g/10 mmol creatinine)</td>
<td>0.25 (2.68)</td>
<td>0.15 (0.25)</td>
<td>NS</td>
</tr>
</tbody>
</table>

eGFR = estimated glomerular filtration rate; NS = not significant.
DISCUSSION

In this retrospective study we did not observe an increased risk of acute rejection within the first three months after renal transplantation in patients using pantoprazole in combination with MMF. Accordingly, there was no relationship between the dose of pantoprazole and the risk of acute rejection.

After oral administration, MMF is rapidly absorbed and undergoes extensive presystemic de-esterification by esterases to MPA. The MPA peak concentration is reached within 1-2 hours. Several investigators showed that PPI co-medication leads to a 34-37% reduction of MPA exposure.10,11 The impairment of MPA exposure following co-administration of MMF and PPI has been demonstrated for pantoprazole, lansoprazole, and omeprazole.6,11 The most commonly prescribed PPI in our centre is pantoprazole. Pantoprazole 40 mg produces a strong and consistent gastric acid suppression.16 Morning or evening intake of pantoprazole is irrelevant because intra-gastric pH elevation under PPI treatment is a permanent effect due to the irreversible inhibition of the gastric proton pump.16 A higher dose of pantoprazole leads to a higher gastric pH and to a lower solubility of MMF since it was approximately 4 mg/l in a buffer with a pH of 4, but only 0.24 mg/l at a pH of 5.2 and only 0.04 mg/l at a pH of 7.17 A secondary peak in the concentration-time profile of MPA occurs after 6-12 hours because of enterohepatic circulation. This secondary peak in the concentration-time curve is not reduced by use of PPI since no significant changes in MPA plasma concentrations between 2-12 hours after the intake were found in patients using a PPI.18 Previous studies have shown that a lower exposure to MPA increases the incidence of acute rejection after renal transplantation.14 On the basis of these data, we hypothesised that the use of PPI in MMF-treated renal transplant patients might result in an increased incidence of acute rejection. As far as we know our study is the first that specifically addresses this issue.

The risk of acute rejection did not differ between pantoprazole- and ranitidine-treated patients, despite a slightly lower total cumulative dose of MMF in the pantoprazole group. Based on an approximately 35% lower exposure to MPA in patients who used the combination of pantoprazole and MMF in the early period after transplantation, a threefold increase in the incidence of acute rejection might occur.10,11 The rejection incidence of 10.4% in the pantoprazole group as well as the relatively narrow 95% confidence interval for the difference with the ranitidine group (-6.9% – 9.5%) make such an increase in rejection incidence highly unlikely.

While most studies indicate that the combined use of PPI and MMF leads to a lower MPA exposure, Kiberd et al. recently found no significant impact of PPI use on total MPA exposure at day 5 after transplantation, although blood levels at two and 12 hours postdose were significantly reduced.19 Because we did not measure MPA levels and gastric pH, we were not able to show a pharmacokinetic interaction between MMF and PPI in our patients. However, the magnitude of such an effect was apparently not large enough to have clinical consequences. Moreover, our study is limited by its retrospective design, which impedes correction for unknown confounders. Furthermore, it should be noted that patients who used cyclosporine were not included in this study. Because cyclosporine has an inhibitory effect on the enterohepatic circulation of MPA, cyclosporine-treated patients might be more prone to underexposure to MPA when MMF is combined with a PPI. Similarly, potential underexposure to MPA might be more problematic in African American patients who were nearly absent in our study population.19 Finally, since we only investigated the effect of concomitant use of pantoprazole and MMF during the first three months after transplantation, we cannot rule out that longstanding concomitant use does increase the incidence of rejection. However, David-Neto et al. recently showed that the effect of simultaneous use of PPI and MMF on MPA exposure was particularly present in the first week post-transplantation.20 Moreover, an increased rejection incidence has especially been associated with inadequate exposure to MPA in the early period after transplantation.1,4 In conclusion, we found no evidence for a higher incidence of acute rejection in patients using pantoprazole in combination with MMF. This was supported by the absence of a significant relationship between the dose of pantoprazole and incidence of acute rejection.

DISCLOSURE

No funding sources for this study. LH received grants for clinical studies from Astellas, Roche and Novartis. The other authors have no other relevant financial relationships to disclose.

REFERENCES


**Nephrocalcinosis as adult presentation of Bartter syndrome type II**

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**ABSTRACT**

Bartter syndrome consists a group of rare autosomal-recessive renal tubulopathies characterised by renal salt wasting, hypokalaemic metabolic alkalosis, hypercalciuria and hyperreninaemic hyperaldosteronism. It is classified into five types. Mutations in the \( KCNJ1 \) gene (classified as type II) usually cause the neonatal form of Bartter syndrome. We describe an adult patient with a homozygous \( KCNJ1 \) mutation resulting in a remarkably mild phenotype of neonatal type Bartter syndrome.

**KEYWORDS**

Hypercalciuria, \( KCNJ1 \) gene, renal salt wasting, renal tubulopathy

**INTRODUCTION**

Bartter syndrome is a rare renal salt-losing disorder presenting with hypokalaemic metabolic alkalosis, hyperreninaemic hyperaldosteronism accompanied by normal or low blood pressure. Bartter syndrome is divided into five types by the involved mutated gene. Type I is caused by mutations in the sodium-potassium-chloride co-transporter gene (\( SLC12A1 \)). Type II is caused by loss of function in the inwardly rectifying potassium channel encoded by the \( KCNJ1 \) gene. Type I and II are also termed the neonatal Bartter syndrome because of their severe presentation in the neonatal period characterised by polyhydramnios leading to premature delivery, polyuria, dehydration, electrolyte disturbances, failure to thrive, elevated prostaglandin levels and nephrocalcinosis. We present here the case of an adult man diagnosed with a late-onset Bartter type II due to a homozygous \( KCNJ1 \) gene mutation, which has not been reported in the literature so far.

**CASE REPORT**

A 35-year-old man of Turkish origin consulted his general practitioner for lower back pain for two months. His medical history was unremarkable and he was not on any medication. Physical examination was unremarkable without dysmorphic features. He was normotensive. His general practitioner had already ordered an X-ray of the lumbar spine which showed extensive calcifications in both kidneys.

Laboratory findings were as follows: serum sodium 136 mmol/l, potassium 2.8 mmol/l, calcium 2.32 mmol/l (corrected for albumin), phosphate 0.65 mmol/l and creatinine 122 µmol/l (measured glomerular filtration rate using a 24-hour urine collection was 45 ml/min/1.73 m²).
Venous pH was 7.44 and the bicarbonate was 33 mmol/l. Aldosterone level was 1257 pmol/l (normal range 56-660 pmol/l) and renin level was 168 ng/l (normal range 3.5-28.5 ng/l). In a 24-hour urine collection, calcium excretion was slightly elevated (4.34 mmol/day). Excretion of sodium, potassium, phosphate, chloride and oxalate in the 24-hour urine was normal.

Our clinical diagnosis for this patient with nephrocalcinosis, hypokalaemia, metabolic alkalosis, hyperreninaemic hyperaldosteronism and a normal blood pressure was Bartter syndrome. DNA was isolated from peripheral blood. Molecular analysis of the SLC12A1 gene (type I), the KCNJ1 gene (type II), the CLCNKB gene (type III) and the CASR gene (type V) was performed.

Bartter syndrome type IV is associated with sensorineural deafness. Type IV was therefore not tested because our patient did not have any hearing complaints. A homozygous missense mutation in the KCNJ1 gene was identified. A cytosine to thymine mutation of the nucleotide 658 (c.658C>T) results in leucine being replaced by phenylalanine at amino acid 220 (p.(Leu220Phe)).

The patient was treated with oral supplementation of potassium and spironolactone. In the follow-up period, his serum potassium improved at a level of 3.2 mmol/l. His serum creatinine stabilised at the level of 140 µmol/l over the next year of follow-up. During the follow-up, the patient had an episode of back pain. The pain had a good response to butylscopolamine bromide. We considered the patient had a renal stone of calcium deposit penetrating into a calyx.

There was no known consanguinity in the family. However, both parents were born in the same small village in Turkey. Parents and siblings were not available for genetic testing.

**DISCUSSION**

This report describes a patient with Bartter syndrome type II caused by a homogenous missense mutation in KCNJ1, with a first presentation in adulthood with nephrocalcinosis. To our knowledge, this is the first report to document this mild phenotype of Bartter syndrome type II caused by homozygous Leu220Phe mutation.

Loss-of-function mutations in KCNJ1 are identified in Bartter syndrome type II. The KCNJ1 gene encodes an ATP-sensitive inwardly rectifying potassium channel (ROMK). ROMK is expressed in the apical membrane of the thick ascending limb and cortical collecting duct. At the level of the thick ascending limb of the loop of Henle, 20% of filtered sodium and potassium by the glomeruli is reabsorbed. Impaired reabsorption will result in a large volume of urine with a high content of Na⁺, K⁺, Cl⁻ and Ca²⁺ in the distal tubule. Na⁺-K⁺-2Cl⁻ co-transporter in the form of an electroneutral co-transport plays a crucial role in reabsorption of electrolytes in the thick ascending limb. Only 20% of the potassium ions is reabsorbed in the ascending limb, which will not provide the necessary amount of potassium ions for the Na⁺-K⁺-2Cl⁻ co-transporter for reabsorption of sodium. ROMK recycles reabsorbed potassium from the intracellular space back into the intraluminal space and thereby provides the amount of potassium ions necessary for Na⁺-K⁺-2Cl⁻ co-transporter. In the case of our patient with Bartter syndrome type II, malfunction of ROMK results in malfunction of Na⁺-K⁺-2Cl⁻ co-transporter, causing hypokalaemia, activated renin-aldosterone axis due to volume depletion, and metabolic alkalosis due to H⁺ loss. Reabsorption of Ca²⁺ is a passive process coupled to Na⁺ reabsorption. Impaired Na⁺ reabsorption results in hypercalciuria and nephrocalcinosis. Calcium deposits in the kidney can be visualised by ultrasonography, abdominal X-ray or CT scan (figure 1).

The homozygous missense mutation Leu220Phe in our patient is located in a domain involved in ROMK regulation. This regulatory region contains a protein kinase C and a Mg²⁺-ATP-binding motif that have been shown to be important in the Mg²⁺-ATP regulation of ROMK. Mutations within this region may disrupt channel regulation and alter ROMK function. Functional studies of the mutation are required to show the altered ROMK function. The missense mutation Leu220Phe in the KCNJ1 gene was described only once in a compound heterozygote setting in a neonate with severe manifestations of the syndrome. We report a remarkably mild phenotype of a patient who was homozygous for this missense mutation. This suggests a high degree of variability regarding severity of disease as shown in another report.Mutations
in the KCNJ1 gene should thus be considered even beyond the neonatal period in patients who present with symptoms of renal salt wasting.

The main treatment for Bartter syndrome is replacement therapy. A large amount of potassium may be required. The addition of potassium-sparing diuretics or an aldosterone antagonist may improve hypokalaemia. Since prostaglandin levels are elevated in affected patients, cyclo-oxygenase inhibitors can be used. Indomethacin has been accepted as standard therapy in children. The use of indomethacin improves growth rate and early treatment in the neonatal period may decrease nephrocalcinosis. However, few data about the long-term outcome of patients with Bartter syndrome are available. Renal failure requiring dialysis is uncommon in Bartter syndrome. However, the oldest patient at the last follow-up was 18 years.

**CONCLUSION**

To our knowledge, we here describe for the first time an adult patient presenting with nephrocalcinosis, hypokalaemia, metabolic alkalosis, hyperreninaemic hyperaldosteronism and a normal blood pressure due to a homozygote mutation in the KCNJ1 gene, coding for the ROMK channel, consistent with Bartter syndrome type II.

**REFERENCES**

A 48-year-old male was referred by the ophthalmologist because of a two-month history of progressive swelling of his eyelids. In the last three weeks he also developed several purple lesions on his legs, neck and groins. The lesions increased in size, were not painful, but did itch occasionally.

Besides fatigue for five months he had no other complaints. His medical history was otherwise unremarkable. On admission physical examination showed a blood pressure of 144/82 mmHg, a pulse of 88 beats/min and a temperature of 37.5 °C. On both eyelids there was a purple raised lesion of 1.5 cm in diameter (figure 1). Further examination showed multiple lesions on the face, in the retroauricular region and on both legs. The mouth showed white patches and on the palate there were multiple purple lesions as well.

The first blood work showed a mild normocytic anaemia (7.4 mmol/l) with no other abnormalities.

WHAT IS YOUR DIAGNOSIS?

See page 98 for the answer to this photo quiz.
A 73-year-old male was admitted with jaundice, mild abdominal pain, dark-coloured urine and light-coloured stools. His medical history included a cholecystectomy 13 years earlier and prostate carcinoma, which was treated with radiotherapy and was in remission with no current medication.

On physical examination severe jaundice was observed. His blood pressure was 104/60 mmHg with tachycardia of 104 beats/min. He had no fever. Examination of the abdomen revealed no abnormalities.

Laboratory tests included an elevation of total bilirubin of 678 µmol/l (conjugated bilirubin 512 µmol/l) with elevated alkaline phosphatase, a serum creatinine of 650 µmol/l, but no electrolyte abnormalities. Cell counter indices showed leucocytosis (25.2 x 10⁹/l) and thrombocytopenia (86 x 10⁹/l). Haemoglobin was 8.7 mmol/l. No biochemical signs of haemolysis were found. Schistocytes were not seen in a peripheral blood smear. A urine sample showed no erythrocytes, and no proteinuria or microalbuminuria. The sodium concentration in the urine was 51 mmol/l.

Ultrasonography of the abdomen revealed normal liver parenchyma, but multiple gallstones in the common bile duct, with associated bile duct dilation. Kidney size was normal with no signs of urinary tract obstruction. An endoscopic retrograde cholangiopancreaticography (ERCP) was performed. Because of fibrosis due to earlier ulceration, the ampulla of Vater was in an unfavourable location. Therefore it was decided to ensure proper drainage of bile by positioning a drain in the common bile duct. Despite hyperhydration and proper drainage of bile with normalisation of hyperbilirubinaemia and clinical improvement, kidney function did not recover. The patient was therefore treated with haemodialysis and a kidney biopsy was obtained (figure 1 and 2).

**WHAT IS YOUR DIAGNOSIS?**

See page 99 for the answer to this photo quiz.
A 28-year-old Bulgarian woman without a notable medical history was presented to our emergency department with unexplained but progressive pain in the lower abdomen radiating to her back without fever. She showed no other focal complaints. Her vital signs revealed a body temperature of 36.5 °C, a blood pressure of 122/76 mm/Hg, heart rate of 58 beats/min and a respiratory rate of 18 breaths/min with a saturation of 98% without receiving extra oxygen. On physical examination, we found three palpable cervical lymph nodes <1 cm. Several abdominal masses were found, painful on palpation, especially on the left side of the abdomen. The liver was also enlarged and filled the abdomen up to the edge of the pelvis. Laboratory examination showed a raised C-reactive protein level of 35 mg/l (normal value 0-10 mg/l), leukocyte count of 9.0 x 10^9/l (normal value 3.5-10.0 x 10^9/l), an eosinophilia of 11 % (normal value 0-5%) and a haemoglobin level of 7.8 mmol/l (normal value 7.5-9.5 mmol/l). A transvaginal ultrasound was performed by the gynaecologist, which showed several cysts, and a magnetic resonance imaging was performed.

**WHAT IS YOUR DIAGNOSIS?**

See page 100 for the answer to this photo quiz.
A solitary lung mass in a 46-year-old man

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CASE REPORT

A 46-year-old man with a 15 pack-year smoking history was referred to the pulmonary clinic with an incidental finding of a left pleural-based lung mass on chest X-ray (figure 1). The patient denied any respiratory symptoms, loss of weight or night sweats. He reported to have worked in a shipyard with a history of prolonged exposure to asbestos. Physical examination revealed no evidence of respiratory distress and no other abnormalities. A contrast-enhanced computed tomography (CT) scan of the chest followed which confirmed the X-ray findings (figure 2).

WHAT IS YOUR DIAGNOSIS?

See page 101 for the answer to this photo quiz.

Figure 1. Chest X-ray showing pleural based mass in left lung (arrow)

Figure 2. Chest CT demonstrating a mass, (grey arrow), with converging bronchovascular bundle towards it, known as comet tail sign (white arrow)
The differential diagnosis of the eye lesions included hordeola/chalazia, pyogenic granuloma, angiosarcoma and haemangioma. However, because of the widespread lesions we mainly considered Kaposi sarcoma and bacillary angiomatosis.

Additional history revealed that our patient had a HIV-positive male sexual partner. His HIV test turned out to be positive. The CD4 count was $220 \times 10^6/\text{mm}^3$ and the HIV viral load $92,600$ c/ml. The diagnosis of Kaposi sarcoma was made after a biopsy, which showed an angioma with positivity for human herpes virus 8 (HHV 8).

Kaposi sarcoma is an angioproliferative disorder which is associated with HHV 8. There are four types of KS with a variable course. The uncommon classic type, which is usually indolent, predominantly occurs in older males with Mediterranean roots. The endemic type, which is prevalent in Africa, is independent of HIV infection. The iatrogenic type occurs in immune suppressed patients. Kaposi sarcoma most commonly involves the skin, but it can occur at any site of the body. The cutaneous lesions are often situated on the lower legs, face, oral mucosa and genitalia. The lesions are not painful and can have an assortment of colours due to vascularisation, which can vary from pink to brown. Lymphoedema is often present.

The most frequent sites of noncutaneous Kaposi sarcoma include the gastrointestinal tract and respiratory system. The incidence of Kaposi sarcoma has declined from 6.7% to 2% since the introduction on highly active anti-retroviral therapy (HAART) in 1996.

The treatment of Kaposi sarcoma should always include the introduction of HAART. For some patients this is sufficient. In extensive cutaneous, symptomatic visceral involvement or cutaneous Kaposi sarcoma, which is unresponsive to treatment with HAART, the start of local or systemic chemotherapy is indicated. Radiation therapy is suggested for those with larger lesions which are unresponsive to chemotherapy. Despite therapy, Kaposi sarcoma remains a morbid and occasionally life-threatening condition.

In our patient, we started with HAART, after which the CD4 count increased to $500 \times 10^6/\text{mm}^3$. Because of the extent of the disease our patient was treated with systemic chemotherapy. With liposomal doxorubicin all lesions except those on the feet went into remission. Radiation therapy was recently started for the lesions on his feet.

**REFERENCES**

The kidney biopsy showed bile casts in the tubules, which strongly suggests bile cast nephropathy as the cause of acute renal failure.

Bile cast nephropathy, or cholaemic nephrosis, is a rare cause of renal injury. Only a few cases of bile cast nephropathy have been reported over the past decade. The exact pathophysiological mechanism of bile cast nephropathy is as yet unknown. It is believed that hyperbilirubinaemia causes damage to the kidney in several ways: first, bile casts cause tubular obstruction (as was seen in this patient) and, second, the presence of high concentrations of bile in the renal tubules may be toxic to tubular cells, resulting in impairment of tubular function. Hypertrophy of the tubular cells is observed in patients with bile cast nephropathy. Also in our patient, tubular epithelial cells revealed pronounced reactive changes (figure 2). It must be emphasised, however, that it is often difficult to completely rule out involvement of an additional pre-renal cause of renal insufficiency. On the other hand, in this case the sodium concentration in the urine at presentation and remaining renal failure after complete normalisation of blood pressure would make this less likely. The diagnosis bile cast nephropathy can be suspected when extreme hyperbilirubinaemia and acute kidney failure coincide. It may be confirmed by the observing bile casts in a kidney biopsy and suggested by observing bile crystals in a urine sample. Bile crystals (which were not seen in our patient) may sometimes be observed in urine although their role in pathophysiology remains unclear. Bile cast nephropathy is treated by reversing the liver injury. Recovery of renal function may take several weeks.

In this patient, the liver injury was treated by placing a drain in the common bile duct. Serum bilirubin levels normalised within a few weeks. He remained on haemodialysis for 5 weeks, after which kidney function recovered.

REFERENCES

DIAGNOSIS

Serology showed a positive ELISA and IgG1/IgG4 for *Echinococcus granulosus*. The magnetic resonance imaging showed a large hydatid cyst in the left lower liver lobe, also called the ‘waterlily sign’ (figure 1) and multiple cysts in the liver (figure 2).

Hydatid cysts or hydatid disease is created by the larval stage of the parasitic tapeworm *Echinococcus granulosus*. The disease state is characterised by cyst formation in various organs. Hydatid disease frequently occurs in endemic areas, including several Mediterranean countries, New Zealand, Australia, North America, South America, Central America and Asia.¹

The liver is the most commonly affected organ, followed by the lungs. The initial growth of a cyst is usually asymptomatic, until symptoms are caused by the cyst’s space-occupying mass effect, mechanical obstruction or rupture. Anaphylactic reactions are rare presentations of a ruptured hydatid cyst.² Diagnosis of a hydatid cyst is difficult and hydatid cysts may be misdiagnosed as another disease, which delays the correct treatment.

Treatment strategies pertaining to cystic echinococcosis have been widespread and widely discussed.³ The (laparoscopic) surgical approach seems safe and the objective of surgery is to remove parasitic cysts and fluid completely, a major advantage compared with other types of treatment. But controversies still exist about the preferred operating technique.⁴ Since 1986, Puncture Aspiration Injection Re-aspiration (PAIR) has been proposed as an alternative to surgery. After percutaneous puncture under ultrasonographic guidance, a complete aspiration is performed; the residual cavity is then filled with a protoscolicide, usually ethanol, and re-aspired ten minutes later.⁵ With multiple cysts and multiple initial locations, as in our patient, recurrence in multiple organs and especially in the peritoneum represents a good indication for chemotherapy alone,⁶ which may also be the first step before a hazardous operation in complicated cases. Albendazole is usually preferred at an average daily dosage of 15 mg/kg/day; it must be given continuously, without those treatment interruptions which were recommended in the past. Blood count and transaminases must be checked every week for the first month and every month thereafter. Our patient was treated with albendazole 400 mg twice daily and she was referred to a tertiary centre.

REFERENCES


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A chest CT scan revealed calcified pleural plaques, and an ovoid opacity within the left upper lobe subjacent to a pleural plaque (arrows) is also seen with swelling of the adjacent bronchi and vessels, all of which led to a diagnosis of rounded atelectasis. Crowding of vessels and bronchi close to it is referred to as the ‘comet tail’ sign, which is pathognomonic of this entity. A subsequent positron emission tomography (PET) scan (figure 3) of the chest revealed only mild uptake of 18F-fluorodeoxyglucose, establishing the benign nature of the mass.

Rounded atelectasis represents an unusual form of lung collapse that occurs adjacent to the scarred pleura, which can be easily mistaken for lung cancer. It has been referred to as Blesovsky syndrome, atelectatic pseudotumour and shrinking pleuritis with atelectasis. Two theories are postulated to explain the formation of rounded atelectasis: the favoured one by Schneider and Dernevik suggests that the underlying event is a local pleuritis caused by irritants such as asbestos. The pleura then contracts and thickens, with shrinkage of underlying lung, and atelectasis develops in a round fashion. The other theory postulated by Hanke et al. suggests that in an area of pleural effusion, regional lung becomes adherent to the parietal pleura and interlobar fissure. As the fluid resolves, the more central lung expands, leaving the peripheral lung adherent to the pleura, atelectatic and rolled into a round configuration.

Rounded atelectasis is almost always asymptomatic and a history of asbestos exposure is seen in 70% of cases. However, tuberculosis, pulmonary infarction and malignancy have been implicated in its formation. CT scan features of rounded atelectasis are characteristic, which include a rounded peripheral lung mass, most dense at the periphery that is not completely surrounded by lung. The mass forms an acute angle with the pleura and adjacent pleural thickening is always seen. Air bronchograms may also be present within the mass. The characteristic feature of round atelectasis is the comet tail sign, which describes the crowded and converging bronchovascular bundles entering the mass from all sides. An estimated 50% cases of rounded atelectasis are not detected by chest X-rays. Most authorities agree that CT is an almost perfect tool for confident diagnosis, accurate enough to obviate exploratory or resectional thoracotomy most of the time. However, only one study has addressed this matter systematically which concluded that the comet tail sign is the most reliable sign for diagnosis (sensitivity of 83% and specificity of 92%).

FDG-PET techniques, such as dual time-point FDG-PET, hold promise for even greater diagnostic accuracy (100% sensitivity, 89% specificity). PET scan is mainly useful to differentiate rounded atelectasis from malignant lesions when CT is equivocal. The main differential to this entity is bronchogenic carcinoma; however the characteristic imaging features of rounded atelectasis make other tests unnecessary. No specific treatment is needed for rounded atelectasis and they occasionally disappear spontaneously. Rounded atelectasis per se is not a pre-neoplastic lesion. In a series of 74 patients with rounded atelectasis, followed over 16 years, none turned out to be malignant. However, considering it develops as a sequelae of exposure to a known carcinogen, such patients should be subjected to a close follow-up.

Thus, we reiterate the importance of knowledge of this benign entity to the general internist as it can avoid unnecessary tests and concern to the patient.

REFERENCES
Estimated hospital health costs of chronic abdominal pain in the Netherlands

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A B S T R A C T

Aim: Calculation of the hospital costs of chronic abdominal pain in the Netherlands. 
Design: Cross-sectional study. 
Methods: We selected ‘Diagnosis-Related Groups’ (DRG) of disorders that are associated with chronic abdominal pain from a large teaching hospital and a tertiary referral centre. For each DRG we determined the percentage of patients that can present with abdominal pain. The total costs for both hospitals were calculated using the registered quantity of the DRGs. Each DRG was categorised by somatic and functional origin. The results were subsequently extrapolated to the entire Dutch population demanding hospital care for chronic abdominal pain. Finally, the percentage and associated costs were calculated for patients who had two or more separate diagnoses for chronic abdominal pain in the field of gastroenterology, gynaecology, internal medicine and urology. 
Results: The yearly outpatient and (day) clinical health costs for patients with chronic abdominal pain in the Netherlands were approximately €623 million (gastroenterology €226 million; gynaecology €303 million; internal medicine €63 million; and urology €31 million). Of these diagnoses, 53.6% were related to functional disorders, which accounts for approximately €220 million per year. The yearly costs of patients who had at least two separate diagnoses within one year for chronic abdominal pain were estimated at €23.5 million per year. 
Conclusion: Chronic abdominal pain is a common problem that entails significant healthcare costs in the Netherlands of which functional diagnoses compromise a significant amount.

K E Y W O R D S

Chronic abdominal pain, DRG (diagnosis-related groups), functional disorders, healthcare costs, secondary and tertiary care

I N T R O D U C T I O N

Chronic abdominal pain is a frequently reported symptom in the general practitioners (GP) practice.¹ It occurs more often in women and is defined as recurring pain that persists for at least six months that is not related to the menstrual cycle.²,³ Of patients who consult their GP for chronic abdominal pain, 18-20% have an underlying organic cause.⁴ Hence, the majority of patients (i.e. approximately 80%) have a functional disorder.⁵ In the Netherlands, approximately 500,000 patients with chronic abdominal pain are seen by GPs per year. Fifty percent of patients who suffer from abdominal pain will eventually be referred to a secondary or tertiary referral centre.⁶ We aimed to gain insight into the outpatient and (day) clinical healthcare costs of patients with chronic abdominal pain in the Netherlands. The importance of this study is underscored by the problematic rise in Dutch healthcare costs that has increased from 7.5% of the gross domestic product in the early 1970s to 13% nowadays. More than €80 billion per year is spent on healthcare in the Netherlands.⁷ Better insight into healthcare costs of patients suffering from chronic abdominal pain might result in the development and implementation of cost reduction strategies.
METHODS

The DRG (Diagnosis-Related Groups) datasets of the Academic Medical Centre (AMC, Amsterdam, the Netherlands) and a large teaching hospital (St. Antonius Hospital, Nieuwegein, the Netherlands) were analysed. These datasets contain all DRGs that were closed in the year 2010 in both hospitals in the field of gastroenterology, gynaecology, internal medicine, and urology. Diagnoses were selected that are associated with chronic abdominal pain, excluding upper abdominal pain. A literature review was conducted in order to determine the percentage of patients who can present with chronic abdominal pain for each diagnosis. This resulted in a weighting factor for chronic abdominal pain per diagnosis (table 1). This weighting factor was multiplied by the number of patients and DRGs for each diagnosis for both hospitals. For example, the weighting factor for Crohn’s disease is 0.83 which means that 83% of patients with Crohn’s disease present with chronic abdominal pain. If in one year in a particular hospital 100 DRGs for Crohn’s disease are closed, the calculation would be as follows: 0.83 x 100 = 83 DRGs. In contrast to gastroenterologists, gynaecologists and internists, urologists systematically register the main symptom for each patient in the DRG registration system. Therefore, the weighting factor for urology-related diagnoses is 1.

DRG rates

DRG prices for 2010 were obtained from the website of the Dutch Healthcare Authority (Nederlandse Zorgautoriteit, NZa). The price of each DRG for the St. Antonius Hospital and AMC was determined using an online application tool. The healthcare costs were calculated by multiplying the price per DRG with the patient number for each DRG, including the costs of outpatient and (day) clinical treatment.

Extrapolation to the entire Dutch population

The total number of outpatient visits for all Dutch academic hospitals in 2010 was divided by the number of outpatient visits to the AMC for that same year. For the St. Antonius Hospital a similar calculation was performed for all non-academic hospitals. The ratios were subsequently used to calculate the healthcare costs for all teaching hospitals and tertiary referral centres in the Netherlands, for both somatic and functional diagnoses.

Operation codes

The costs of selected DRGs are not always entirely attributable to chronic abdominal pain. For this reason, operation codes were determined for five randomly selected patients using the same dataset for three random DRG codes for gastroenterology, gynaecology, internal medicine and urology. Next, we assessed which operations are associated with chronic abdominal pain. To calculate the costs, reference prices from the Manual for Cost Research and rates of the Dutch Healthcare Authority were used. A gynaecologist (E.K.) and a gastroenterologist (M.L.) indicated which operations were related to the work-up of patients suffering from chronic abdominal pain.

<table>
<thead>
<tr>
<th>Gastroenterology</th>
<th>Gynaecology</th>
<th>Internal medicine</th>
<th>Urology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic abdominal pain* 1</td>
<td>Abdominal pain, no gynaecological cause* 1</td>
<td>Abdominal pain without diagnosis* 1</td>
<td>Renal tumour 1</td>
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<tr>
<td>Irritable bowel syndrome* 1</td>
<td>Benign adnexal abnormality 0.78</td>
<td>Irritable bowel syndrome* 1</td>
<td>Kidney stone 1</td>
</tr>
<tr>
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<td>Endometriosis 0.69</td>
<td>Ischaemia 0.94</td>
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<tr>
<td>Crohn’s disease 0.83</td>
<td>Malignancy ovarian 0.45</td>
<td>Crohn’s disease 0.83</td>
<td>Bladder tumour 1</td>
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<tr>
<td>Infectious-(entero) colitis 0.8</td>
<td>Colorectal cancer 0.44</td>
<td>Infectious (entero) colitis 0.8</td>
<td>Bladder infection 1</td>
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<td>Prolapse 0.44</td>
<td>Chronic obstruction 0.56</td>
<td>Bladder prostatic obstruction 1</td>
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<td>Ulcerative colitis 0.52</td>
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<tr>
<td></td>
<td>tuba-ovarian abscess 0.3</td>
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<td>Cervix carcinoma 0.17</td>
<td>Diverticulitis 0.33</td>
<td>Other bladder pathologies 1</td>
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<tr>
<td></td>
<td>Endometrium carcinoma 0.17</td>
<td></td>
<td>Prostate inflammation/abscess 1</td>
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<tr>
<td></td>
<td>Chorionic carcinoma 0.05</td>
<td></td>
<td>Congenital renal pathology 1</td>
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<td></td>
<td>Extra uterine gravidity 0.05</td>
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<td>Bladder problems* 1</td>
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<td></td>
<td>Sexual problems* 0.02</td>
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<td>Prostaticynia/ Chronic pelvic pain* 1</td>
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<td></td>
<td>A-(hypo) contractile bladder* 1</td>
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<td></td>
<td>Urge incontinence/ overactive bladder 1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Various urological disorders 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No urological disorder* 1</td>
</tr>
</tbody>
</table>

Table 1. Diagnoses that are associated with chronic abdominal pain in the field of gastroenterology, gynaecology, internal medicine and urology and the corresponding weighting factors. Functional diagnoses are highlighted by the asterisk sign (*)
addition, a weighting factor was calculated by dividing the costs that were related to chronic abdominal pain by the total costs. These weighting factors were multiplied by the total DRG cost price resulting in healthcare costs that were related to chronic abdominal pain. To examine whether the costs of randomly selected DRG codes corresponded with the transaction codes, outcomes were analysed using SPSS (software version 20).

**Costs of two separate diagnoses of functional abdominal pain**

The costs of two separate diagnoses (defined as different DRGs that were opened for the same symptom by at least two different specialists within one year) were calculated using a second DRG dataset from the St. Antonius Hospital. This dataset included patients with the following functional DRGs: abdominal pain without gynaecological cause, chronic abdominal pain, dyspareunia, irritable bowel syndrome, no urological diagnosis and hypo/acontractile bladder. For each functional diagnosis, the number of patients who visited at least two different specialists for the same symptom within one year was examined.

**RESULTS**

**Healthcare costs of patients with chronic abdominal pain**

The total healthcare costs of patients with chronic abdominal pain in the St. Antonius Hospital and the AMC in 2010 were estimated at €18.8 million and €2.1 million, respectively (table 2).

**Extrapolated healthcare costs of chronic abdominal**

The ratios for the St. Antonius Hospital and AMC were 45.4 and 8.3, respectively. In order to extrapolate the calculated costs to the Dutch situation, outcomes of the St. Antonius Hospital were multiplied by 45.4 and for the AMC by 8.3. The cost price of all DRGs for patients with chronic abdominal pain in all Dutch teaching hospitals and tertiary referral centres was approximately €850 million and €17.7 million, respectively (table 3). The total costs of DRGs that were related to chronic abdominal pain were estimated at €870 million in 2010 (table 3).

**Transaction codes**

Weighting factors were calculated using transaction codes in order to convert the calculated costs into actual costs related to chronic abdominal pain (table 3). The weighting factors were 0.67 with a standard deviation (SD) of 0.16 for gastroenterology, 0.75 with an SD of 0.19 for gynaecology, 0.88 with an SD of 0.11 for internal medicine, and 0.57 with an SD of 0.24 for urology. These weighting factors were multiplied by the total cost per DRG. The Dutch healthcare costs that are related to chronic abdominal pain in secondary and tertiary care were estimated at €623 million per year (table 3).

Next, we examined whether the costs of the transaction codes corresponded with the costs of the selected DRG codes. To this end, the costs of randomly selected patients were compared with the price that is related to the DRG code. Nine out of 12 codes that were selected did not show a significant difference (p>0.05).

**Costs of functional abdominal pain**

Of DRGs for patients with chronic abdominal pain, 53.6% were related to a functional disorder. The healthcare costs of patients with chronic abdominal pain due to a functional disorder were estimated at €220 million per year, and this accounts for 35.3% of the total healthcare costs of patients with chronic abdominal pain: 64% of €220 million is related to gastrointestinal diseases. Of the patients with a functional disorder (i.e. 3435 out of 7096 functional DBCs) within the specialty of gastroenterology and internal medicine, 48.4% were diagnosed with irritable bowel syndrome (IBS). Patients with IBS are responsible for 36.7% of the total hospital costs of functional abdominal pain.

**Healthcare costs of patients with chronic abdominal pain caused by two separate diagnoses**

Of the patients with a functional diagnosis, 3.9% were seen by at least two specialists (gastroenterologist, gynaecologist and/or urologist) for the same symptom within a one-year time frame. Approximately 31.5% of the total costs (163,000/518,000) are spent on functional abdominal pain. When these results are extrapolated to the entire Dutch population, the costs of two or more separate diagnoses for chronic abdominal pain are approximately €23.4 million per year, of which €7.4 million is spent on functional disorders.

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<table>
<thead>
<tr>
<th>Table 2. Health care costs of patients with chronic abdominal pain in the AMC and St. Antonius Hospital in the year 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. Antonius</td>
</tr>
<tr>
<td>AMC</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Table 3. Extrapolated total (corrected) health care costs in the Netherlands of chronic abdominal pain in 2010 for gastroenterology, gynaecology, internal medicine and urology

<table>
<thead>
<tr>
<th></th>
<th>Gastroenterology</th>
<th>Gynaecology</th>
<th>Internal medicine</th>
<th>Urology</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-academic hospitals</td>
<td>€333,998,357</td>
<td>€397,387,017</td>
<td>€64,537,682</td>
<td>€54,236,457</td>
<td>€850,159,513</td>
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<tr>
<td>Academic hospitals</td>
<td>€3,822,399</td>
<td>€6,736,214</td>
<td>€6,797,468</td>
<td>€319,501</td>
<td>€17,693,675</td>
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<tr>
<td>Total</td>
<td>€3,157,820,756</td>
<td>€4,044,123,21</td>
<td>€71,335,150</td>
<td>€54,576,048</td>
<td>€867,855,185</td>
</tr>
</tbody>
</table>

**Discussion**

Chronic abdominal pain is a common problem that is associated with an impaired quality of life and high treatment and diagnostic costs. Hence, it is important to gain more insight into this multifactorial symptom. Here, we have analysed the healthcare costs of patients with chronic abdominal pain in secondary and tertiary care in the Netherlands using DRG datasets from an academic and a large teaching hospital. This study is an important first step towards transparency about healthcare costs in general and of patients with chronic abdominal pain in particular. The present study has its limitations. First of all, it is questionable to what extent international literature can be extrapolated to the Dutch situation with strong adherence of patients to their general practitioner. Secondly, calculations were made using DRG datasets from an academic and a non-academic hospital. These outcomes were extrapolated to the entire Dutch population and are therefore an estimation of reality. Moreover, it should be noted that DRG cost prices are fixed prices that are comparable with the real prices in daily practice. This does not necessarily mean that the price per DRG reflects the actually incurred costs. ‘Operation codes’ were therefore used to determine abdominal pain-related DRG costs employing randomly selected patients from the DRG datasets and the operation codes.

A significant difference was seen in the number of patients with chronic abdominal pain who were referred to the AMC and St. Antonius Hospital: 1990 patients were referred to the department of gastroenterology, gynaecology, internal medicine, or urology in the AMC in one year, whereas 23,359 patients visited these specialties at the St. Antonius Hospital. This explains the difference in healthcare costs between these two hospitals, as depicted in Table 3, and illustrates the role of academic tertiary care providers.

The present study reveals that more than half (53.6%) of patients with chronic abdominal pain have a functional disorder and is a functional bowel disorder of unknown aetiology, and is the most common gastrointestinal disorder in the GP’s practice. The prevalence and incidence of IBS in the GPs practice is 10.5 per 1000 and 5.6 per 1000, respectively. On average the GP sees two patients with IBS per week. Here we show that IBS patients are responsible for high healthcare costs (82.4 million per year) in secondary and tertiary care, which equals 36.7% of the total healthcare costs of functional abdominal pain. Identification of patients with functional abdominal pain might result in the development and implementation of cost reduction strategies. It has for example been shown that these patients may benefit from receiving information and nutritional and lifestyle advice. Moreover, psychotherapy and pelvic physiotherapy might be effective in treating these patients.

**Conclusion**

Patients with chronic abdominal pain frequently visit their GP. About 50% of these patients are referred to a (non)academic hospital. We demonstrate here that approximately €623 million per year is spent in the Netherlands on hospital costs for patients with chronic abdominal pain. This equals 0.9% of the total Dutch healthcare budget. Approximately 50% of patients with chronic abdominal pain have a functional disorder and this patient subgroup is responsible for high diagnostic and treatment costs (approximately €220 million per year). A significant proportion (3.9%) of patients with a functional diagnosis is referred to two or more specialists within one year for the same symptom. Cost reduction strategies that are aimed at identifying and treating patients with functional abdominal pain might result in a reduction of healthcare expenses.

**Disclosures**

Dr. Mark Löwenberg has served as speaker for Abbott/Abbvie, Dr. Falk, Ferring, MSD and Tramedico. This study did not receive any grant support.
REFERENCES

Trends in the outcomes of Dutch haematological patients receiving intensive care support

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ABSTRACT

Background: Because of the assumed dismal prognosis there is still reluctance to admit haematological patients to the intensive care unit (ICU). This study was conducted to determine trends in outcome of allogeneic haematopoietic stem cell transplant (HSCT) recipients transferred to the intensive care unit in a Dutch tertiary care hospital.

Methods: All patients who received allogeneic HSCT between 2004-2010 were included in the analyses. Baseline and outcome characteristics were compared and risk factors for ICU admission and survival were identified. Changes in outcome over time of three cohorts of HSCT recipients were investigated.

Results: Of 319 consecutive HSCT recipients, 49 (15%) were transferred to the ICU for a median (IQR) of 10 (6-45) days following their transplantation, of whom 43% were severely neutropenic and 90% had received systemic immunosuppressive therapy for graft-versus-host disease prophylaxis. Univariate logistic regression showed that transplantation from an unrelated donor and myeloablative conditioning were significant risk factors for ICU admission. Prolonged use of vasopressors, invasive mechanical ventilation and male gender were significant predictors for ICU mortality, while neutropenia and graft-versus-host disease were not. Over the years, APACHE-II severity of illness scores remained unchanged (21.02±7.1, 20.12±5.6, 21.24±6.6), while 100-day post-transplant mortality of patients who had been transferred to the ICU decreased significantly from 78% (2004/2005) to 57% (2006/2007), and 35% (2008/2009). Conclusions: While for allogeneic HSCT patients the severity of illness on admission to the ICU did not change, the 100-day post-transplant survival improved. These data indicate that reluctance to submit haematological patients to the ICU is not warranted.

KEYWORDS

Haematopoietic stem cell transplant, haematological malignancy, intensive care unit admission, risk factors, outcome

INTRODUCTION

Patients with haematological malignancies are currently treated with intensive cytotoxic therapies often culminating in an allogeneic haematopoietic stem cell transplant (HSCT). A clear reduction in transplant-related mortality (TRM) was observed between 1967-2002, mainly due to prompt administration of antibiotics at the onset of fever, better prevention of infectious complications and improved clinical care.1-3 Life-threatening complications now occur more frequently as a result of therapy rather than the haematological disease itself.4,5 These complications occur acutely, typically during the period of neutropenia when patients are profoundly immunocompromised,6 or during neutropenia recovery.7 It is inevitable that some patients will develop medical problems requiring transfer to the intensive care unit (ICU), either for close monitoring or for intensive treatment. In the past, neutropenic patients who developed organ failure were considered to have such a dismal prognosis that physicians were reluctant to even consider admitting them to an ICU.8 Since 2002, improved outcomes for these patients have been reported, and the importance of neutropenia as a predictor for ICU mortality was debated.9

Respiratory insufficiency associated with sepsis is the most common indication for admission from the haematology ward to the ICU.1 Approximately one in four HSCT recipients require endotracheal intubation and mechanical
ventilation for acute respiratory failure. Severe sepsis and septic shock are the most frequently observed reason for ICU admission. The outcome of those patients who need critical care appears to have improved, although in the subgroup of HSCT recipients receiving mechanical ventilation the reported mortality rate still exceeds 80% and acute graft-versus-host disease (aGvHD) is reported to be an independent predictor for death, specifically in combination with mechanical ventilation. Early initiation of non-invasive ventilation is associated with significant reductions in the rates of endotracheal intubation and serious complications and an improved likelihood of survival until hospital discharge. These results led to improved awareness of the benefits of early admission to an ICU, resulting in more allogeneic stem cell transplant recipients being transferred to the ICU. Nevertheless, also in the Netherlands, important differences between centres concerning ICU admission policies exist and more evidence is needed to show that ICU treatment of this specific transplant group is not futile.

In this study we investigated the changes in outcome over time of three cohorts of HSCT recipients and compared the outcome of those that needed intensive care treatment to those who did not.

**Design and Methods**

**Design**

The records of all consecutive patients admitted to the Department of Haematology of Radboud University Medical Center, a tertiary academic hospital, between 1 January 2004 and 1 January 2010, were retrospectively analysed. HSCT recipients were identified and only their first unplanned referral to the ICU (<100 days) was included in the study. An unplanned admission was defined as an admission because of acute deterioration and not for scheduled activities that needed intensive monitoring (e.g. broncho-alveolar lavage with non-invasive ventilation support). Demographic data as well as relevant haematological data including underlying disease, donor type, type of transplant and presence of GvHD were retrieved from electronic patient files. Risk scores for TRM developed by the European Group for Blood and Marrow Transplantation (EBMT) were calculated. Clinical data during ICU admission and discharge, the reason for admission, the severity of illness during the first 24 hours, as well as three outcome measures namely, mortality, and the length of ICU admission and hospital stay were collected. The severity of illness on admission to the ICU was determined by indicators of organ failure and the APACHE II score. The type and duration of mechanical ventilation, renal replacement therapy and vasopressor use were extracted from the medical records. The study has been carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees and informed consent.

**Treatment protocol**

The myeloablative (MA) conditioning regimen consisted mainly of high-dose cyclophosphamide with either idarubicin when a sibling donor was available or antithymocyte globulin (ATG) when the donor was unrelated, with or without total body irradiation. The non-myeloablative (NMA) conditioning regimen consisted mainly of cyclophosphamide and fludarabine, completed with ATG in case of an unrelated donor. ATG was added to the conditioning regimen to attain T lymphocyte depletion to prevent GvHD. During the study period the method of preparation and composition of the stem cell product did not change. Patients did not receive haematopoietic growth factors and anti-microbial prophylaxis consisted of 500 mg ciprofloxacin given twice daily and 500 mg valaciclovir given three times daily. Fluconazole was given at 200 mg a day only to those who were colonised with *Candida albicans*. Vital signs (temperature, heart rate, blood pressure, respiration rate, oxygen saturation) were monitored at least four times daily with an overnight control being included during severe neutropenia to avoid any delay in starting broad-spectrum antibacterial therapy at the onset of fever. Empirical therapy was started once the axillary temperature equalled or exceeded 38.5°C.

**ICU transfer criteria**

No explicit ICU admission policy was adopted. The decision to admit a patient to one of the level 3 general ICUs of our hospital was made by the senior haematologist and the senior intensivist.

**Statistical analysis**

Continuous variables were summarised using mean values and standard deviations (SD) or median values and interquartile range (IQR) if data were not normally distributed. To compare characteristics we applied the independent *t*-test for continuous variables and chi-squared or Fisher’s exact tests in case of percentages. Univariate logistic regression analyses were used to identify factors associated with ICU admission and ICU mortality. The power of this study was inadequate to perform multivariate analyses. Two-tailed *p*-values <0.05 were considered to indicate statistical significance. A hundred days post-HSCT survival was presented in a Kaplan-Meier curve comparing the three periods using the log-rank test. All statistical analyses were carried out with SPSS version 18.0.
RESULTS

ICU-group characteristics
Between 1 January 2004 and 1 January 2010, 319 patients received an allogeneic HSCT, of whom 49 patients were transferred to the ICU for a median (IQR) of 10 (6-45) days following their transplantation. The most common underlying diagnoses were acute myeloid leukaemia (n=14, 29%), non-Hodgkin’s lymphoma (n=10, 20%) and myelodysplastic syndrome (n=8, 16%). The depth of compromised immunity at the moment of ICU transfer was emphasised by the fact that 43% of the patients were severely neutropenic (neutrophil count of ≤0.5 x 10^9/l) on ICU admission and 90% had received systemic immunosuppressive therapy for GvHD prophylaxis. Infectious complications were the main reason for ICU admission (86%), with respiratory insufficiency reported as the main symptom (67%), followed by haemodynamic instability, sepsis and septic shock. Mortality rates at 100-days post-HSCT were significantly higher for the patients who required an ICU admission (53 versus 8% in HSCT patients who did not need intensive care, p<0.01). Length of stay in the hospital was significantly longer (median 45 days; range 36-70) for patients requiring an ICU admission compared with those without ICU admission (29 days; range 23-39); p<0.01.

Risk factors for ICU admission
The characteristics of ICU patients were compared with those without intensive care treatment. Age and gender were distributed equally in both groups (table 1). Univariate analysis identified two haematological risk factors for ICU admission to be significant: an unrelated donor graft (OR=2.5, 95% CI 1.3-4.6) and MA conditioning (OR=2.3, 95% CI 1.1-4.7). The power of this study was inadequate to perform a multivariate analysis. The onset of aGvHD grade 2-4 within 100 days for those admitted to the ICU was 29% (14/49), similar to those not admitted to the ICU (30%).

Changes in ICU characteristics over the years
There were no changes in the number of days from HSCT to ICU admission (median 10, IQR 6-45 days after HSCT), length of ICU stay (median 4, IQR 1-12 days) or time post-ICU to hospital discharge (median 15, IQR 1-35 days) over time, nor did the APACHE II severity of illness on ICU admission and EBMT estimated risk of not surviving for five years change during the study period (table 2). The proportion of patients requiring endotracheal intubation

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Table 1. Demographic factors associated with ICU admission before 100 days post-HSCT (2004-2009, n=319)

<table>
<thead>
<tr>
<th></th>
<th>HSCT-recipients without ICU admission (n=270)</th>
<th>HSCT-recipients with ICU admission (n=49)</th>
<th>P-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.2 (± 11.0)</td>
<td>47.4 (± 11.3)</td>
<td>0.64*</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>167 (62%)</td>
<td>29 (59%)</td>
<td>0.75b</td>
<td></td>
</tr>
<tr>
<td>Unrelated donor</td>
<td>89 (33%)</td>
<td>27 (55%)</td>
<td>&lt;0.01b</td>
<td>2.5 (1.3-4.6)</td>
</tr>
<tr>
<td>Myeloablative conditioning</td>
<td>162 (60%)</td>
<td>38 (78%)</td>
<td>0.02a</td>
<td>2.3 (1.1-4.7)</td>
</tr>
<tr>
<td>EBMT estimated risk (n=237/43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1 (0%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>63 (27%)</td>
<td>14 (33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>173 (73%)</td>
<td>29 (67%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean (± standard deviation) or n with (%); *independent T-test; ¯Chi²-test; ¯Fisher’s exact test.

Table 2. Demographics, ICU characteristics and outcome of patients transferred to an ICU within 100 days post-HSCT in two-year periods (n=49)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.3 (±11.5)</td>
<td>47.6 (±10.3)</td>
<td>47.8 (±11.2)</td>
</tr>
<tr>
<td>APACHE II on admission</td>
<td>21.0 (±7.1)</td>
<td>20.1 (±5.6)</td>
<td>21.2 (±6.6)</td>
</tr>
<tr>
<td>EBMT estimated risk</td>
<td>4.0 (±1.0)</td>
<td>3.6 (±1.4)</td>
<td>2.8 (±1.1)</td>
</tr>
<tr>
<td>Invasive ventilation (days)</td>
<td>0.4 (±0.1)</td>
<td>1.5 (±0.5)</td>
<td>1.3 (±0.6)</td>
</tr>
<tr>
<td>Non-invasive ventilation (days)</td>
<td>0.0 (±0.0)</td>
<td>0.3 (±0.1)</td>
<td>0.2 (±0.0)</td>
</tr>
<tr>
<td>Vasopressor use (days)</td>
<td>0.2 (±0.3-9)</td>
<td>0.4 (±0.3-0)</td>
<td>0.0 (±0.0-1.4)</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>4 (44%)</td>
<td>8 (35%)</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>7 (78%)</td>
<td>12 (52%)</td>
<td>7 (41%)</td>
</tr>
<tr>
<td>100 day post HSCT mortality</td>
<td>7 (78%)</td>
<td>13 (57%)</td>
<td>6 (35%)</td>
</tr>
</tbody>
</table>

Data are expressed as mean (± standard deviation), median [IQR] or n with (%).
tended to decrease, but this did not reach statistical significance. In contrast, the number of non-invasive ventilation days increased (p=0.02). The number of days that vasopressor medication was required remained unchanged.

ICU mortality was 44% (2004/2005) to 35% (2006/2007) and 24% (2008/2009) and hospital mortality 78% to 52% and 41%, but these trends did not reach statistical significance. In contrast, the number of non-invasive ventilation days increased (p=0.02). The number of days that vasopressor medication was required remained unchanged.

ICU mortality was 44% (2004/2005) to 35% (2006/2007) and 24% (2008/2009) and hospital mortality 78% to 52% and 41%, but these trends did not reach statistical significance. In contrast, the number of non-invasive ventilation days increased (p=0.02). The number of days that vasopressor medication was required remained unchanged.

Figure 1 illustrates the decrease in the 100-day post-HSCT mortality for patients who had been admitted to the ICU (p=0.02). A similar decrease was found for patients given MA conditioning (78% to 56% and 36%, respectively) and NMA conditioning (no patients in first period, 60% and 33% in period 2 and 3, respectively). While these improvements did not reach statistical significance, likely due to a type 2 error, they do illustrate that in both groups a comparable improvement in outcome is observed over time. The 100-day post-transplant mortality of the complete group of patients (n=319) remained constant over time between 15-19%.

Factors associated with ICU survival
Characteristics were compared between ICU survivors and non-survivors to determine the factors that were associated with survival of the patients who needed an ICU admission (table 3). Age and HSCT-related characteristics including donor type, bacteraemia, neutropenia and EBMT estimated risk score were similar in both groups. The duration that vasopressor medication was required (p<0.01), the number of days invasive ventilation was required (p<0.01) and male gender (p=0.04) were significant univariate predictors for ICU mortality. The APACHE II score (p=0.07) and receipt of MA conditioning (p=0.08) also tended to be related to ICU mortality. Neutropenia and both the presence of aGVHD grade 2-4 on ICU admission and the onset of aGVHD within 10- days post-HSCT were not shown to be risk factors for ICU survival.

DISCUSSION
The present study shows that the proportion of HSCT patients admitted to the ICU during the last decade has risen. Receiving stem cells from an unrelated donor and MA conditioning were shown to be the major risk factors for ICU admission as one in four required ICU admission. While their disease severity on ICU admission, as determined by APACHE-II, remained similar, the 100-day transplant-related mortality decreased. Factors associated with ICU mortality were duration of vasopressor therapy, invasive mechanical ventilation and male gender. No correlation was found between the presence of neutropenia or GVHD and the risk for ICU admission or ICU mortality. ICU and post-ICU hospital mortality was low in our population compared with recent literature. Improved outcome for HSCT recipients might be explained by the fact that ICU treatment in general has improved, as is illustrated by higher ICU survival rates for the general adult ICU population as well as in our own hospital. In addition, haematologists are more aware of the fact that admission to the ICU is feasible and effective, provided it is arranged at an early stage of deterioration. Nevertheless, APACHE-II scores during the study period did not decrease. While this cannot be deduced from our data, we have the impression that attitudes changed over time from ‘no patient to be transferred to the ICU, unless…’ to ‘if needed, every patient should be transferred to the ICU, unless…’. Some authors propose that ‘unlimited ICU treatment for a limited period’, with full ICU support for e.g. four days and re-evaluation on day 5 could be an appropriate strategy of care for those patients with an unknown disease status or disease recurrence with available treatment options. Our data show that 39% of the 100-day survivors needed six days or more on the ICU with a range for ICU survivors of 1-50 ICU days, implying that a decision about futility of treatment cannot be made within 4-6 days. Long-term physical, mental and social consequences of prolonged ICU admission and the effects of more extensive use of mechanical ventilation are now being studied in larger populations to determine the long-term effects of ICU treatment.

The finding that the duration of invasive mechanical ventilation and duration of vasopressor use predict ICU mortality is not surprising or new. It is well known that respiratory failure that requires mechanical ventilation and vasopressors indicates sepsis and shock and predicts mortality in almost all patient populations. Several studies have reported the use of mechanical ventilation...
in this profoundly immunocompromised population to be predictive for ICU mortality\(^1\) and this is supported by the high mortality rates reported.\(^2\) In our study population the use of non-invasive ventilation increased, relative to invasive ventilation over the years, and probably contributed to the better survival rates. However, prolonged use of non-invasive ventilation is still controversial.\(^3\) The benefit of organ support in patients with late-onset complications related to aGvHD and high-dose corticosteroid treatment is contentious.\(^4\) GvHD is regarded a poor prognostic factor for the critically ill HSCT recipient.\(^5,6\) It is remarkable that we found no indication that GvHD was related to ICU admission, nor ICU mortality. However, with the use of partially T-cell depleted grafts the overall incidence of GvHD was modest and the incidence of severe and refractory aGvHD was low. So, at least in this context, there should be no restrictions imposed on transferring these patients to an ICU when indicated.

As most ICU indications are associated with an infectious cause, haematology wards should optimise their procedures for early recognition and adequate treatment of infectious complications and their haemodynamic sequelae.\(^7\) ICU survival seems importantly related to the extent of organ dysfunction,\(^8\) so employing monitoring systems such as vital signs based early warning scores to recognise acute clinical deterioration\(^9,10\) should be encouraged. Clearly, guidelines are needed to help haematologists decide when to transfer a patient to the ICU. As long as no explicit criteria for admission to the ICU are available, early consultation of intensive care physicians might improve accessibility to the ICU at an early stage of deterioration. The APACHE II might also help as it provides a clear indication of the severity of illness once the patient is admitted to the ICU even though it has not been validated for patients with haematological malignancies nor for HSCT recipients.\(^11,12\)

Several limitations of our study need to be addressed. Obviously, caution is required as our study was retrospective in nature and the cohorts were relatively small in size. The absence of statistical significance of some endpoints, for example influence of MA/NMA conditioning on ICU mortality, is likely the result of limited power. Nevertheless, we were able to show an effect on clinically relevant outcome measures using a homogeneous cohort of haematological patients. The decrease in ICU and post-ICU hospital mortality did not reach statistical significance, possibly due to the limited power of the study. However, the impact of this decrease over time is relevant and shows better survival rates of HSCT patients requiring ICU treatment. In addition, the increased use of NMA regimens may be a confounder as the number of patients with NMA conditioning increased simultaneously with the observed decrease in mortality. Nevertheless, the reduction in mortality was similar for both patients given MA and NMA conditioning, indicating that the type of conditioning regimen is unlikely to explain the observed improvement in survival.

### Table 3. Demographic, haematological and ICU risk factors for ICU mortality (2004-2009, n=49)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>ICU survivors (n=33)</th>
<th>ICU non-survivors (n=16)</th>
<th>P-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47 (±12)</td>
<td>48 (±11)</td>
<td>0.77(^7)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>16 (49%)</td>
<td>13 (81%)</td>
<td>0.04(^6)</td>
<td>0.2 (0.1-0.9)</td>
</tr>
<tr>
<td>Haematological parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBMTC estimated risk (n=43):</td>
<td></td>
<td></td>
<td>1.00(^4)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>10 (31%)</td>
<td>4 (29%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>19 (66%)</td>
<td>10 (77%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloablative conditioning</td>
<td>23 (70%)</td>
<td>15 (94%)</td>
<td>0.08(^4)</td>
<td>0.2 (0.0.0-1)</td>
</tr>
<tr>
<td>Unrelated donor</td>
<td>17 (51%)</td>
<td>10 (62%)</td>
<td>(0.47)^h</td>
<td></td>
</tr>
<tr>
<td>Bacteraemia on admission (n=42)</td>
<td>6/27 (22%)</td>
<td>6/15 (40%)</td>
<td>0.29(^4)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia on admission (n=40)</td>
<td>10/27 (37%)</td>
<td>7/13 (54%)</td>
<td>0.31(^b)</td>
<td></td>
</tr>
<tr>
<td>GvHD on ICU admission</td>
<td>2 (6%)</td>
<td>2 (13%)</td>
<td>0.39(^4)</td>
<td></td>
</tr>
<tr>
<td>GvHD &lt;day 100</td>
<td>10 (30%)</td>
<td>4 (25%)</td>
<td>1.00(^4)</td>
<td></td>
</tr>
<tr>
<td>ICU parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II on admission</td>
<td>(19.6 (± 5.7))</td>
<td>22.9 (± 6.5)</td>
<td>0.07(^8)</td>
<td>1.1 (1.0-1.2)</td>
</tr>
<tr>
<td>Invasive ventilation (days)</td>
<td>0.0 [0.0-5.1]</td>
<td>7.9 [3.3-23.0]</td>
<td>(&lt;0.01)^c</td>
<td>1.0 (1.0-1.1)</td>
</tr>
<tr>
<td>Non-invasive ventilation (days)</td>
<td>0.2 [0.0-0.7]</td>
<td>0.1 [0.0-0.3]</td>
<td>0.68(^c)</td>
<td></td>
</tr>
<tr>
<td>Vasopressor use (days)</td>
<td>0.0 [0.0-0.7]</td>
<td>2.4 [0.6-5.1]</td>
<td>(&lt;0.01)^c</td>
<td>1.5 (1.2-2.0)</td>
</tr>
</tbody>
</table>

Data are expressed as mean (± standard deviation), median [IQR] or proportions with \(n\); ‘\(^\text{a}\)’ independent t-test; ‘\(^\text{b}\)’ Chi²-test; ‘\(^\text{c}\)’ Mann-Whitney-U test; ‘\(^\text{d}\)’ Fisher’s exact test.
CONCLUSIONS

In line with general medical ICU patients, outcomes appear to have improved for allogeneic HSCT recipients who required intensive care treatment. Neutropenia and aGvHD were not associated with ICU survival. It appears plausible that an early transfer to the ICU could further improve short- and long-term survival. ICU admittance criteria and guidelines for early transfer to the ICU should be developed.

ACKNOWLEDGEMENT

The authors would like to thank J. van der Velde, senior ICT developer, for providing data from the ICU database for the benefit of the study.

REFERENCES

To the Editor,

The BCR/ABL tyrosine kinase inhibitor nilotinib is used for the treatment of chronic myelogenous leukaemia (CML). Nilotinib is considered well tolerated with few side effects including elevated levels of pancreatic enzymes (lipase and amylase), hyperbilirubinaemia and hyperglycaemia. However, several reports on the occurrence of accelerated atherosclerosis and peripheral arterial occlusive disease (PAOD) in patients treated with nilotinib were published recently.

We report a patient who subsequently developed angina pectoris, caused by a left anterior descending (LAD) stenosis, intermittent claudication and three ischaemic cerebrovascular events in a relatively short timeframe after starting nilotinib.

**CASE**

The 69-year-old patient was diagnosed with breast cancer 20 years ago, for which she was curatively treated with surgery and radiotherapy. Fifteen years before presentation, she was diagnosed with CML, which was initially treated with hydroxycarbamide and interferon-alpha until the cytogenetic response decreased and imatinib (400 mg once daily) was started. Three years ago, a second primary breast tumour was diagnosed, with metastases in the pleura and lymph nodes, for which letrozole (2.5 mg once daily) was started. Last year, after 14 years of imatinib treatment, BCR/ABL positive cells were detected by PCR (>10% of all cells), after which imatinib was discontinued and nilotinib (400 mg twice daily) was started. Shortly hereafter, our patient developed hyperglycaemia, for which metformin was started. A few months after the initiation of nilotinib, the plasma concentration was determined to be 2061 mg/l, far above the minimum threshold set at our clinic (500 mg/l). Because of the very high plasma concentration, the dosage was reduced to 400 mg once daily. Seven months after commencing nilotinib treatment the patient suffered from angina pectoris due to a stenosis in the LAD. A drug-eluting coronary stent was inserted and acetylsalicylic acid, clopidogrel, amlodipine and bisoprolol were started. Despite antiplatelet therapy, the patient started to suffer from intermittent claudication. This year, 12 months after the start of nilotinib, the patient presented with partial aphasia due to an ischaemic cerebrovascular accident (CVA), for which simvastatin was added. Unfortunately, the patient had a second ischaemic CVA three months later, resulting in severe aphasia and wheelchair dependency. Acetylsalicylic acid was discontinued and acenocoumarol was started. Another three months later, despite adequate anticoagulation, the patient developed a third ischaemic CVA, resulting in epilepsy.

**DISCUSSION**

Our patient, without cardiovascular risk factors, developed angina pectoris, intermittent claudication and three ischaemic CVAs during her short course of treatment with nilotinib. Vascular events started soon after initiation of nilotinib, suggesting a causal relationship. We found several recent case reports in which PAOD and an ischaemic CVA, respectively, were diagnosed during nilotinib therapy. Also, the clinical development program of another TKI, ponatinib, was very recently halted due to a very high incidence of arterial thrombotic events (11.5%) leading to cerebrovascular events in 4.0% of the patients. This might suggest a potential group effect for newer tyrosine kinase inhibitors. In light of these recently reported findings and because of the rapid aggravation of vascular events in our patient just after the start of nilotinib treatment, a role for nilotinib in the development of the ischaemic CVAs is possible. Additionally, in our patient a high plasma concentration of nilotinib was measured. Efficacy of nilotinib is considered...
to be related to the plasma concentration, therefore a minimum threshold of 500 mg/l was set at our clinic. Two reports describe a positive correlation between plasma levels and side effects (pancreatic enzymes and hyperbilirubinaemia), suggesting there is an upper safety limit for the plasma concentration of nilotinib. The association between high plasma concentrations of nilotinib and severe adverse events, such as a CVA, has not yet been investigated.

Our patient also used letrozole for breast cancer; a potential contribution of this drug to the vascular events cannot be excluded. Cardiovascular complications including CVAs can occur as a side effect of letrozole in 2-6% of the patients. However, ischaemic events never occurred during our patient’s prior treatment and started just after nilotinib was initiated.

The mechanisms by which nilotinib could cause these serious side effects are poorly understood. Potential roles of discoidin domain receptor 1 (DDR1), KIT and the platelet-derived growth factor receptor (PDGFR) are suggested; however, evidence for the contribution of these kinase targets is lacking. We postulate the need for studies to elucidate the mechanism of action of nilotinib and possible other TKIs in the development of serious vascular events, to be able to understand and hopefully prevent future events.

Clinicians should be aware of the potential role of nilotinib in the development of vascular events and take this knowledge into account during clinical decision-making, for example in patients with pre-existing cardiovascular risk factors.

REFERENCES

To the Editor,
We read the recently published article ‘Red cell distribution width as predictor for mortality in critically ill patients’ by Meynaar et al.1 In the mentioned article, the authors aimed to evaluate whether red cell distribution width (RDW) is a significant risk factor for hospital mortality in critically ill patients and to investigate whether RDW is a parameter indicating inflammation. They concluded that RDW level was an independent predictor of mortality in critically ill patients on ICU admission. The low cost and easy attainability of this parameter may strengthen its usefulness in daily practice in the near future. We would like to thank the authors for their contribution.

RDW, which is used in the differential diagnosis of anaemia, is an automated measure of the variability of red blood cell size.2 Previously it was shown that RDW is an independent variable of prognosis in patients with cardiovascular diseases such as heart failure, myocardial infarction, stroke, and pulmonary hypertension.2-6 In addition, it was also found to be related to mortality and other severe adverse outcomes in renal and infectious diseases.7 Ageing, malnutrition, iron or vitamin B12 deficiency, bone marrow depression, chronic inflammation and any medication may affect RDW levels.2 These factors could affect RDW results. Thus, it would have been useful if the authors had mentioned these RDW-affecting factors. Moreover, it would have been contributory to know the time elapsed between taking the blood samples and measuring RDW since the RDW value may be affected by a delay.8

In a recent study, atrial natriuretic peptide (ANP) was demonstrated to be a valuable predictor in early diagnosis of sepsis in ICU patients.9 Recent studies have shown that the neutrophil-to-lymphocyte ratio and mean platelet volume (MPV) are also associated with inflammatory diseases and mortality in critically ill patients.10-12 In this view, it would also have been relevant if the authors had included these parameters in the study.

We are of the opinion that the findings of Meynaar et al. will lead to further studies and research concerning the relationship between RDW and mortality in critically ill patients. So, RDW should be considered with other inflammatory markers (e.g. procalcitonin, atrial natriuretic peptide and brain natriuretic peptide) to provide certain information about the inflammatory status of the patient.

REFERENCES

Aims and scope
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Journal abbreviations should conform to the style used in the Cumulated Index Medicus. Examples:


Please note that all authors should be listed when six or less; when seven or more, list only the first three and add et al. Do not include references to personal communications, unpublished data or manuscripts either ‘in preparation’ or ‘submitted for publication’. If essential, such material may be incorporated into the appropriate place in the text. Recheck references in the text against the reference list after your manuscript has been revised.

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Figures must be suitable for high-quality reproduction (>300 DPI). Submit line drawings made in Word or other computer programmes but not in a PowerPoint file. Colour figures are occasionally possible and will be charged to the authors. Legends for figures should be typed, with double spacing, on a separate page.

Case reports

Case reports containing concise reports on original work will be considered for publication. Case reports which are relevant for understanding the pathophysiology or clinical presentation of disease may also be accepted under this heading. Selection of case reports will be based on criteria as outlined in a special report by the editors (Drenth et al. The case for case reports in the Netherlands Journal of Medicine. Neth J Med. 2006;64(7):262-4). We advise potential authors to take notice of the instructions in this report. Articles published in this section should be no longer than 1000 words, and supplied with a summary of about 60 words, preferably no more than two figures and/or tables, and no more than 15 references. In addition, we require that authors of case reports answer the following two questions (Neth J Med. 2008;66(7):289-90): 1) What was known on this topic? and 2) What does this add? The answers will appear in a separate box in the text.

Mini reviews

Mini reviews are concise notes that bring the reader up to date with the recent developments in the field under discussion. The review article should mention any previous important reviews in the field and contain a comprehensive discussion starting with the general background of the field. It should then go on to discuss the salient features of recent developments. The authors should avoid presenting material which has already been published in a previous review. The manuscript should be divided as follows: title page, abstract and main text. The text may be subdivided further according to the areas to be discussed. The text should not exceed 2500 words.

Letters to the editor (correspondence)

Letters to the editor will be considered by the editorial board. Letters should be no more than 400 words. Please use SI units for measurements and provide the references conform the Vancouver style (N Engl J Med. 1991;324:424-8). No more than one figure is allowed. For letters referring to articles previously published in the Journal, the referred article should be quoted in the list of references.

Photo quiz

A photo quiz should not exceed 500 words and include no more than two figures and four references conform the Vancouver style. Abbreviations of measurements should be quoted in SI units.

Book reviews

The editorial board will consider articles reviewing books.

Reviewing process

After external and editorial review of the manuscript the authors will be informed about acceptance, rejection or revision. We require revision as stated in our letter.

Proofs

Proofs will be sent to the authors to be carefully checked for printer’s errors. Changes or additions to the edited manuscript cannot be allowed at this stage. Corrected proofs should be returned to the editorial office within two days of receipt.

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