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**The Journal of Medicine**

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*“Green urine: what is your diagnosis?”*

COGNITIVE AND PSYCHOLOGICAL PROBLEMS IN PITUITARY DISEASE

•  
CHRONIC HEPATITIS E AFTER ORGAN TRANSPLANTATION

•  
ACUTE KIDNEY FAILURE WITH VEGF INHIBITORS

•  
ECONOMICS OF MESALAZINE IN ULCERATIVE COLITIS

•  
APO-E1 MUTATION IN HYPERLIPOPROTEINAEMIA

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VITAMIN D FOR HYPOCALCAEMIA

•  
RECOMMENDATIONS REGARDING SELF-MONITORING OF GLUCOSE

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# Guidelines: the new catechism of modern medicine?

M. Levi

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Not very long ago, the ultimate sources of medical knowledge were textbooks. Textbooks provided guidance on diagnostic and therapeutic management of virtually all known diseases and were crucial foundations for knowledge-based medicine. Textbooks were written by experts, usually highly respected key opinion leaders in a given field, who wrote the chapters in these books with much endeavour and determination and to the best of their knowledge. In fact, textbook medicine represented a highly organised form of authority-based medicine. In more recent years, however, when medicine began moving at a much faster pace, many physicians came to realise that textbook information was often outdated (not in the last place due to the unbelievably long production schedules of publishers), not always evidence-based, was often not very accessible and was relatively hard to handle from a convenience point of view. Although not completely extinguished, the prominent place of textbooks in medicine is rapidly losing ground.

In a more evidence-based approach to medicine, diagnostic and therapeutic management recommendations are summarised in guidelines. Guidelines contain practical advice for many clinical situations, preferably based on clinical trials but in many cases also relying on descriptive studies, case series or even on consensus or expert opinion. This last form of 'evidence' renders the distinction between evidence-based medicine and authority-based medicine less sharp than often thought. Guidelines make the practice of medicine more uniform and may also provide guidance for young physicians in situations that may be complex and require a series of simultaneous diagnostic and therapeutic interventions.<sup>1</sup> The guidelines for acute medicine, as published by the Netherlands Association of Internal Medicine ('Acute Booklet'), is a very good example of highly effective evidence-based assistance to residents on call and seeing patients at the emergency department. Use of these and other guidelines has been easily and very solidly implemented in day-to-day medicine.<sup>2</sup>

Many journals like to publish guidelines, which are well written and often cited. The ten guidelines that were published in the Netherlands Journal of Medicine in the last two years were 3.2 times more often downloaded in the Journal's database and received 1.6 times more citations than other articles in the Journal.<sup>3-12</sup>

However, we must be careful that these practice guidelines are not becoming the new catechism of medicine. Very often a resident, when asked why she (or he) has chosen a particular diagnostic approach or therapeutic intervention, replies that this strategy was 'advocated in Up-to-Date' or was done 'according to the Acute Booklet'. Also, when a discussion starts on the daily morning report on the best treatment choice for a specific patient, many interns and residents (and senior colleagues alike) as in a reflex reach for the PDA containing all sorts of guidelines in their pocket and start looking what 'the bible' has to say on this subject.

Obviously, guidelines are carefully drafted and often provide solid support for good clinical practice. However, guidelines can never take into account individual patient properties and specific clinical situations. For example, treating a ketoacidosis in a dialysis patient exactly according to the standard protocol in the general guidelines for treatment of ketoacidosis will certainly lead to major complications or even death in this patient. The underlying problem is of course that (1) it is often forgotten that guidelines are true for groups of patients but need tailoring to a specific patient, and (2) that the guidelines are often based on clinical trial evidence, which is applicable to populations that may differ from the patients that are often seen in hospitals.<sup>13</sup> For example, in the six pivotal trials that demonstrated the superiority of warfarin over placebo in the prevention of thromboembolic complications in patients with atrial fibrillation, 28,787 patients were screened but only 12.6% of these patients were included in the study. Similarly, only 14,614 out of 36,945 patients (23%) with myocardial infarction or

unstable angina were included in five major trials on the use of vitamin K antagonists for the secondary prevention of thromboembolic events.<sup>14</sup> The fact that the majority of patients were not considered to be eligible for inclusion in the clinical trials may have a major impact on the external validity of the trials. In fact, many of the patients that we see in our office or in the hospital may be quite different from these trial populations.<sup>15</sup>

Guidelines virtually never mention the type of patients to whom the evidence is applicable. That would not be a problem in itself if the trial population were to properly reflect the whole group of patients. However, this is often not the case. A large review of 214 trials of anticoagulants in patients with acute myocardial infarction found that in more than 60% of these trials patients aged over 75 years were excluded, whereas patients of this age often present with myocardial infarction in real practice.<sup>16</sup> It is not always easy, and sometimes dangerous, to translate the evidence coming from these selected trial populations to the more general population. After the publication on the beneficial effect of spironolactone in patients with severe heart failure, for example, the prescription of this agent in patients who would never have been admitted to the original clinical trial resulted in excessive rates of hyperkalaemia and related morbidity and mortality.<sup>17,18</sup>

Taken together, the development and implementation of guidelines has provided a solid platform for the introduction of evidence-based medicine in clinical practice. However, we must be careful to use guidelines for what they are: handy collections of clinical evidence translated into management advice, useful to guide but certainly not dictate treatment of patients. Hence, guidelines are not the catechism of modern medicine but –if properly used– may undoubtedly be helpful to improve modern medicine.

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# Cognitive impairment and psychopathology in patients with pituitary diseases

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## ABSTRACT

Patients who are considered to have been successfully treated for pituitary disease because they are in long-term remission of functioning or non-functioning macroadenomas, still report reduced quality of life and persistent morbidity and have (slightly) increased mortality. It is likely that the causes are multi-factorial, including intrinsic imperfections of surgical or endocrine replacement therapy, but also of persistent effects of hormone excess on the central nervous system affecting personality and behaviour. In agreement, recent studies demonstrate that patients in long-term remission for acromegaly and Cushing's disease have a higher prevalence of psychopathology and more maladaptive personality traits, display different and less effective coping strategies, and experience more negative illness perceptions. These new findings are intriguing in view of the general impairments in health-related quality of life, suggesting that the effects of previous hormone excess on the central nervous system can be long-lasting and to a certain extent even be irreversible. This review aims to address the effects of the treatment of pituitary disease on quality of life and neuropsychological functioning. Further research is needed to gain more insight into irreversibility of hormone excess syndromes. However, since coping strategies are altered, it is tempting to speculate that quality of life might be improved by targeted interventions.

## KEYWORDS

Cognition, psychopathology, Cushing, acromegaly, pituitary adenoma

## INTRODUCTION

Pituitary adenomas are neuroendocrine tumours. Neuroendocrine tumours represent a heterogeneous group of tumours that also include carcinoid tumours, non-carcinoid

tumours of the gastrointestinal tract (such as insulinomas and gastrinomas), tumours of the autonomic nervous system (paragangliomas, pheochromocytomas), and medullary thyroid carcinoma.<sup>1</sup> Neuroendocrine tumours usually retain the characteristics of the original endocrine tissue, and thus often produce hormones and express hormone receptors. In addition, they grow slowly and often exhibit a specific genetic pattern. Functioning pituitary tumours cause the clinical syndromes of acromegaly (growth hormone (GH)), Cushing's disease (ACTH), prolactinoma (prolactin) and secondary hyperthyroidism (thyroid-stimulating hormone) due to pathological secretion of the specific hormone. Approximately 50% of pituitary tumours are not endocrine active: the so-called non-functioning macroadenomas (NFMA). Although pituitary adenomas are benign tumours, they can cause serious morbidity due to overproduction of pituitary hormones and/or due to local mass effects resulting in pituitary insufficiency and optic chiasm compression. The treatment of pituitary adenomas includes transsphenoidal surgery, medical therapy (e.g. with somatostatin analogues, GH receptor antagonists or dopamine agonists), and/or radiotherapy.<sup>2,3</sup> However, despite curative treatment of these adenomas *per se*, multiple physical and psychological symptoms may persist even when long-term remission has been present for many years. In this review, we will address the short- and long-term psychological consequences of pituitary adenomas in the Leiden cohort of patients who were in long-term remission after surgical cure but appeared to have persistent impairments in quality of life.

## TREATMENT OF PITUITARY ADENOMAS: THE HISTORICAL PERSPECTIVE

Pituitary adenomas, especially Cushing's disease, result in severe comorbidity and highly increased mortality when left untreated.<sup>4</sup> Although surgical tumour removal

was introduced by Harvey Cushing in the beginning of the 20th century, morbidity and mortality remained very high in this period. However, with the introduction of the microscopic transsphenoidal technique in the 1970s, surgical morbidity and mortality reduced dramatically (to below 1%). Nowadays, surgical treatment is the cornerstone of treatment for patients with pituitary adenomas.<sup>2</sup> Remission rates induced by transsphenoidal pituitary surgery in referral centres amounted to 50 to 70% for macroadenomas and 80 to 90% for microadenomas.<sup>5</sup> The most important side effect of surgical treatment is new pituitary insufficiency, developing in 10 to 15% of patients. However, many patients with NFA, up to 90%, and 10 to 50% of patients with functioning adenomas already have deficits preoperatively, some of which can be resolved after onset of cure (i.e. hypogonadism).<sup>6-8</sup>

When surgery does not lead to remission, radiotherapy or medical treatment, such as somatostatin analogues, dopamine agonists or pegvisomant, are available for functioning tumours. Depending on the disease, medical treatment has a more or less prominent role. For prolactinoma, dopamine agonists are the treatment of choice. For acromegaly, somatostatin analogues are either first or second choice, followed by pegvisomant if needed, reserving radiotherapy for selected cases. For Cushing's disease, either reoperation or irradiation are secondary treatment options. New developments suggest Pasireotide as potential treatment for Cushing's disease.

Hormone insufficiency is diagnosed by dynamic testing and hormone deficits are replaced if necessary using hormone replacement therapy, including GH, usually resulting in dramatic improvement in quality of life and symptoms. However, quality of life fails to normalise in the long term, and we do not yet exactly know why this is the case. Intrinsic imperfections of endocrine replacement therapy is one possibility but potential long-lasting effects of hormones on the central nervous system affecting personality and behaviour has not been considered until recently, although psychological disturbances had already been reported in patients with pituitary adenomas 100 years ago.<sup>9</sup> However, now that the final outcome is expected to be nearly normal health, the focus on an unsatisfactory degree of remission has regained much attention.<sup>10</sup>

## MORTALITY IN OPTIMALLY TREATED PATIENTS

In the Leiden cohort of patients treated for pituitary adenomas, we addressed the long-term consequences of these diseases and their treatment. Based on these clinical observations, the question arose whether remission in the long term equals cure. If that were the case, mortality would have to be normal and as well as disease-related morbidity, in this case with a focus on the long-term

mental sequelae. A Kaplan-Meier Survival Curve can best illustrate mortality. In the Leiden series of patients who were treated by a single neurosurgical procedure by the same neurosurgeon for either acromegaly, Cushing's disease or NFA, we documented the number of observed deaths and compared these with the expected number of deaths obtained from the Dutch population.<sup>11</sup> This obtained standardised mortality ratio was 1.24 for NFA, indicating a 24% increased death rate. For acromegaly, the standard mortality ratio was 1.32, whereas for Cushing's disease the increase in mortality was even significantly higher: 80%. These observations point towards long-lasting hormone-specific effects, especially of cortisol overexposure, on mortality, despite long-term remission.

## PITUITARY HORMONES, THE STRESS RESPONSE AND BEHAVIOUR

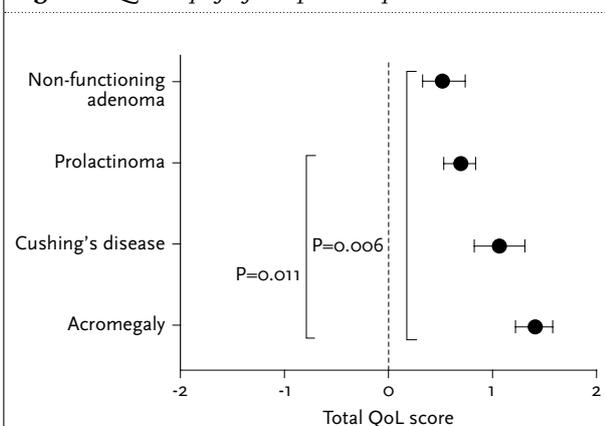
When focusing on mental sequelae in endocrine disease, it is crucial to realise that from an evolutionary point of view, a normal stress response is a prerequisite for normal adaptive behaviour.<sup>12</sup> The main mediator of the stress response is cortisol (or corticosterone in rodents). When an individual is exposed to a stressor, changes occur rapidly within seconds to minutes through stimulation of the sympathetic nervous system and cortisol secretion. In addition, the stress response is characterised by slower changes (that occur within minutes to hours) via stimulation of both the mineralocorticoid and glucocorticoid receptors in the central nervous system. In the end, all these changes occur only with the purpose to induce the required behavioural adaptations in order to enable the individual to adequately cope with the stressor. However, when a stressor becomes chronic, a so-called vulnerable phenotype develops that is characterised by neurodegenerative changes and cognitive impairment.<sup>12</sup> It is not surprising that Cushing's disease, which can be considered *the* clinical human monosymptomatic equivalent for severe chronic stress, is associated with behavioural abnormalities. In addition, patients with NFA can be considered to be a model for the consequences of pituitary insufficiency *per se*, because of the high rate of hypopituitarism present in these patients. In this respect it is intriguing that one of the most potent physiological stressors is hypoglycaemia. During an insulin tolerance test (ITT), the induction of hypoglycaemia is able to evoke all classical features of the stress response characterised by catecholamines and cortisol secretion. The insulin-induced hypoglycaemia test, however, is also a very potent stimulator of GH secretion, and is therefore considered to be the golden standard test for the diagnosis of cortisol and GH deficiency.<sup>13,14</sup> Thus, by definition, patients with cortisol and GH excess or deficiency cannot exhibit a

normal stress response, and are likely to represent human models for the effects of impaired stress responsiveness on psychopathology and cognitive function.

## QUALITY OF LIFE AND PSYCHOLOGICAL FUNCTIONING

In the last decade, quality of life (QoL) was evaluated in the Leiden cohort of patients with pituitary adenomas using general health-related questionnaires both in untreated and treated disease. These studies demonstrated that QoL generally improves after treatment, but also that QoL remains impaired even after successful treatment, with disease-specific features (*figure 1*).<sup>15-18</sup> It appeared that patients treated for acromegaly were most impaired in QoL, when compared with patients treated for Cushing's disease, prolactinoma or patients treated for NFA.<sup>19</sup> However, these results were obtained using general health questionnaires and not disease-specific ones. Specifically, patients treated for acromegaly predominantly reported impairment in physical performance and an increase in bodily pain, whereas patients treated for Cushing's disease also reported impairments in physical functioning. In addition, these QoL studies revealed psychological impairments on various quality of life questionnaires, both in general health and disease-specific questionnaires. As stated previously, the QoL questionnaires are not designed for an in-depth assessment of psychological functioning. Whereas the biological effects of cortisol and GH excess on psychological functioning have been reported in several studies in untreated Cushing's disease and acromegaly and in some studies after short-term remission,<sup>20</sup> it was unknown if, and to which extent, cognitive dysfunction and psychopathology was present in these patients in the long term.

**Figure 1.** *Quality of life in pituitary adenomas*



Adapted from Van der Klaauw et al., 2008.<sup>19</sup>

## PSYCHOLOGICAL FUNCTIONING IN CUSHING'S DISEASE

In agreement with the crucial role of cortisol in the regulation of the stress response, patients with active Cushing's disease do manifest cognitive impairments, especially in the memory domain. In addition, psychopathology and maladaptive personality traits are often observed during the active phase of Cushing's disease. Previous studies reported impairments in memory, visual and spatial information, reasoning, verbal learning, and language performance.<sup>21-24</sup> Structures important in cognitive functioning, such as the hippocampus and cerebral cortex, are rich in glucocorticoid receptors and are therefore particularly vulnerable to the cortisol excess present in Cushing's disease.<sup>12,23,25</sup> A large number of studies in humans and animal models have documented that prolonged, increased endogenous or exogenous exposure to glucocorticoids may have long-lasting adverse effects on behavioural and cognitive functions, due to functional and, over time, structural alterations in specific brain target areas.<sup>26,27</sup> A limited numbers of studies that have reported the effects of treatment indicate that significant improvements in both physical and psychiatric symptoms occur within the first year after successful surgery.<sup>20</sup>

## PSYCHOLOGICAL FUNCTIONING IN ACROMEGALY

GH and IGF-1 receptors are widely distributed throughout the central nervous system, including the limbic system and the frontal lobe.<sup>28,29</sup> In accordance, impaired cognitive function and maladaptive personality have also been documented in patients with active acromegaly.<sup>30-32</sup> In addition, substitution of GH-deficient patients with recombinant human GH resulted in a rapid and sustained amelioration of cognitive functioning and general well being.<sup>33,34</sup> However, in active acromegaly, many of the systemic changes induced by GH and/or IGF-1 excess, such as arthropathy and cardiac valvulopathy, are not completely reversed upon successful treatment of acromegaly,<sup>35,36</sup> which may also be true for the effects of GH and/or IGF-1 on the central nervous system. For instance, 36% of the patients that were considered cured from acromegaly showed elevated scores for anxiety and depression.<sup>15</sup>

## ADDITIONAL OBSERVATIONS AND MISCLASSIFICATIONS OF PSYCHOPATHOLOGY IN PITUITARY PATIENTS

Pituitary disease and/or its treatment can affect mood and personality changes by disrupting the connections

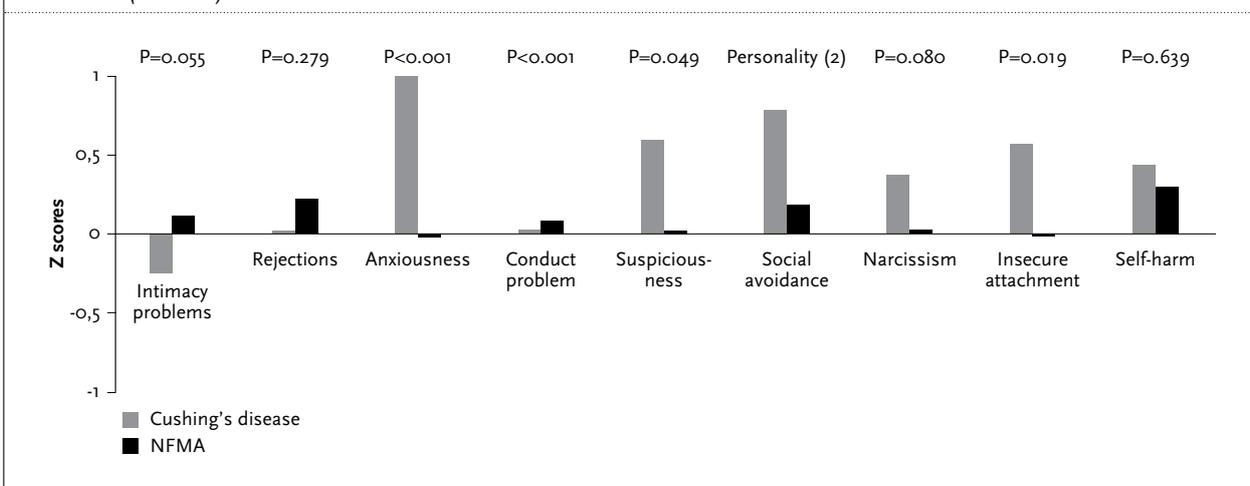
between the prefrontal cortex with other limbic structures, thereby impairing the behavioural control exerted by the prefrontal cortex on the limbic system.<sup>37</sup> The literature reports on such anecdotal cases, for instance by Weitzner *et al.*<sup>38</sup> who reported on patients with pituitary disease and apathy syndrome, patients who had previously been incorrectly classified as having major depressive disorder and had been treated accordingly with antidepressants for a long period of time. This, together with our general impression that patients treated for Cushing's disease behave differently when compared with patients treated for other pituitary adenomas, we hypothesised that hormone-specific effects may be long-lasting or even be irreversible.

### COGNITIVE FUNCTION AND PSYCHOPATHOLOGY DURING LONG-TERM FOLLOW-UP

Specifically, we hypothesised that patients with a long-term cure of both Cushing's disease and acromegaly showed cognitive dysfunction, persistent psychopathology and maladaptive personality traits. For this purpose, we studied patients cured of Cushing's disease and of acromegaly and age- and gender-matched controls. In addition, we included patients treated for non-functioning pituitary macroadenomas (NFMA) and additional controls, matched to these patients for age and gender. The cognitive evaluation consisted of multiple tests, which evaluated global cognitive functioning, memory, and executive functioning. In patients treated for Cushing's disease, cognitive function, reflecting memory and executive functions, was impaired despite long-term remission.<sup>39</sup>

These findings were not replicated in patients successfully treated for acromegaly.<sup>40</sup> We then decided to extend these observations and asked patients and controls to complete questionnaires focusing on frequently occurring psychiatric symptoms in somatic illness including the Apathy Scale, Irritability Scale, Hospital Anxiety and Depression Scale (HADS), and Mood and Anxiety Symptoms Questionnaire short-form (MASQ-30). Personality was assessed using the Dimensional Assessment of Personality Pathology short-form (DAPP). After a mean remission duration of 13 years for both Cushing's disease and acromegaly, patients cured from Cushing's disease (compared with matched controls) scored significantly worse on virtually all questionnaires. Compared with NFMA patients, patients treated for Cushing's disease scored worse on apathy, irritability, negative affect and lack of positive effect, somatic arousal, and 11 out of 18 subscales of the personality scales.<sup>41</sup> Patients cured of acromegaly (compared with matched controls) scored significantly worse on virtually all psychopathology questionnaires and on several subscales of the personality scales. These differences, although less accentuated, were also found when the patients cured of acromegaly were compared with NFMA patients.<sup>40</sup> In patients with prolactinomas, the impaired quality of life despite long-term biochemical control with dopamine agonists (and no surgical intervention!) is intriguing, because the current challenges in these patients relate to intrinsic imperfections of long-term medical treatment, and the fact that the disease recurs in the majority of the patients after withdrawal of dopamine agonist treatment.<sup>42</sup> In agreement, others have now replicated our findings of altered personality profile, also in patients with prolactinomas.<sup>43</sup>

**Figure 2.** Personality traits in patients treated for Cushing's disease and patients treated for non-functioning pituitary adenomas (NFMA)



The zero Z score represents the scores for the healthy matched control subjects. Adapted from Tiemensma *et al.*<sup>42</sup>

## COPING AND ILLNESS PERCEPTIONS

Previous studies in other (chronic) diseases have indicated that QoL and psychological factors, such as illness perceptions and psychopathology, are related. Coping strategies may affect quality of life that is impaired in patients treated for pituitary adenomas. Additionally, illness perceptions pertain to the pattern of beliefs patients develop about their illness. Illness perceptions are also determinants of quality of life (QoL), but factors contributing to persisting impaired QoL after treatment for pituitary disease remain largely unknown. Therefore, coping strategies and illness perceptions, as potentially modifiable psychological factors, were explored in relation to QoL in patients after long-term remission of pituitary disease. In the first study,<sup>44</sup> patients treated for Cushing's disease, for acromegaly and for NFMA, were compared with three reference populations: an a-select sample from the Dutch population, patients with chronic pain, and patients receiving primary care psychology services. Furthermore, the three patient groups were compared with each other. The Utrecht Coping List assessed coping strategies. Patients with pituitary adenomas (when compared with the a-select sample) reported less active coping, sought less social support, and reported more avoidant coping. In contrast, patients treated for pituitary adenomas reported somewhat better coping strategies than patients with chronic pain and those with psychological disease. When patients with different pituitary adenomas were compared, patients treated for Cushing's disease sought more social support than patients treated for NFMA. Thus, patients treated for pituitary adenomas

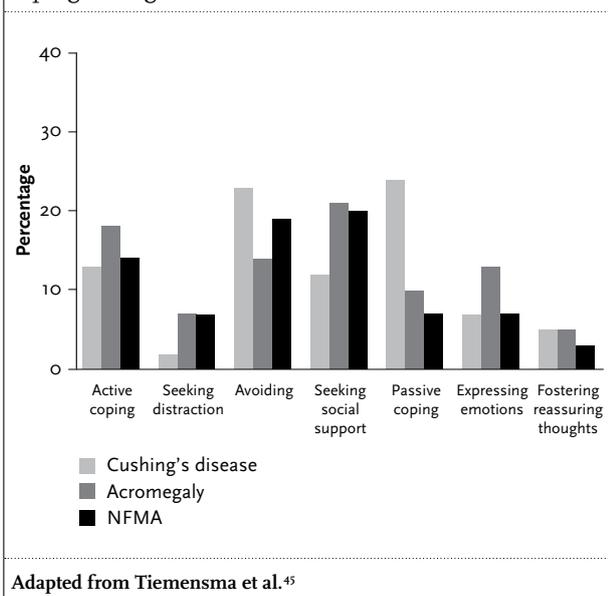
display different and less effective coping strategies compared with healthy controls.<sup>44</sup>

Illness perceptions were evaluated using the Illness Perception Questionnaire (IPQ)-Revised, and QoL was measured using the physical symptom checklist, EuroQoL-5D (EQ-5D), and the CushingQoL. Reference data were derived from recent studies and included patients with vestibular schwannoma, acute or chronic pain, and chronic obstructive pulmonary disease (COPD). Illness perceptions strongly correlated with QoL. Patients with either acromegaly or CS had negative illness perceptions compared with patients with vestibular schwannoma and patients with acute pain, and also reported more illness-related complaints.<sup>45,46</sup> There were also some differences in illness perceptions between patients with CS and patients with chronic pain and patients with COPD, but there was no distinct pattern. Noteworthy, patients after remission of acromegaly had a good understanding of their disease, but they experienced a lack of personal control and were not likely to seek medical care.<sup>46</sup>

## CONCLUSION

Patients who are considered to be successfully treated for pituitary disease show a higher prevalence of psychopathology and more maladaptive personality traits, suggesting that the effects of previous glucocorticoid and GH excess on the central nervous system can be long lasting and even irreversible. The additional observations that patients treated for pituitary adenomas also display different and less effective coping strategies and experience more negative illness perceptions are intriguing in view of the general impairments in health-related quality of life. It is tempting to speculate that quality of life might be improved by targeted interventions that could help to stimulate patients to use a more active coping strategy and to seek social support instead of an avoiding coping strategy, and by addressing illness perceptions, for example, by a self-management intervention program.

**Figure 3.** Different personality traits result in different coping strategies



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# Chronic hepatitis E after solid organ transplantation

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## ABSTRACT

Large outbreaks of acute hepatitis E, caused by hepatitis E virus (HEV) genotypes 1 and 2, are known from developing countries with suboptimal sanitation infrastructure. An increasing incidence of HEV infections is being reported in industrialised countries, caused mainly by HEV genotypes 3 and 4, which are often found among pigs. Recent evidence suggests that in immunocompromised patients about 50% of the cases of acute hepatitis E evolve to chronic hepatitis with rapid progression to cirrhosis. Thus, HEV should be considered a cause of chronic hepatitis in immunocompromised patients, such as solid organ transplant recipients. Because an antibody response to HEV may be absent in these patients, an HEV RNA test should be carried out when serum liver tests are elevated over months. In small case series, ribavirin has been shown to represent a promising treatment option for chronic HEV infection. To increase the awareness for HEV infection in immunocompromised patients, a representative case report of an HEV-infected renal transplant recipient with chronic hepatitis E, successfully treated with ribavirin, is presented. Studies are required to determine the optimal duration of ribavirin therapy and to assess outcome for solid organ transplant recipients with chronic HEV infection.

## KEYWORDS

Hepatitis E, transplantation, infection

## INTRODUCTION

Hepatitis E virus (HEV) is a global pathogen that can cause epidemic, endemic, sporadic and zoonotic cases of acute hepatitis. Large outbreaks of hepatitis E are

seen in developing countries with suboptimal sanitation infrastructure. However, an increasing incidence of HEV infection is found in industrialised countries of the Western hemisphere. In the Netherlands, HEV infection is considered to be one of the three most important emerging infectious diseases: whereas less than 0.5% of the population had had contact with HEV 15 years ago, a recent survey showed that more than 15% of the population has meanwhile developed HEV antibodies as a sign of former exposure to HEV (see below). In the Western world, the course of endemic HEV infection is generally self-limiting and asymptomatic in immunocompetent individuals. In contrast, immunocompromised patients are at risk to develop chronic HEV infection with progressive liver disease as reported in various case series since 2008. Patients with haematological disorders,<sup>1,3</sup> HIV infection<sup>4,5</sup> and after solid organ transplantation under immunosuppressive therapy<sup>6-9</sup> appear at particular risk to develop chronic hepatitis E that rapidly evolves to cirrhosis. Potentially effective therapeutic interventions by use of ribavirin in chronic hepatitis E have only recently been documented. To further raise the awareness of the community in the Western hemisphere for the risk of chronic hepatitis due to HEV infection in immunocompromised patients, but also to demonstrate the most recent development of promising therapeutic approaches, we report a case of a renal transplant patient with Bechterew's disease, who developed chronic hepatitis E, but was cured with ribavirin monotherapy.

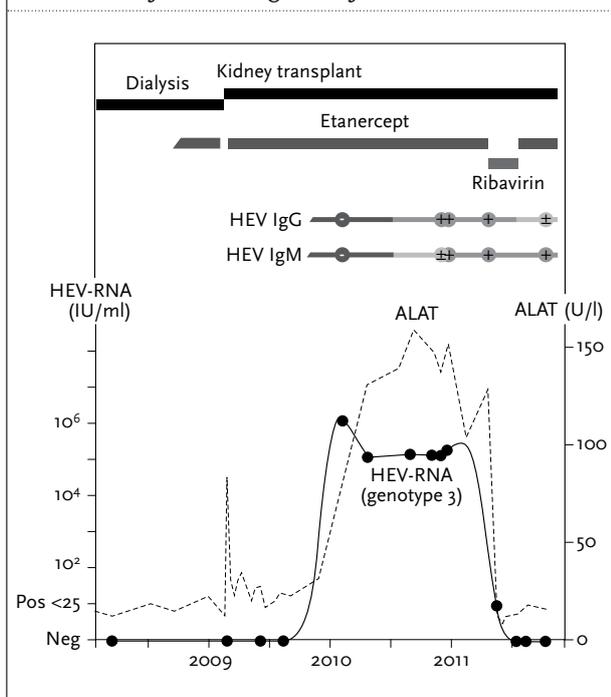
## CASE REPORT

A 51-year-old bank manager was known with a medical history of arterial hypertension, hypertension-related

renal insufficiency, and Bechterew's disease. In July 2010 he received a living related kidney transplant. After transplantation, serum liver tests increased temporarily, but returned to normal levels within two weeks. His further postoperative course was uneventful. Before transplantation, serological tests for hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and varicella zoster virus were all negative. The immunosuppressive regimen after kidney transplantation consisted of prednisolone 10 mg twice daily (bid), mycophenolate mofetil 1 g bid and tacrolimus 4 mg bid. For his Bechterew's disease, he received etanercept 25 mg twice weekly. One year after kidney transplantation alanine aminotransferase (ALAT [normal  $\leq 45$  U/l]: 132 U/l), aspartate aminotransferase (ASAT [ $\leq 40$ ]: 65 U/l), and gamma-glutamyltransferase ( $\gamma$ GT [ $\leq 60$ ]: 139 U/l) became elevated (figure 1). Prothrombin time and total bilirubin remained within the normal range. Ultrasound of the liver did not show any abnormalities. Serological and molecular testing, respectively, for HAV, HBV, HCV, and

CMV remained negative. Unexpectedly, serological tests for hepatitis E were positive (HEV IgM positive, HEV IgG weakly positive). Retrospective testing of former specimens revealed positive HEV RNA (genotype 3) in serum one year after transplantation onwards, coinciding with the rising serum liver tests. The patient (95 kg, 198 cm) was treated with ribavirin at a dose of 800 mg bid for three months. Maintenance immunosuppressive drug treatment was diminished (prednisolone 5 mg bid, mycophenolate mofetil 1500 mg bid and tacrolimus 500 mg bid) and etanercept was temporarily discontinued, but had to be restarted because of severe symptoms of Bechterew's disease. At the start of ribavirin therapy, creatinine clearance was  $>60$  ml/min, haemoglobin was 7.2 mmol/l, and HEV RNA in serum was strongly positive (figure 1). No deterioration of kidney function or haemoglobin count was observed during treatment. Two months after the start of ribavirin therapy, all serum liver tests had returned to normal and HEV RNA was negative. Three and six months after the end of the ribavirin treatment, the serum liver tests remained normal and serum HEV RNA remained negative. The patient is doing well.

**Figure 1.** A 51-year-old patient with arterial hypertension-associated renal insufficiency and Bechterew's disease developed chronic hepatitis E one year after living-related kidney transplantation and was treated with ribavirin monotherapy for three months. His immunosuppressive medication, HEV RNA, and serum ALAT (normal  $\leq 40$  U/l) are documented between 2009 and early 2012. Immunosuppressive drug therapy with prednisolone, mycophenolate mofetil and tacrolimus was diminished after the diagnosis of HEV



## BACKGROUND

### Biology and epidemiology

HEV is a *hepevirus*,<sup>10</sup> consisting of a capsid containing a positive-stranded RNA genome, and it is not enveloped. Phylogenetic studies have unravelled four genotypes. HEV genotype 1 and 2 infections are restricted to humans whereas genotypes 3 and 4 appear to be zoonotic, infecting various animal species such as pigs, wild boar and deer as well as humans.

Epidemiological studies revealed that genotypic distribution of HEV is area specific. Genotypes 1 and 2 are prevalent in the highly disease-endemic regions, which cover the tropical and subtropical parts of Asia, Africa and Central America.<sup>11,12</sup> HEV genotype 1 and 2 infections are most commonly transmitted through faecally contaminated water via the oral route. Materno-foetal and transfusion-related transmissions have only occasionally been reported.<sup>13,14</sup> Various endemic outbreaks of hepatitis E genotype 1 and 2 have been documented. Young adults are most often infected. Pregnant women are at particular risk: they have a higher disease attack rate and are much more likely to develop fulminant liver failure with fatal outcome in up to 22% (all genotype 1 infections).<sup>15</sup> The pathophysiological mechanisms leading to fulminant liver failure after HEV infection in pregnant women are not understood, but have been attributed to pregnancy-related immunological or hormonal alterations.<sup>16,17</sup>

In regions with lower HEV infection rates, such as Western Europe, the United States, and developed countries of

Asia and the Pacific region, hepatitis E was long thought to be related to travel to endemic regions. This view has recently changed since an increasing number of sporadic, autochthonous HEV infections have been reported, particularly in Western Europe. Viral strains isolated from HEV-infected patients without a history of travel to high-risk areas were classified as genotype 3 and 4. This strongly suggests a zoonotic origin. First, human HEV isolates genotype 3 and 4 appear to be the same strains that also frequently infect pigs. Secondly, interspecies transmission from human to pig and from swine to nonhuman primates has been demonstrated.<sup>18,19</sup> Thirdly, molecular typing in Japan demonstrated a link between cases of hepatitis E after eating raw or undercooked pig meat and HEV strains isolated from domestic swine, wild boar and sika deer.<sup>20,21</sup>

In contrast to predominant infection of young adults in the endemic areas in Asia and Africa, in Western Europe and the US mostly elderly subjects and people with coexisting illness are affected, while fulminant disease in pregnant women is not reported.<sup>11</sup> It is assumed that HEV genotype 3 is less virulent than the genotype 1 and 2 strains, which may explain the predilection of elderly and immunocompromised persons for HEV genotype 3 infection. In addition, this may explain why epidemic outbreaks with genotype 3 have not been observed so far in the Western world. Subclinical infection with HEV genotype 3 may explain the relatively high seroprevalence of anti-HEV antibodies in these areas.<sup>22</sup> The geographical distribution of genotype 4 is limited to Asian countries and has not been associated with disease in immunocompromised patients so far.

### Seroprevalence in Europe

A study in 1995 among Dutch blood donors reported a seroprevalence of 0.4%.<sup>23</sup> Seroprevalence in the South-West of France (according to testing of blood donors) has meanwhile dramatically increased from 16.6 to 52.5%, suggesting that the disease is highly endemic in this region.<sup>24</sup> In the UK, HEV RNA was detected in six out of 880 pools of blood donations (with 48 donations per pool), indicating a considerable rate of silent ongoing HEV infections among British blood donors.<sup>25</sup> The incidence of *de novo* HEV infections after kidney transplantation was calculated as 3.2 cases/100 person-years in a recent analysis.<sup>22</sup> Accordingly, seroprevalence studies had previously reported anti-HEV IgG antibodies in 6 to 16% of renal transplant recipients.<sup>26</sup>

### CLINICAL MANIFESTATIONS

Clinical features of HEV infection differ between the hyperendemic and the low prevalence areas. Incubation

time is approximately 30 days. In hyperendemic areas the most commonly observed clinical presentation is a typical acute icteric hepatitis resembling hepatitis A and other forms of acute viral hepatitis. A pre-icteric and an icteric phase of the illness can be distinguished. The initial pre-icteric phase is characterised by fever, anorexia, distaste for food, vomiting, abdominal pain and diarrhoea. These symptoms last for about three days. The onset of the icteric phase is marked by disappearance of the prodromal symptoms. It is usually self-limiting and improves within 10 to 24 days. Hepatomegaly and splenomegaly are common during the icteric phase.<sup>11,27</sup> Less frequently, liver injury is mild and can be asymptomatic or accompanied by only non-specific symptoms. Acute hepatic decompensation may be particularly seen in persons with pre-existing liver disease or with genotype 1 infections during pregnancy.

In low prevalence areas, patients with symptomatic hepatitis E genotype 3 typically are older, predominantly male with higher frequency of underlying liver disease, alcohol abuse, or an immunocompromised state. The clinical presentation is often non-specific, the spectrum ranges from asymptomatic elevation of serum transaminases to a severe icteric hepatitis. In clinical case series, jaundice was the most common symptom (68-86%) followed by asthenia, fever, joint and muscle pains and abdominal discomfort.<sup>11,27</sup> Extrahepatic clinical manifestations such as pancreatitis, haematological manifestations, autoimmune and neurological disorders have infrequently been reported.<sup>11</sup>

### CHRONIC HEPATITIS E

Chronic hepatitis E, genotype 3, in low-endemic regions was first described in immunocompromised patients in 2008. Various case series reported chronic hepatitis E in patients who developed elevation of serum transaminases after kidney, liver and heart transplantation.<sup>9,26,28-30</sup> Chronic HEV infection was also reported in patients with haematological malignancies, human immunodeficiency virus infection or those receiving anticancer chemotherapy.<sup>11,5,31</sup> Symptoms in these patients are mild or unnoticed and elevation of serum transaminases may be the only sign during routine follow-up. Rapid progression of chronic hepatitis E to cirrhosis is observed in these patients. Furthermore, extrahepatic manifestations such as HEV-induced glomerulonephritis, which recovered after HEV clearance, have been observed after organ transplantation.<sup>32</sup>

All recently described cases of chronic hepatitis E in low prevalence areas were caused by HEV genotype 3. The way of transmission of HEV genotype 3 has been a matter of intense discussion since. Apart from zoonotic infection,

other modes of transmission have been suggested in immunocompromised organ transplant recipients. Transmission of the virus from the donor organ has been reported in a liver transplant recipient who subsequently developed cirrhosis and hepatic decompensation.<sup>33</sup> Transmission via blood transfusions was unravelled in a number of haemodialysis patients.<sup>34-36</sup> Although reactivation of the virus has not been observed after solid organ transplantation, as is seen in other chronic viral infections such as hepatitis B during immunosuppression, reactivation of HEV was discussed in one patient with allogenic stem cell transplantation.<sup>2</sup>

## DIAGNOSIS

The diagnosis of HEV infection is based on detection of HEV IgG and IgM antibodies in blood and of HEV RNA in blood and stool. Both HEV IgM and IgG ELISA based assays are available, but have not been standardised so far. Sensitivity and specificity may vary considerably between different assays and even between batches of a given assay. HEV IgM antibodies are detectable as soon as symptoms occur. IgG antibodies may reach a sensitivity of 72% to 98% and a specificity of 78% to 96% to diagnose HEV infection in immunocompetent patients,<sup>37</sup> but are less accurate in immunocompromised individuals. HEV IgG may persist for years.

Molecular detection of HEV RNA can be achieved by PCR from serum, bile and stool. Nucleic acid testing as a diagnostic marker of HEV infection has limitations in immunocompetent patients, because the period of viral shedding is limited to only one to two weeks around the time of ALAT elevation and jaundice.<sup>11</sup> Still, HEV PCR is a crucial tool in immunocompromised patients. In these patients, the diagnosis can be easily missed as they often remain seronegative, whereas HEV RNA remains detectable during chronic infection. Furthermore, diagnostic testing for hepatitis E in transplant patients may be delayed as increased levels of serum liver tests (ALAT, ASAT) are frequently seen as a consequence of drug toxicity or are related to other hepatotropic viral infections. Histological findings in liver biopsies may vary from portal hepatitis with dense lymphocytic infiltrates, piecemeal necrosis and fibrosis to cases with severe fibrosis or cirrhosis and are not specific for hepatitis E.

## TREATMENT OF CHRONIC HEPATITIS E

Acute hepatitis E is self-limiting and usually does not need any treatment. In contrast, up to 60% of immunocompromised patients<sup>6</sup> develop chronic hepatitis after HEV infection (HEV RNA persistently positive, >6 months

in serum or stool) without treatment. Decreasing the number and dose of immunosuppressive drugs can be the first approach to control chronic hepatitis E in (renal) transplant recipients.<sup>38</sup> Most recently, advances have been made by the use of peg-interferon and ribavirin in chronic hepatitis E.

### Peg-interferon therapy of chronic hepatitis E in transplant patients

Three case series have reported successful results with three to 12 months of peg-interferon therapy in six liver transplant recipients and in one patient on haemodialysis after kidney transplantation. Sustained viral response (SVR), defined as negative serum HEV RNA six months after cessation of therapy, was reported in five of the seven patients. In the first report, 12 months of peg-interferon therapy resulted in sustained response in two of three liver transplant recipients chronically infected with hepatitis E.<sup>39</sup> Similar results were obtained with a three-month course of peg-interferon therapy in two of three patients with HEV infection who also underwent liver transplantation.<sup>40</sup> In the third report three months of peg-interferon therapy also led to SVR in a patient with kidney transplant failure and haemodialysis who did not spontaneously clear HEV after withdrawal of immunosuppressive therapy.<sup>41,42</sup> Of note, as the use of peg-interferon therapy could enhance allogenic immunity, it has to be given with caution in transplant patients and should be avoided in kidney transplant patients because of a high risk of acute organ rejection in these patients.<sup>43</sup>

### Ribavirin therapy of chronic hepatitis E in transplant recipients

Three case series have reported promising results with three months of ribavirin therapy in patients with kidney, pancreas and heart transplantation. Sustained viral response was reported in 78% of the reported cases. In the largest series, ribavirin therapy in kidney transplant recipients led to an SVR six months after cessation of therapy in four out of six patients.<sup>28</sup> The second report documented SVR in two patients with chronic hepatitis E after kidney and pancreas transplant, respectively, following three months of ribavirin therapy.<sup>44</sup> A third case report showed SVR after ribavirin therapy in a patient with chronic hepatitis E after heart transplantation.<sup>30</sup> The major adverse effect of ribavirin is haemolytic anaemia, which usually occurs within the first two weeks of treatment and may be reversible after dose reduction. Close monitoring of haemoglobin levels is therefore advised. Nevertheless, the otherwise good tolerability of ribavirin monotherapy makes this medication an attractive option for treatment of chronic hepatitis E after solid organ transplantation. The case reported by us above confirms this conclusion.

### Therapy in patients with HIV or haematological malignancies

SVR after a combined regimen of peg-interferon and ribavirin for chronic HEV infection was reported in a case of co-infection with HIV-1 and HEV.<sup>45</sup> Successful treatment of chronic hepatitis E by three-month ribavirin treatment was reported for three cases with haematological malignancies.<sup>3,41,46</sup> Although the afore-mentioned results are promising, only small case series are available and larger trials with longer follow-up are necessary.

### PREVENTIVE STRATEGIES

In endemic areas the main measures to prevent hepatitis E are better public education regarding hygiene and provision of safe drinking water.<sup>11,47</sup> In areas of zoonotic transmission, proper cooking of pig and deer meat is advised. However, it is questionable whether direct contact with HEV-positive pork meat explains the current rise in infections with endemic hepatitis E in the Western world. Other food products may also be involved, for example fruit and vegetables may be contaminated via the use of HEV-positive water.<sup>48</sup>

Two HEV recombinant protein vaccines have been successfully developed against proteins from the highly conserved open reading frame 2 of the virus.<sup>49,50</sup> The vaccines showed 96 and 100% efficacy, respectively, but they are not yet commercially available.

### CONCLUSION

Hepatitis E virus (HEV) (human genotype 1 and 2) is a global pathogen that is responsible for large outbreaks of hepatitis E in developing countries. HEV (genotype 3) has been found to cause occasional autochthonous infections, also in low endemic, developed areas in Europe or the United States. In immunocompromised patients, HEV can cause chronic hepatitis with rapid progression to cirrhosis. Because the anti-HEV antibody response can be absent or delayed in immunocompromised patients, an HEV RNA test should be carried out when serum liver tests are elevated. Recent advances have been made with peg-IFN and ribavirin treatment for chronic hepatitis E. Considering the side effects of peg-IFN and its potential to induce allogenic immunity, ribavirin treatment should be the first choice for chronic hepatitis E in transplant patients. Adequate follow-up is necessary to assess the long-term outcome for immunocompromised patients with chronic HEV infection. Hepatitis E vaccines, currently under investigation, may be beneficial for patients infected with HEV genotype 1 or 2 in the near future.

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# Kidney injury during VEGF inhibitor therapy

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## ABSTRACT

Antiangiogenic therapy targeting vascular endothelial growth factor (VEGF) or its receptor (VEGFR) has proven its effect in the treatment of several types of cancer, including renal cell carcinoma (RCC). However, treatment can be accompanied by notable adverse effects. Mild proteinuria and hypertension are often seen, but sometimes nephrotic range proteinuria and/or renal insufficiency develop. In recent years insight into the toxic effects of anti-VEGF therapy in the kidney has increased. A few biopsies have been done and thrombotic microangiopathy is reported in the majority of cases. However, other patterns of kidney injury have been described as illustrated by the case of a 62-year-old patient who presented two years after initiation of the VEGFR inhibitor cediranib with a nephrotic syndrome and acute renal failure. Kidney biopsy disclosed focal segmental glomerulosclerosis (FSGS) and interstitial nephritis. Partial remission was achieved after stopping the cediranib and a short course of prednisone. We review the different forms of kidney injury that could be caused by anti-VEGF therapy.

## KEYWORDS

Kidney toxicity, anti-VEGF therapy, FSGS, cediranib

## INTRODUCTION

Vascular endothelial growth factor (VEGF) is an important signalling protein involved in angiogenesis, a key process in cancer growth and dissemination. Thus, inhibition of VEGF signalling has become a target for antitumour therapy and many new drugs are being developed. Based on their mechanism of action, three classes of agents can be discerned: 1) antibodies against VEGF (e.g.

bevacizumab); 2) soluble receptors (VEGF Trap) that bind and inactivate VEGF; and 3) VEGF receptor tyrosine kinase inhibitors (e.g. sorafenib, sunitinib).<sup>1</sup> Inhibitors of the VEGF pathway, angiogenesis inhibitors, have been effective in reducing tumour growth and improving patient survival in several types of cancer, especially metastatic renal cell carcinoma (RCC). In the past few years it has become evident that angiogenesis inhibitors may cause renal and vascular damage. These adverse events may be more common than previously thought and the long-term effects of antiangiogenic treatments are largely unknown.<sup>2</sup> Also insight into the pathophysiological mechanisms involved in these side effects has increased, although many questions remain to be answered.

We describe a patient who developed a severe nephrotic syndrome and acute renal failure after prolonged use of cediranib (AZD2171), a tyrosine kinase inhibitor that selectively blocks all three known VEGF receptors, VEGFR-1, -2 and -3. We summarise literature data on anti-VEGF-induced proteinuria.

The patient, a 62-year-old male, was admitted because of progressive kidney failure and hypercalcaemia. Three years before he underwent a nephrectomy because of clear cell RCC. One year after the nephrectomy and two years before admission cediranib (AZD2171) 30 mg once daily was started within a phase II trial because of progression of para-aortic lymph nodes and development of multiple lung metastases. At the start of therapy he had no proteinuria and a normal glomerular filtration rate. The patient experienced the frequently occurring adverse events of mild diarrhoea and hypertension, which was well controlled with enalapril 5 mg once daily. Six weeks before presentation pravastatin was started because of hypercholesterolaemia, but he had stopped this drug after four weeks because of general malaise.

At presentation he complained of apathy, loss of appetite and aggravated diarrhoea. The blood pressure was 120/80 mmHg, the pulse 68 beats/min. There was slight pitting oedema at the ankles. Laboratory results were as follows: serum creatinine 235  $\mu\text{mol/l}$  (2.7 mg/dl), urea 41.2 mmol/l, albumin 23 g/l, calcium 3.0 mmol/l (corrected for low albumin), and total cholesterol 8 mmol/l. Urine microscopy demonstrated 1 to 4 erythrocytes (20% dysmorphic) per high power field; no red cell casts were seen. A 24-hour collection of urine contained 11.3 g protein. Thus the patient was diagnosed with a nephrotic syndrome and acute kidney failure. Cediranib was discontinued and the hypercalcaemia was corrected with intravenous fluids. Two weeks after discontinuing the cediranib, the creatinine was still elevated at 268  $\mu\text{mol/l}$  and the patient complained of fluid retention. Furosemide was initiated and a kidney biopsy was performed: on light microscopy the tip variant of focal segmental glomerulosclerosis (FSGS) was demonstrated. There was global interstitial fibrosis with tubular atrophy and a diffuse interstitial infiltrate with monocytes, plasma cells and eosinophils. No signs of thrombotic microangiopathy were seen. Immunofluorescence showed no specific findings. Electron microscopy revealed some swollen endothelial cells and also partial podocyte foot process effacement. There were no electron-dense depositions (*figure 1*).

It was concluded that FSGS, caused by cediranib, was the cause of the proteinuria, whereas the renal insufficiency was more related to the interstitial nephritis. The latter may have been caused by pravastatin, a drug recently introduced in our patient. Statins are a known cause of tubulo-interstitial nephritis.<sup>3</sup> In view of the severity and persistence of the renal failure and the cellular infiltrate,

we decided to treat our patient with prednisone (80 mg/day starting dose, with rapid tapering and stopped at three months) and cediranib was stopped indefinitely. The serum creatinine decreased and also his oedema disappeared.

One year after discontinuation of the cediranib, the serum creatinine was 110  $\mu\text{mol/l}$  and urine protein excretion was 0.73 g/24 hours.

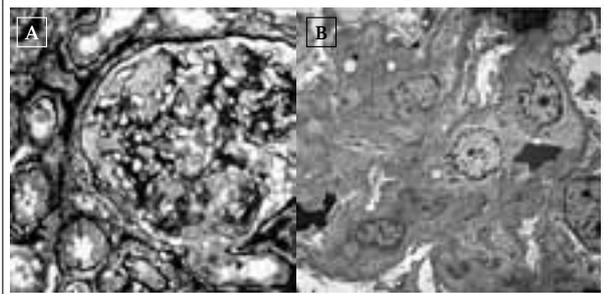
## VEGF INHIBITORS AND KIDNEY TOXICITY

Proteinuria as well as hypertension are well-known dose-dependent adverse events of angiogenesis inhibitors. A meta-analysis demonstrated that treatment with bevacizumab, a recombinant humanised monoclonal antibody against VEGF, resulted in overt proteinuria (>0.5 g/day) in 21 to 41% of the patients with low-dose bevacizumab and up to 64% in the high-dose group.<sup>2</sup> The relative risks for hypertension were 3.0 and 7.5, respectively. Although less well studied, the small tyrosine kinase inhibitors and VEGF Trap can also cause hypertension and proteinuria.<sup>4-8</sup> One phase I study in Japanese patients demonstrated proteinuria in 27/40 (68%) and hypertension in 32/40 (80%) patients receiving cediranib. The proteinuria was not quantified and different doses were used.<sup>9</sup>

Usually, proteinuria induced by inhibitors of VEGF signalling is not severe and resolves when the drug is discontinued, although nephrotic range proteinuria (>3.5 g/day) has been described in up to 6.5% of patients treated with bevacizumab for metastatic renal cancer.<sup>10</sup> Less often acute renal failure evolves. *Table 1* shows the biopsy-proven cases of (mostly severe) proteinuria and/or renal failure linked to anti-VEGF(R) therapy.<sup>11-27</sup>

From *table 1* it is evident that in all these patients there was an indication for renal biopsy, most patients presenting with nephrotic proteinuria (13/20) and/or severe renal failure. Causative agents belonged to all three different classes of VEGF-signalling directed therapy. Various patterns of renal injury were observed, the most common being thrombotic microangiopathy in 13 of 22 patients. An FSGS pattern of injury was seen in five patients, a tubulo-interstitial nephritis in three. In most patients studied by electron microscopy there was evidence of swollen endothelial cells and foot process effacement. In two of the patients with FSGS lesions there was evidence of a collapsing FSGS, which might have been the consequence of the simultaneously used pamidronate. Pamidronate is a well-known cause of collapsing FSGS. Of note, the incidence of proteinuria was higher with bevacizumab and pamidronate when compared with bevacizumab without pamidronate (33.9 vs 18.5%,

**Figure 1.** (A) Glomerulus with FSGS tip lesion. Near the urinary pole (bottom) there is a glomerular segment with collapse and also a few endocapillary mononuclear inflammatory cells and foam cells. Surrounding this segment mild epithelial hyperplasia can be seen. Podocytes globally appear swollen. (B) Electron microscopy. A glomerular segment is shown with wrinkling of the glomerular basement membrane (collapse). Podocytes show extensive foot process effacement. There is swelling of the endothelial cells



$p < 0.05$ ).<sup>14</sup> Our patient did not receive pamidronate for the treatment of hypercalcaemia.

The literature data do not provide details on follow-up in all patients; in general withdrawal of anti-VEGF treatment resulted in a decrease of proteinuria.

## PATHOPHYSIOLOGY

In recent years the role of VEGF in the kidney has been clarified. VEGF is produced by the glomerular podocytes and to a lesser extent in the (proximal) tubular epithelial cells. Seven different subtypes of VEGF have been described of which VEGF-A is the most predominant in angiogenesis. Three VEGF-receptors types are known: VEGFR-1 or Flt-1, VEGFR-2 or Flk-1/KDR and VEGFR-3 or Flt-4. In the kidney VEGFR-2 predominates and is mainly found in the mesangium and in endothelial cells and tubular capillaries. Interaction of the podocytes and endothelial cells by VEGF expression appears to be vital for the development and maintenance of the glomerular filtration function by inducing endothelial fenestrations and maintaining glomerular permeability.

Specific knockout of VEGF in podocytes in mice resulted in nephrotic range proteinuria, endotheliosis, loss of podocytes and hyaline deposits, as seen in kidney biopsies of patients with preeclampsia.<sup>9</sup> Pharmacological inhibition or targeted heterozygotic deletion of VEGF-A in mice resulted in a reduction of endothelial fenestrations in the glomerulus as well as downregulation of the key endothelial protein nephrin, resulting in glomerular cell detachment and swelling and therefore malfunction of the glomerular filtration apparatus.<sup>28,29</sup> Moreover, overexpression of soluble Flt-1 seems to be an important cause of preeclampsia. By neutralising VEGF, endothelial dysfunction is induced. This underscores the importance of VEGF for the endothelium.

In contrast, in a mouse model, upregulation of VEGF-A resulted in collapsing glomerulopathy.<sup>28</sup>

In our patient, histology demonstrated FSGS (tip variant) accompanied by a chronic active tubulo-interstitial nephritis. Based on the findings in animal models, one might have expected a thrombotic microangiopathy rather than FSGS in our patient. Still, more cases of FSGS and interstitial nephritis linked to anti-VEGF therapy have been published. What could be the explanation? We

**Table 1.** Kidney biopsies of proven kidney lesions attributed to anti-VEGF(R) therapy

Ref	Anti-VEGF	Disease	Age	Sex	Onset	Proteinuria	Creatinine ( $\mu\text{mol/l}$ ) <sup>b</sup>	Histology
11	Bevacizumab	HC	59	M	9 months	3.4 g <sup>a</sup>	N/A	TMA
11	Bevacizumab	HC	74	M	3 months	2.7 g <sup>a</sup>	N/A	TMA
11	Bevacizumab	BC	56	M	9 months	0.16 g/24 h	274	TMA
11	Bevacizumab	SCLC	62	M	3 months	0.5 g	504	TMA
11	Bevacizumab	PC	61	M	5 months	4.6 g/24 h	230	TMA
11	Bevacizumab	Ovarian	59	F	9 months	0.8 g/24 h	80	TMA
12	Bevacizumab/ sunitinib	RCC	70	M	2 weeks	5.3 g/10 mmol <sup>a</sup>	N/A*	TMA
13	Bevacizumab	NSCLC	N/A	N/A	N/A	Nephrotic	N/A	Cryoglobulin GN
14	Bevacizumab	Breast	N/A	F	N/A	Nephrotic	N/A	Collapsing FSGS
15	Bevacizumab	PC	71	M	1 month	9.6 g/24 h	97	ICGN
16	VEGT TRAP	Ovarian	59	F	1 week	16.6 g/l	71	TMA
17	Bevacizumab	RCC	59	M	9 months	Nephrotic	141	TMA/IgA deposits
18	Bevacizumab	Breast	59	F	3 months	3.6 g/24 h	282	TMA/collapsing FSGS
19	Bevacizumab	LM	26	M	2 weeks	N/A	414	AIN
20	Sunitinib	MM	50	M	1 month	3.2 g/24 h	651	ATN
21	Sunitinib	SH	44	F	4 weeks	1.1 g/24 h	64	TMA
22	Bevacizumab	NSCLC	67	M	6 weeks	9.5 g/24 h	461	MPGN
23	Sunitinib	RCC	66	M	10 months	5.4 g/24 h	167	TMA/FSGS
24	Sunitinib	RCC	66	M	10 days	0.7 g/24 h	400	AIN
25	Sunitinib	RCC	61	M	9 months	1.1 g/10 mmol <sup>a</sup>	583	FSGS/AIN
26	Sunitinib	GIST	72	M	6 months	10.1 g/24 h	170	FSGS/TMA
27	Bevacizumab	SCLC	67	M	15 months	5.7 g/24 h	478	Crescentic GN

AIN = acute interstitial nephritis; ATN = acute tubular necrosis; BC = bronchoalveolar carcinoma; FSGS = focal segmental glomerulosclerosis; GIST = malignant gastrointestinal stromal tumour; GN = glomerulonephritis; HC = hepatocellular carcinoma; ICGN = immune-complex glomerulonephritis; LM = leiomyosarcoma; MPGN = membranoproliferative glomerulonephritis; N/A = not available; NSCLC = non-small cell lung cancer; PC = pancreatic cancer; RCC = renal cell carcinoma; SCLC = small cell lung cancer; TMA = thrombotic microangiopathy; \*GFR 23 ml/min; <sup>a</sup>protein/creatinine ratio; <sup>b</sup>for mg/dl divide by 88.

can only speculate. As mentioned above inhibition of VEGF not only results in endothelial damage, but also causes loss of nephrin. Congenital loss of nephrin is associated with the development of a congenital nephrotic syndrome and FSGS. Thus, in our patient the phase of thrombotic microangiopathy might have been skipped (possibly due to adequate antihypertensive therapy) and FSGS may have been the consequence of long-term inhibition of nephrin. Alternatively, development of FSGS in this case may be governed by the nephrectomy three years before. After nephrectomy adaptive hyperfiltration occurs. In animal models of nephron reduction VEGF is necessary for compensatory glomerular and tubular hypertrophy. Later in the process VEGF levels decrease paralleled by development of glomerulosclerosis and tubular atrophy.<sup>30</sup> Possibly, this process was influenced by the use of cediranib.

Few cases of biopsy proven anti-VEGF associated kidney injury have been published, given the frequency of proteinuria. In recent years new light has been shed on the paracrine and autocrine (on the podocyte) roles of VEGF. In many patients no biopsy is done because of decreasing proteinuria or improvement of kidney function after withdrawal of the offending agent or simply because one is reluctant to do a biopsy in a single kidney. We expect that more cases of FSGS would be found if biopsies were performed.

The clinical experience with long-term treatment with VEGFR inhibitors in cancer patients is limited. The most commonly used VEGFR inhibitors, sunitinib and sorafenib, were already approved after the successful phase II studies. The dose-defining phase I studies were based on dose escalation, in which dose-limiting toxicity was determined in only short periods (usually three to four weeks). The frequently occurring mild proteinuria that has been described originates from these phase I and II studies. Insights into the development of proteinuria during prolonged use of VEGFR inhibitors are lacking. Registered treatment strategies for metastatic RCC are the VEGFR inhibitors sunitinib, sorafenib and pazopanib, mTOR inhibitors temsirolimus and everolimus and the combination of the VEGF-antibody bevacizumab with interferon-alpha. Proteinuria is a class effect of all VEGF(R) targeting agents.<sup>31</sup> Unfortunately, mTOR inhibitors are also associated with the development of proteinuria, although this association seems less severe.<sup>32</sup> Knowledge about the effects of sequential use of different VEGF-targeting therapy or sequential use of VEGFR inhibitors and mTOR inhibitors on the clinical course of proteinuria is not available. Therefore, we decided to wait for as long as possible to restart anticancer therapy.

In conclusion, angiogenesis inhibitors can induce a nephrotic syndrome and possibly acute failure. Awareness of these, although infrequent, adverse events is mandatory. Development of these adverse events should lead to prompt discontinuation of the medication or lowering the dose. In most cases this will lead to (partial) remission of proteinuria. Further insight into the development of renal injury by angiogenesis inhibitors will require increased use of renal biopsies in patients who develop proteinuria and/or renal insufficiency during treatment with these agents.

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# The economics of mesalazine in active ulcerative colitis and maintenance in the Netherlands

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## ABSTRACT

**Background:** In this study we investigate the costs and benefits of topical mesalazine combined with oral mesalazine therapy for active ulcerative colitis (UC), and once daily (OD) mesalazine 2 grams versus twice daily (BID) for maintaining UC remission.

**Methods:** Two decision analytic models were constructed to evaluate treatment costs and quality-adjusted life years (QALYs) associated with mesalazine. The first model explored 4 g oral mesalazine in combination with 1 g topical mesalazine during active UC compared with 4 g oral mesalazine monotherapy for achieving clinical remission. The second model compared remission rates at one year for OD 2 g oral mesalazine compared with BID 1 g adjusted for compliance. All direct costs were obtained from established treatment costs in the Netherlands.

**Results:** The average cost of treatment to transition an active UC patient into remission using oral plus topical mesalazine or oral mesalazine monotherapy was €2207 (95% CI: €1402 to €3332) and €2945 (95% CI: €1717 to €4592), respectively. The annual average cost-saving of adding topical mesalazine delivered for four weeks during active UC was €738. The average annual costs of maintenance of remission with OD and BID therapy were €1293 (95% CI: €1062 to €1496) and €1502 (95% CI: €1262 to 1708), respectively with an annual average per person savings of €209.

**Conclusion:** Topical mesalazine during acute UC flares results in lower costs due to reduced healthcare consumption attributed to faster symptom resolution. Furthermore, as a result of lower costs and modest QALY gains, maintenance therapy using OD mesalazine is the dominant treatment option if compared with BID mesalazine.

## KEYWORDS

Mesalazine, cost-effectiveness analysis, ulcerative colitis, economic evaluation, maintenance therapy

## INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease of the rectum and colon that is characterised by periods of remission with occasional, unpredictable episodes of relapse causing acute rectal bleeding, urgent diarrhoea and abdominal discomfort. Typically, the age of onset is between 20 to 40 years of age although the disease can be found in all age groups. Geographic variations have also been observed with 21 to 243 cases per 100,000, with 40% greater prevalence in Northern Europe compared with Southern Europe.<sup>1</sup> Additionally, previous studies have indicated that prevalence is increasing, therefore suggesting a need to understand disease aetiology and define cost-effective treatment practices to minimise the financial costs of care.<sup>2</sup> UC is a chronic condition that requires lifetime management. Because UC is lifelong, and often requires chronic therapy for maintaining remission,<sup>3</sup> defining cost-effective practices for this population is critical for optimising outcomes at low cost. However, because of the lifelong nature of UC, running long-term clinical trials to answer important research questions is not always feasible. Therefore, economic modelling is seen as a valid approach to fill gaps in our understanding of the costs and benefits of different therapies in the absence of long-term trials.<sup>4</sup> Treatment practices are increasingly influenced by cost-effectiveness in addition to medical benefits. In the Netherlands, since 2005, in addition to meeting efficacy, safety and quality standards, new medicines

must prove to be cost-effective compared with current treatment practices to obtain reimbursement under the Dutch system for medicines with proven added value.<sup>5</sup> Although cost-effectiveness standards were introduced formally at the national level in 2005, the practice of cost-effectiveness has been used since the 1980s for informing local formulary committees and treatment practices in the Netherlands.<sup>6</sup>

To inform treatment practices and formulary decisions in the Netherlands, we have developed two economic evaluations that explore the costs and consequences of mesalazine therapy in different situations. The first analysis compares the costs and benefits of adding topical mesalazine to treat mild-to-moderately active UC and the second evaluation compares the costs of OD 2 g with BID 1 g mesalazine for maintenance of remission. The models described here are based on a previously reported economic evaluation comparing OD and BID mesalazine dosing.<sup>7,8</sup> Although previous studies have reported the cost-effectiveness of these interventions, due to differences in treatments practice and costs in different countries it is often necessary to conduct country-specific economic analyses with local adaptations to test whether previous findings are valid.<sup>9</sup>

## METHODS

To assess the cost-effectiveness of mesalazine in active and quiescent UC, we adapted two previously described cost-effectiveness analyses. The model adaptation reflected both the differences in treatment practices and the costs of care in the Netherlands. Because the model frameworks have been previously described in detail,<sup>7,8</sup> we only discuss the relevant elements of the adaptations for the Netherlands in this publication.

### Research framework

The cost-effectiveness of introducing 1 g topical mesalazine at bedtime for four weeks in combination with 4 g oral mesalazine during active UC compared with 4 g oral mesalazine monotherapy was based on the randomised study reported by Marteau *et al.*<sup>10</sup> The study previously reported by Marteau observed remission rates of 64% (95% confidence interval 50% to 76%) and 43% (95% confidence interval 28% to 58%) that were significantly different for combined oral and enema therapy compared with oral monotherapy, respectively. The improved remission rates were achieved without any increase in adverse events.<sup>10</sup> These clinical differences served as the basis for economic modelling.

The economic evaluation in acute UC is based on the ability to achieve remission in mild to moderately active UC based on changes from baseline in the Ulcerative Colitis

Disease Activity Instrument (UCDAI).<sup>11</sup> The randomised study population considered in the analysis was >18 years of age with extensive UC and UCDAI scores  $\geq 3$  and  $\leq 8$ .<sup>10</sup> Five health states were considered in the active UC economic model: (1) combination therapy with oral mesalazine and topical mesalazine or oral mesalazine monotherapy; (2) mesalazine-refractory active UC; (3) steroid-refractory active UC; (4) infliximab-responsive active UC; and (5) remission. Following health state (1), the subsequent health states were comparable in both treatment arms.

### Maintenance of remission

In quiescent UC, we evaluated costs and outcomes of OD 2 g with BID 1 g dosing based on the randomised controlled study results reported by Dignass *et al.*<sup>12</sup> The main clinical outcome was remission defined as UCDAI scores  $\leq 1$ . The maintenance population recruited into the study were patients in UC remission (UCDAI <2), who had experienced a relapse requiring adjustments to their maintenance therapy within the past year. In the economic evaluation, UCDAI scores were converted into health state utilities based on two UC health states: (1) remission and (2) active UC treatment costs.

### Treatment practices in the Netherlands

In the Netherlands, usually a step-up regimen for treatment of active disease and maintenance of remission in UC is followed, according to national guidelines. In case of active UC, topical or oral mesalazine therapy, or a combination of both, is used depending on the extent and severity of the disease. The next step would be the addition of corticosteroids (topically and/or orally) and finally, if these fail as well, the initiation of rescue therapy (infliximab or cyclosporine). The first choice for maintenance therapy is mesalazine, typically in a dose of 2 to 4 g orally. In case of proctitis, mesalazine can be prescribed topically. Step-up includes thiopurines and, when these fail, infliximab.<sup>13-15</sup> The outcome measures included in the economic models are described in *table 1*.

### Resource utilisation items

The model was constructed from resource items in the Netherlands. The perspective applied in the analyses was the health service which included hospital and pharmacy costs. Resource use costs for consultation (e.g. specialist, general practitioner, IBD nurse) and follow-up visits were derived from the Dutch guideline for conducting costing research comprising of standardised prices.<sup>16</sup> Furthermore, unit costs for diagnosis (e.g. laboratory tests, endoscopy, X-ray), mesalazine and other treatments (e.g. beclometasone, prednisolone, Imuran, infliximab) were derived from official Dutch tariffs.<sup>17</sup> All costs were expressed in year-2010 values.

**Table 1.** Main outcomes included in model and variance applied in sensitivity analysis

Parameter	Point estimate	Variance	Reference
<b>Acute UC parameters and variance</b>			
Remission with 4 g oral mesalazine and 1g mesalazine enema*	0.64	(0.50-0.76)	10
Remission with 4 g oral mesalazine and placebo enema*	0.43	(0.28-0.58)	10
Probability success with prednisolone*	0.68	(0.43-0.87)	14
Probability success with infliximab*	0.39	(0.30-0.48)	15
<b>Maintenance therapy</b>			
OD 1-year relapse rate (95% CI)	0.738 <sup>†</sup>	(0.670-0.806)	12
BID 1-year relapse rate (95% CI)	0.636 <sup>†</sup>	(0.564-0.708)	12
Compliance OD <sup>‡</sup>	0.791	(0.593-0.989)	12
Compliance BID <sup>‡</sup>	0.798	(0.598-0.997)	12

<sup>†</sup>The difference in the primary outcomes was shown to be statistically significantly different based on Kaplan-Meier estimated UC-DAI remission rates at one year after randomisation; <sup>‡</sup>Compliance based on weighted compliance over entire study period with  $\pm 25\%$  variance applied. There was no significant difference between compliance rates; \*Based on reported outcomes at 8 weeks. BID = twice daily; OD = once daily.

Treatment costs for maintenance and active UC were estimated based on standard treatment practices in the Netherlands for managing acute UC events and applying Dutch tariffs to resources consumed. Annual drug costs were adjusted for mesalazine compliance rates reported for OD and BID maintenance therapy.<sup>12</sup>

**Modelled outcomes**

Ulcerative colitis is known to impact the quality of life of patients; therefore, the primary outcome of interest in the two economic models was the average QALY change based on the intention-to-treat populations from the randomised controlled trials. This is also the accepted outcome metric recommended by the Dutch authorities for making responsible budgetary and resource allocation decisions.<sup>18</sup> The QALYs were derived from previously reported UC health state utilities for remission and acute flares of 0.84 and 0.78, respectively,<sup>19</sup> and applied to the duration of time spent in each health state. Additional outcomes assessed in the model included the average cost of treatment over a defined period of time, costs per QALY and the incremental cost per QALY between different treatment options for active UC and maintenance. Because the time horizon considered in both models was less than one year, discount of costs and outcomes was not performed.

**Sensitivity analysis**

Variations in critical model parameters were evaluated using probabilistic sensitivity analysis (PSA). In the Netherlands, PSA, also referred to as second-order analysis, is recommended by the national body that evaluates

uncertainty around distributions for critical parameters where uncertainty may exist.<sup>18</sup> The point estimates and distributions assessed in the sensitivity for the maintenance and acute UC models are shown in *table 1*.

For each analysis, cost-effectiveness acceptability curves (CEAC) were generated using the net benefit approach to reflect uncertainty in the model. The CEAC output is useful for expressing the proportion of simulations in which one intervention is more cost-effective compared with the other across a range of willingness-to-pay (WTP) thresholds.<sup>20</sup>

**RESULTS**

**Active UC**

The average cost of treatment for a patient to transition from active UC to remission using oral mesalazine in combination with topical mesalazine or oral mesalazine monotherapy was estimated to be €2207 (95% CI: €1402 to €3332) and €2945 (95% CI: €1717 to €4592), respectively (*table 2*). This represents an average cost saving of €738 associated with topical mesalazine delivered for four weeks during active UC. The major cost difference between treatments occurred during steroid-refractory active UC as patients progressed to more expensive immunomodulating agents. A small incremental QALY increase of 0.01 was observed for patients treated with 1 g mesalazine enema compared with placebo-treated patients.

The average cost-effectiveness ratios for mesalazine enema and placebo enema were €3954 and €5345, respectively. The incremental analysis defined as  $(\text{Cost}_{4g \text{ oral} + 1g \text{ enema}} - \text{Cost}_{4g \text{ oral} + \text{placebo enema}}) / (\text{QALY}_{4g \text{ oral} + 1g \text{ enema}} - \text{QALY}_{4g \text{ oral} + \text{placebo enema}})$  indicated use of mesalazine enema to be the dominant treatment option in acute UC in the Netherlands (i.e. less costly and produces better outcomes).

**Table 2.** Average cost and QALYs for subjects treated with oral and topical mesalazine or oral mesalazine alone after 32 weeks of treatment<sup>‡</sup>

	4g oral mesalazine + 1g mesalazine enema	4g oral mesalazine + placebo enema
Average treatment costs	€2207	€2945
95% CI	(€1402-€3332)	(€1717-€4592)
Incremental treatment costs		(€738)
QALYs	0.56	0.55
95% CI	(0.55-0.57)	(0.54-0.56)
Incremental QALYs		0.01
Average cost-effectiveness ratios	€3954	€5345
95% CI	(€2491-€6023)	(€3089-€8468)
Incremental cost-effectiveness ratio	<b>Topical mesalazine dominant</b>	

<sup>‡</sup> Based on Monte Carlo simulation derived from 10,000 samplings.

The disaggregated assessment of costs indicated that topical mesalazine represented 2.2% (€49) of the total treatment costs. The costs of consultations and diagnostics represented 21% and 20% of total costs for topical mesalazine and placebo-treated subjects, respectively. The remainder of costs were attributed to aggressive pharmacological interventions used to treat patients refractory to mesalazine therapy in acute UC.

The model also generated cost-effectiveness acceptability curves over a range of different willingness to pay thresholds in the Netherlands ranging from €0 to €40,000 per QALY. The output suggests that over a range of willingness to pay thresholds, mesalazine enema has a greater than 95% chance of being cost-effective compared with no enema in active UC (figure 1).

### Maintenance

The average annual treatment costs for OD and BID therapy from the baseline model were €1293 (95% CI: €1062 to 1496) and €1502 (95% CI: €1262 to 1708), respectively with an annual average per person saving of €209 (table 3). The average annual mesalazine costs for OD (€700) and BID (€706) were similar, even after adjusting for differences in compliance rates. The average costs for treating relapse events with mesalazine OD and BID were €592 (95% CI: €467 to 730) and €795 (95% CI: €658 to 939), respectively. In addition to the annual cost-savings achieved with OD 2 g mesalazine, a small incremental QALY improvement of 0.004 was also observed, indicating OD was the dominant treatment option for maintaining remission.

**Table 3.** Base case average annual treatment costs and incremental cost-effectiveness ratios comparing 2g mesalazine OD and BID‡

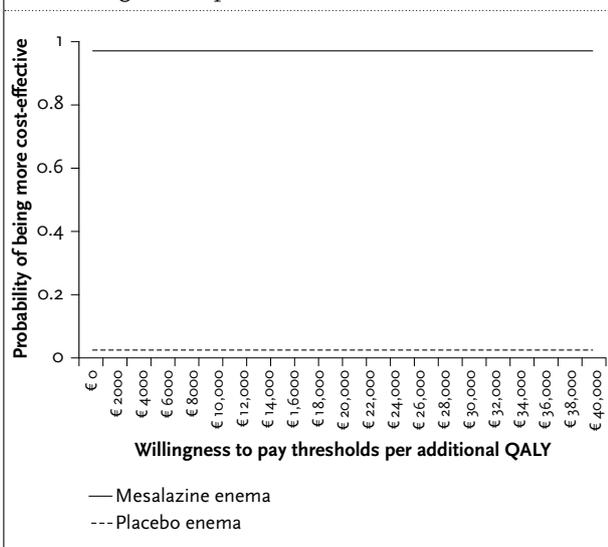
	Mesalazine 2g OD	Mesalazine 1g BID
Annual treatment costs‡ (95% CI)	€1293 (€1062-€1496)	€1502 (€1262-€1708)
Incremental cost per year (OD-BID)	(€209)	
QALYs (95% CI)	0.931 (0.928-0.933)	0.927 (0.924-0.929)
Incremental QALYs per year (OD-BID)	0.004	
Cost-effectiveness ratios (95% CI)	€1388 (€1265-€1502)	€1620 (€1362-€1847)
Incremental cost-effectiveness ratio	<b>2g OD dominant treatment option</b>	

‡ Based on Monte Carlo simulation derived from 10,000 samplings. BID = twice daily; OD = once daily. BID = twice daily; OD = once daily.

The disaggregated costs indicate mesalazine costs represent 54% and 47% of total costs for OD 2 g mesalazine and BID 1 g mesalazine-treated subjects, respectively. Ancillary costs of treating flares over the course of one year represented 46% and 53% of the costs for OD 2 g mesalazine and BID 1 g mesalazine-treated subjects, respectively.

Over the examined range of willingness to pay (WTP) thresholds from €0 to €40,000, mesalazine 2 g OD was found to deliver a higher proportion of benefits compared with mesalazine 1 g BID, with a 90% chance of being cost-effective for a WTP threshold per QALY of zero. As the WTP reached €40,000 per QALY, the likelihood that 2 g OD was more cost-effective was approximately 95% (data not shown). As health authorities would prefer to pay less per QALY this suggests 2 g OD represents a better treatment choice and in only 5% of cases 1 g BID would represent a more cost-effective option.

**Figure 1.** Cost-effectiveness acceptability curve comparing probability of being more cost-effective at different QALY willingness to pay thresholds for acute UC management options



### DISCUSSION

In the economic analysis of active UC we have shown that adding topical mesalazine offers cost savings for health services. The costs associated with returning a patient with mild to moderately active UC to remission in the Netherlands are approximately €2207 and €2945, respectively, for topical mesalazine compared with no topical mesalazine (placebo). This suggests an average saving of €738 per mild-to-moderately active UC patient treated. To achieve this result requires adding 1 g topical mesalazine for four weeks to 4 g oral mesalazine at a cost of approximately €49. The clinical effect size and resulting QALY differences described in the model are modest, suggesting the analysis is almost entirely influenced by avoiding the costs of treating the acute events.

The costs for returning a patient with active UC to remission are comparable with previous studies. In 2003 Bassi *et al.* reported six-month costs of patients experiencing an acute flare excluding hospitalisation to be  $\leq 765$  over a six-month period.<sup>21</sup> A more recent study in the United Kingdom reported 12-week costs associated with treating moderately active UC of  $\leq 2382$  per patient compared with  $\leq 2474$  dependent on whether first-line therapy of high dose (4.8 grams per day) or standard dose (2.4 grams per day) mesalazine was used.<sup>22</sup> However, in the study reported by Buckland, topical mesalazine was not considered in the analysis which may account for the small cost difference of  $\leq 92$ , in contrast with the cost differences reported in the analysis described here of  $\text{€}738$ .

The reduced costs and modest benefits of topical mesalazine are based on the ability to prevent progression to more expensive interventions used during acute events. Despite the benefits of topical mesalazine described here, and in head-to-head clinical trials,<sup>10</sup> there has been a downward trend in the utilisation of topical mesalazine during the period 1992 to 2009.<sup>23</sup> This downward trend in topical mesalazine use is concerning, considering the increasing incidence of UC and the likelihood of achieving downstream cost-savings is likely to be important for many local health authorities working with fixed budgets.<sup>24</sup>

One of the important aspects to this study is that health costs spent on pharmaceutical products such as topical mesalazine can save money for more expensive hospital-delivered care. This is an important message because funding silos within health services often means that budget holders only consider reimbursement decisions based on the impact within their own budget.<sup>6</sup> In the case of topical mesalazine, increasing pharmaceutical costs will save costs for treating acute events within hospital budgets. The maintenance of remission analysis described here highlights that OD 2 g mesalazine therapy is cost saving for maintaining UC remission compared with BID 1 g. The cost-effectiveness results described here likely represent an underestimate of mesalazine benefits because they do not include potential benefits in terms of occurrence of colorectal cancer (CRC) achieved with mesalazine therapy.<sup>25-27</sup> If the benefits associated with CRC prevention were included, then the costs of maintenance therapy would likely be lower from reduced resource use costs associated with treating CRC. Conversely, should mesalazine compliance in real-world settings be reduced and significantly more flares occur, the average cost-effectiveness ratios would increase.

The annual treatment costs for maintaining UC remission were  $\text{€}1293$  ( $\text{€}1062$  to  $\text{€}1496$ ) and  $\text{€}1502$  ( $\text{€}1262$  to  $\text{€}1708$ ) for OD and BID treatment practices. These annual treatment costs are broadly in line with previously reported European annual treatment costs for UC of  $\text{€}1524$ .<sup>28</sup> Furthermore, the effect size based on improved QALYs

between OD and BID mesalazine was only 0.004 QALYs between the two interventions. This highlights that the cost-effectiveness is influenced entirely by the costs associated with high-cost interventions used to treat acute UC events.

One of the limitations of our analysis is that we did not account for the indirect costs of the disease leading to lost productivity attributed to impaired health. In the case of UC, these costs may be substantial and could represent more than 50% of the total societal cost of UC.<sup>29</sup> However, due to limitations on working status in our clinical trial population we are unable to evaluate these costs in our analysis, although their inclusion in this analysis is not likely to influence the overall conclusions described in this paper because indirect costs normally follow direct costs, which were reported here.

Previous studies in the United States have suggested that maintenance therapy with mesalazine may not be justifiable, indicating the need to put the maintenance cost-effectiveness findings described here into perspective. In the study reported by Yen *et al.*,<sup>30</sup> the cost-effectiveness results were shown to be sensitive to the costs of mesalazine therapy and rate of flare reduction during maintenance therapy. In the study reported by Yen *et al.* the costs of mesalazine therapy are twice those in the Netherlands, which would likely influence the findings should a comparable study be conducted in the Netherlands. Furthermore, the analysis reported by Yen *et al.* also suggested a reduction in flare of 0.54 over a two-year period with maintenance therapy compared with no maintenance. Applying the rate of flare reduction reported by Yen *et al.* and factoring in the annual costs of maintenance therapy in the Netherlands, this would suggest a cost per flare avoided of  $\text{€}2593$ . The estimated cost per flare avoided is comparable with the costs associated with treating a flare, suggesting maintenance therapy may be cost-neutral in the Netherlands.

## CONCLUSIONS

In the Netherlands, and in many other countries, mesalazine is the cornerstone first-line therapy for maintaining remission and treating acute flares in mild-to-moderately active UC patients. Although daily treatment costs with mesalazine are relatively inexpensive, widespread acceptance and use of mesalazine suggests the budgetary impact could be important for guiding treatment practices and budgetary considerations. Because mesalazine is widely used we sought to establish the costs and consequences of its use in two clinical situations. The analysis described here indicates that the addition of 1 g topical mesalazine in combination with 4 g oral mesalazine is cost saving compared with oral monotherapy. The saving is achieved by

a moderate improvement in QALYs and reduced progression to more expensive interventions in those patients not responding to oral monotherapy. Furthermore, for maintenance of remission we established that OD 2 g is cost saving compared with BID 1 g. The saving with OD 2 g was achieved by reducing the number of people who experienced acute UC flares. It is envisaged that the findings reported here can be aligned with clinical guidelines to support the efficient use of healthcare resources in UC.

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# *APOE1* mutation in a patient with type III hyperlipoproteinaemia: detailed genetic analysis required

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## ABSTRACT

We present the case of a patient with clinical features of familial dysbetalipoproteinaemia (FD) including high levels of total cholesterol, hypertriglyceridaemia and the presence of palmar xanthomas. Whereas genotype analysis identified the *APOE3E3* isoform, sequence analysis revealed the presence of one *APOE1* allele due to a mutation, p.Lys164Glu, which leads to loss of function of apolipoprotein E (ApoE), a rare cause of dominant FD.

## KEYWORDS

ApoE, *APOE1E3*, dysbetalipoproteinemia, hypertriglyceridemia, type III hyperlipidemia,

## INTRODUCTION

Familial dysbetalipoproteinaemia (FD), or type III hyperlipoproteinaemia, is a genetic disorder of lipoprotein metabolism that predisposes affected subjects to premature development of atherosclerotic disease. The disorder is characterised by elevated plasma total cholesterol (TC) and triglyceride (TG) levels caused by the accumulation of predominantly very-low-density lipoprotein (VLDL) and chylomicron remnants. Affected individuals often have tuberous or tubero-eruptive xanthomas on the extensor surfaces of their extremities as well as palmar crease xanthomas.<sup>1</sup>

The clinical diagnosis of FD is based on the routine measurement of plasma TC, VLDLc, LDLc, TG and apolipoprotein (apo)B levels. TC/apoB and TG/apoB ratios allow differentiation between different lipid abnormalities.<sup>2</sup>

### What was known about this topic?

Familial dysbetalipoproteinaemia (FD) is a genetic disorder of lipoprotein metabolism predisposing affected subjects to the development of premature atherosclerotic disease. The disorder is characterised by elevated plasma cholesterol and triglyceride levels due to the accumulation of chylomicron and VLDL remnants. The primary molecular defect in FD is the presence of the homozygous *APOE2* isoform; however, rare cases of dominant FD have been reported.

### What does this case add?

Clinicians should not rule out the diagnosis of FD after a 'negative' routine *APOE* genotype analysis, since routine *APOE* genotype assessment does not reveal rare variants causing dominant FD. In patients with a laboratory and clinical phenotype suggestive for FD, sequencing of *APOE* could be considered,

FD is characterised by relatively normal apoB levels in the presence of elevated levels of TC and TG. A ratio of TG/apoB of <10 mmol/g excludes chylomicronaemia and an TC/apoB ratio  $\geq 6.2$  (mmol/g) is suggestive for the presence of large cholesterol-rich buoyant apoB particles, the remnants. If available, VLDL remnant particles may be isolated by ultracentrifugation followed by cholesterol, TG and apoB analysis.

The primary molecular cause of FD is the presence of homozygosity for *APOE2*. Part of the apoE is present on chylomicron and VLDL remnant particles, where it serves as a ligand for receptor-mediated uptake and internalisation by binding to the LDL receptor (LDLr) and LDL receptor-related protein (LRP1). The *APOE* gene is located on chromosome 19q13.2 and is polymorphic. The molecular bases of *APOE* isoforms are cysteine-arginine interchanges at the residues 130 and 176 from the ATG start site (nucleotides were numbered according to the official nomenclature provided by the Human Genome Variation Society ([www.hgvs.org/nomenclature/mutnomen](http://www.hgvs.org/nomenclature/mutnomen)); previous residue number: 112 and 158) that determine three co-dominant alleles, designated *E2*, *E3* and *E4*. These polymorphisms lead to the presence of six different genotypes in the human population: three homozygous (*E3E3*, *E2E2*, *E4E4*) and three heterozygous (*E2E3*, *E2E4*, *E3E4*).

ApoE2 differs from the most common isoform *E3* by a single amino acid substitution (p.Arg176Cys) resulting in defective binding to the lipoprotein receptors causing accumulation of chylomicron- and VLDL-remnant particles in the plasma of affected subjects.<sup>3</sup> Although FD has a distinct genetic basis, phenotypic expression requires accompanying factors such as obesity, type 2 diabetes, other forms of hyperlipidaemia such as familial combined hyperlipidaemia and hypothyroidism. Even then, only one out of 100 subjects will actually go on to develop the phenotype of FD.<sup>4</sup> To date, the exact reasons for the differential penetration of the phenotype of the disease remain to be elucidated. Besides *APOE2E2*, several other rare mutants of *APOE* have been associated with FD including apolipoprotein E3-Leiden.<sup>5,6</sup> In contrast to *APOE2E2*, these rare isoforms are characterised by an autosomal dominant inheritance pattern. In addition, these forms are phenotypically expressed in the absence of secondary factors such as diabetes and obesity. One of these rare *APOE* variants is *APOE1* p.Lys164Glu (previously common nomenclature p.Lys146Glu). Two families with this variant have been previously described.<sup>7,8</sup>

Diagnosis of FD as the cause of dyslipidaemia is important to achieve optimal treatment efficacy. Since statin response in FD will be limited, the focus of treatment will be on lifestyle changes. Furthermore the strong fluctuations in lipid levels commonly seen in FD may otherwise wrongly be attributed to medication non-compliance. This in a background where the majority of patients receiving statin therapy fail to reach adequate cholesterol levels.<sup>9</sup>

## CASE REPORT

A 46-year-old female of Dutch ancestry was referred to our lipid clinic for diagnosis and treatment of severe dyslipidaemia despite the use of simvastatin 40 mg. On physical examination she presented with clinical

features of hypertriglyceridaemia including palmar linear xanthomas ('palmar streaks') and eruptive xanthomas at the extensor surfaces of the arms. She was lean (body mass index (BMI) 22 kg/m<sup>2</sup>), with a blood pressure of 116/72 mmHg. There were no signs of atherosclerotic disease. Laboratory analyses revealed a plasma TC of 14.8 mmol/l, TG 7.6 mmol/l and apoB 1.75 g/l suggesting the presence of a (familial) combined dyslipidaemia.<sup>2</sup> Of note, lipoprotein (Lp(a)) was significantly elevated (1180 mg/l). LDLc could not be calculated using the Friedewald formula due to elevated plasma TG levels. Other laboratory analyses did not show abnormalities; especially plasma glucose and thyroid-stimulating hormone (TSH) levels were within normal limits. The patient used 2-3 units of alcohol per week and had a seven pack-year smoking history. The patient's mother and brother suffered from premature cardiovascular disease and hypercholesterolaemia.

During follow-up, TC levels showed profound variations, ranging from 14.76 mmol/l to 7.92 mmol/l. These large variations in plasma TC combined with elevated plasma TG levels and the presence of palmar linear xanthomas raised the possibility of FD, despite the high levels of apoB and subsequent low TC/apoB ratio. Routine *APOE* genotyping revealed an *APOE3E3* genotype. In view of a high clinical probability of FD, full *APOE* sequence analysis was performed. A single substitution of lysine for glutamic acid at position 164 was observed (*APOE1*), confirming the diagnosis of autosomal dominant FD. The patient was treated with rosuvastatin 10 mg per day and ciprofibrate 100 mg/day and was advised to adhere to a low-fat diet. These therapeutic interventions resulted in a plasma TC of 4.95 mmol/l, LDLc 2.96 mmol/l and TG of 1.90 mmol/l. Treatment was well tolerated.

## DISCUSSION

We identified a patient with FD associated with the rare *APOE1* mutation on an *APOE3E3* background. The region of *APOE* involved in the interaction with the LDLr is located in the centre of the protein, at residues 154-168. The key feature of the binding domain is the presence of an  $\alpha$ -helix that is rich in basic amino acids. Replacement of the positively charged lysine by glutamic acid at residue 164 results in defective binding by disrupting the direct interaction of the basic residues of *APOE* with the LDLr.<sup>8</sup> The dominant expression of FD associated with the presence of an *APOE1* isoform may be due to an over-expression of the *E1* allele as well as a decreased clearance rate of the apoE1-containing particles from the plasma.<sup>10</sup> Since routine *APOE* genotyping only discriminates between amino acid changes at positions 130 and 176, the

*APOE1* mutation can only be assessed by full sequencing of the *APOE* gene.

Several special aspects of this case deserve closer attention. First, the profound elevations in plasma apoB together with a family history of premature cardiovascular disease suggested primarily the presence of familial combined hypercholesterolaemia, and not FD which is characterised by relatively normal apoB levels. The increased level of plasma apoB may partially be explained by the extremely high levels of plasma Lp(a), since Lp(a) is a circulating complex of several apo(a) molecules together with one apoB molecule.<sup>11</sup>

Second, this case demonstrates the importance of thorough clinical phenotyping in order to determine the cause of a dyslipidaemia. The presence of the spontaneous large variation in TC values combined with physical stigmata was highly suggestive for the presence of FD. However, FD does not normally occur in premenopausal women. Moreover, there were no luxating factors (lean physique, low alcohol consumption and a healthy diet). Together these observations suggested the presence of dominant FD. As a result, full sequencing of *APOE* was performed, in spite of the high apoB levels and the initially established *APOE3E3* genotype.

## CONCLUSION

Whereas FD is associated with the *APOE2E2* genotype, other variants have been described. Routine *APOE* genotyping does not reveal these extremely rare variants. Since patients require treatment to lower cardiovascular risk, clinicians should either assess the amount of TG-rich remnant particles or sequence the full *APOE* gene in patients with a high suspicion of FD.

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# Altered mental status in a young male

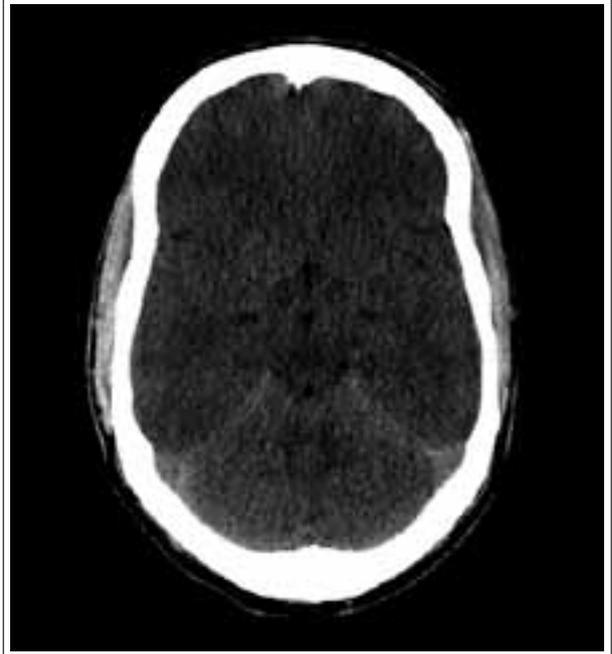
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## CASE REPORT

A 28-year-old male was brought into the Emergency Department of our hospital by ambulance because of an altered mental status. He had attended a dance party the night before and after going to sleep at 7 am, his girlfriend had not been able to wake him up at 10 am in the morning. She suggested that he might have used recreational drugs at the party. The patient had no medical history and was not taking any medication. Physical examination showed a blood pressure of 130/75 mmHg, heart rate of 70 beats/min, ventilation rate of 16 breaths/min, and a temperature of 35.1 °C. At physical examination he was sweating excessively, his pupils were myotic and only slightly reactive to light. At arrival the Glasgow Coma Scale (GCS) was E1M4V1. The rest of his neurological examination revealed no abnormalities. The capillary refill and skin turgor were normal suggesting an euvoelaemic state. There were no signs of head trauma. His ECG showed no abnormalities. Blood glucose was 5 mmol/l, further laboratory evaluation revealed a sodium content of 122 mmol/l and a urinary sodium concentration of 148 mmol/l. Soon after arriving, the patient awoke and was physically aggressive and had to be sedated using 5 mg of midazolam and after that with 50 mg of promethazine. To rule out intracerebral causes, a non-contrast CT was taken, showing the image as published here (*figure 1*).

Figure 1. Axial slide of a CT scan of the brain



## WHAT IS YOUR DIAGNOSIS?

See page 284 for the answer to this photo quiz

# Green coloured urine

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## CASE REPORT

A 45-year-old Caucasian man with a long-standing history of sarcoidosis was admitted to the intensive care unit for acute respiratory failure requiring mechanical ventilation. He had no other significant past medical history. Home medications included low-dose prednisone, tear drops and amlodipine. Laboratory tests revealed a normal white cell count, renal and liver function. Chest X-ray showed a reticulonodular pattern. The patient was empirically started on ceftriaxone and azithromycin. He was also given high-dose methylprednisolone, heparin for deep vein thrombosis prophylaxis and pantoprazole. While intubated, he needed high doses of propofol and fentanyl to prevent patient-ventilator dyssynchrony. Forty-eight hours later his urine started turning green (*figure 1*). A urine dipstick and microscopy were normal. Urine porphyrins were undetectable. Blood tests were negative for leucocytosis or hyperbilirubinaemia.

**Figure 1.** Green coloured urine in the bag



## WHAT IS YOUR DIAGNOSIS?

See page 285 for the answer to this photo quiz

# Intra-thoracic mass on CT in a breast cancer patient

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## CASE REPORT

A 67-year-old woman with an irresectable local recurrence of breast cancer received first-line palliative endocrine treatment. Two years previously, her left-sided primary breast tumour (T<sub>4</sub>N<sub>0</sub>M<sub>0</sub>, oestrogen positive, progesterone and Her-2-neu negative) was treated with neoadjuvant chemotherapy, mastectomy, adjuvant radiotherapy, and endocrine therapy (tamoxifen). However, she developed a local recurrence, which proved to be irresectable. The tumour had grown from the thoracic wall towards the mediastinum (*figure 1*). Palliative treatment with exemestane, an aromatase inhibitor, was started. Throughout the first months of treatment with exemestane, the patient complained of progressive left-sided chest pain and necrosis of the tumour (ulcer). No swelling was present, nor were there any other symptoms. During follow-up, three months after starting exemestane, the following mass was seen on CT imaging (*figure 2*).

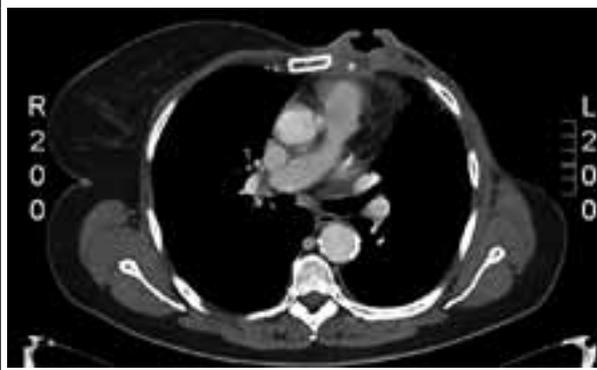
## WHAT IS YOUR DIAGNOSIS?

See page 286 for the answer to this photo quiz

**Figure 1.** Transversal CT image showing an extensive local recurrence of the breast tumour



**Figure 2.** Transversal CT image showing the pseudoaneurysm on the base of the ulcerative recurrence



## DIAGNOSIS

Before the CT scan, we considered several diagnoses to explain the comatose state of our patient. 3,4-Methylenedioxymethamphetamine (MDMA) use with excessive water intake could explain the hyponatraemia and the comatose status. The non-contrast CT taken showed extensive brain oedema. The urine toxicology screening was positive for amphetamines. Combined with the laboratory results the diagnosis of MDMA-induced syndrome of inappropriate antidiuretic hormone synthesis (SIADH) causing symptomatic hyponatraemia with brain oedema was made. MDMA is a party drug that has become more popular over the last decade. Its effects on neurotransmitters are on the serotonin, noradrenalin and dopamine system giving the '3E' effect of euphoria, empathy and energy. The adverse effects can be serious and even fatal. The most dangerous of these being hyperthermia, hepatotoxicity and rhabdomyolysis.<sup>1</sup> It is also associated with long-term damage as significant deficits in neurocognitive function (particularly immediate and delayed verbal memory) and increased psychopathological symptoms.<sup>2</sup> Acute lowered serum sodium levels can also occur, leading to brain oedema with cerebral damage as shown in this case

report. ADH release from the neurohypothalamus has been proven to be affected by serotonin in animal experiments. MDMA, being a serotonin agonist, can stimulate ADH release.<sup>3</sup> Combined with excessive fluid intake it can lead to dangerously low sodium levels which can cause brain oedema.

Fluids were restricted, but as the sodium concentration dropped further, the patient was treated with hypertonic fluid infusion (NaCl 3%). Approximately 12 hours later, the sodium concentration normalised and the patient recovered fully.

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## DIAGNOSIS

Propofol is a short-acting, intravenous sedative hypnotic for inducing and maintaining anaesthesia or sedation. The above case depicts a benign discoloration of urine seen in less than 1% of patients who are on a propofol infusion. The famous Greek philosopher Hermogenes described the colour of urine as an indicator of many disorders in ancient times.<sup>1</sup> Bodenham and colleagues were probably the first to report propofol-induced green urine.<sup>2</sup> A number of other authors have reported this entity since.<sup>3,5</sup> It usually manifests two to three days after starting the infusion; resolution of discoloration is rapid after discontinuation of propofol. Propofol is metabolised in the liver and excreted in urine predominantly as 1-glucuronide, 4-glucuronide and 4-sulphate conjugates of 2,6 diisopropyl-1, 4 quinol, which can cause greenish discoloration of urine. Alkalinisation of urine increases the formation of these phenolic derivatives.<sup>3,4</sup> Hence green urine is more commonly seen in patients who develop respiratory alkalosis while on a ventilator. The compensatory increase in renal bicarbonate excretion leads to increased urine pH favouring formation of phenolic metabolites. However, not all patients on propofol who have alkaline urine develop greenish discoloration. This may be related to some genetic differences in its metabolism in different individuals and races. The differential diagnosis of green urine is diverse and before attributing it to propofol, other causes must be explored (*table 1*). Green urine associated with propofol is benign; prompt recognition of this phenomenon may limit unnecessary laboratory tests and avoid undue anxiety among caregivers.

**Table 1.** Causes of green urine

Drugs/ingestions	Metabolic disorders	Infections	Miscellaneous
Cimetidine	Hartnup disease	Pseudomonas	Bile via vesico-entestinal fistula
Promethazine	Indicanuria	urinary tract infection	Green beer
Indomethacin			Some green dyes
Metoclopramide			
Flutamide			
Methylene blue			
Asparagus			
Clorets (chlorophyll)			
Wilisan pills (Chinese herbal medication)			

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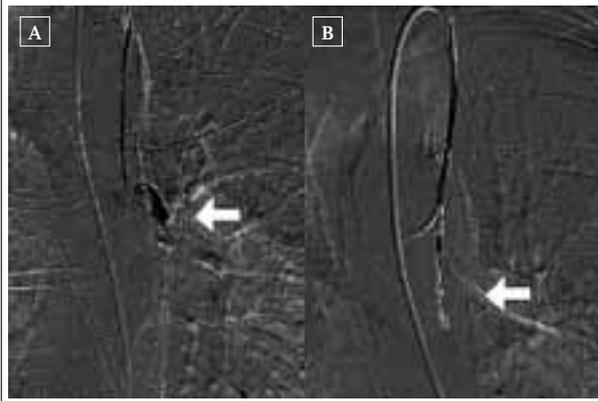
## DIAGNOSIS

A contrast-enhanced CT scan, three months after start of exemestane, showed a newly formed pseudoaneurysm of the left internal mammary artery (*figure 2*) and progressive tumour growth. Pseudoaneurysms are vascular anomalies; the continuity of all three layers of the arterial wall is disrupted and blood flows into a confined cavity. The connection with the vessel remains, causing a patent flow in the extravascular space. In this case, the diagnosis was already confirmed with the contrast CT showing contrast enhancement in the pseudoaneurysm, but in general pseudoaneurysms of the breast are diagnosed by Doppler ultrasound. Colour Doppler ultrasound can be used to show blood filling of the cavity in phase with the cardiac cycle.<sup>1</sup> An angiogram shows the internal mammary artery and pseudoaneurysm of the described patient in more detail (*figure 3*).

The majority of pseudoaneurysms occur after iatrogenic trauma of the vessels. In general pseudoaneurysms are rather common. Most occur in the groin, aorta, pulmonary arteries and visceral arteries (coeliac branches, hepatic artery and splenic artery). With the increase of angiographic procedures the incidence is rising.<sup>2</sup> Pseudoaneurysms of the breast are rare. Most pseudoaneurysms in the breast presented in the literature occurred following ultrasound-guided needle biopsy procedures.<sup>3</sup> Incidentally, spontaneous pseudoaneurysm is reported, mostly in women with hypertensive disease or after blunt trauma.<sup>1</sup> However, in our case most likely tumour necrosis adjacent to the mammary artery or tumour growth into the vessel wall caused disruption of the arterial wall.

A pseudoaneurysm may be asymptomatic, but some can present with pain (mass effect) or as a palpable pulsating mass. If untreated serious complications such as enlargement or rupture, pressure on adjacent structures, pressure necrosis of overlying skin and distal thromboembolism may occur. Therefore, pseudoaneurysms are considered a medical emergency and are treated with either percutaneous embolisation or surgical removal.<sup>4</sup> Some pseudoaneurysms of the breast can successfully be treated by external, ultrasound-guided compression.<sup>5</sup> This patient was treated with coiling of the left internal mammary artery followed by palliative chest wall irradiation (*figure 3*).

**Figure 3.** Angiogram before coiling of the pseudoaneurysm (A). The contrast fills both the vessels and the pseudoaneurysm (white arrow). After coiling the artery (B), the pseudoaneurysm is no longer filled with contrast and is no longer visible



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# What do professionals recommend regarding the frequency of self-monitoring of blood glucose?

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## ABSTRACT

**Background:** Patients' adherence to guidelines regarding self-monitoring of blood glucose (SMBG) is limited. However, there are no previous reports about the recommendations that are given in clinical practice concerning SMBG. The aim of this study was to investigate what healthcare providers recommend to insulin-treated patients with diabetes regarding frequency and timing of SMBG.

**Methods:** In this cross-sectional descriptive study, primary care assistants, diabetes specialised nurses and doctors in the Netherlands were invited via e-mail to complete an internet survey.

**Results:** A total of 980 (14%) professionals returned the questionnaire. Insulin pump users and patients with type 1 diabetes (T1DM) on 4 injections a day were advised to perform SMBG daily by 96% and 63% of the professionals, respectively. The majority of the professionals advised these patients to perform 3-4 measurements per day. There was less agreement on the timing (pre- and/or postprandial). Patients with type 2 diabetes (T2DM) on four injections were advised to perform SMBG less frequently. There was a wide variation in recommendations that were given to patients with T2DM on less intensive insulin regimens.

**Conclusion:** This study investigated SMBG from a professional's perspective. A considerable and relevant variation in the recommendations about the number and timing of SMBG was observed. The most striking differences were found in patients with T2DM on less intensive insulin regimes, also with respect to the frequency of SMBG. Well-designed studies are necessary in order to give a more evidence-based advice on the basic frequency and timing of SMBG.

## KEYWORDS

Diabetes, frequency, insulin-treated, self-monitoring of blood glucose

## INTRODUCTION

A broad consensus exists on the importance of self-monitoring of blood glucose (SMBG) in subjects with diabetes who are treated with insulin. The aim of SMBG is to achieve optimal glycaemic control in order to decrease the risk of long-term complications of diabetes.<sup>1-3</sup> The results of SMBG are used to assess the efficacy of therapy, and to guide adjustments in medication, food intake and physical activity. However, the optimal frequency and timing of SMBG are not known.<sup>3,7</sup> In absence of clear evidence-based recommendations, Diabetes United Kingdom (UK) has undertaken further consultation with professionals and people with diabetes, leading to a wider consensus on the recommendations. An overview of the recommendations of Diabetes UK and the recommendations of the Netherlands, the USA and Canada is presented in *table 1*.<sup>4,7</sup> The recommendations of Diabetes UK, the American Diabetes Association (ADA) and the Canadian Diabetes Association do not differ much. However, the Dutch recommendations generally advise a lower frequency of SMBG.<sup>5</sup>

Several studies investigated the adherence to the SMBG guidelines among patients with diabetes by using questionnaires or databases on the dispensing of blood glucose strips.<sup>8-11</sup> The results of these studies show that patients do not perform SMBG on a regular basis, and patients' adherence regarding SMBG is limited. However,

**Table 1.** Guidelines regarding the frequency and timing of self-monitoring of blood glucose in insulin-treated patients with diabetes

	The Netherlands	UK	ADA	Canada
T1DM and T2DM: 1 or 2 insulin injection(s)	1 day a week or every 2 weeks: 4 times preprandial or 8 times a day	T1DM: $\geq 2$ times a day T2DM: 1-2 times a day, varying the time	T2DM: unclear: SMBG may be useful as a guide to the success of therapy	2 injections: $\geq 3$ times a day, pre- and postprandial 1 injection: $\geq$ once a day at variable times
T1DM and T2DM: MDI	3 days a week: 4 times preprandial or 2 days a week: 8 times	2-4 times a day	$\geq 3$ times a day	$\geq 3$ times a day, pre- and postprandial
T1DM and T2DM: CSII	3 days a week: 4 times preprandial or 2 days a week: 8 times	4-6 times a day	$\geq 3$ times a day	$\geq 3$ times a day, pre- and postprandial

CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

there are no previous reports about the recommendations that are given in clinical practice concerning blood glucose testing.

The aim of this study was to investigate what healthcare providers in the Netherlands recommend to insulin-treated patients with diabetes, who are in stable good glycaemic control, regarding the frequency and timing of SMBG.

## MATERIALS AND METHODS

### Design

In this cross-sectional descriptive study, an internet survey was used to collect data. The study was part of a larger survey. The other part of the internet survey was a questionnaire with ten questions about the interpretation of haemoglobin A1C (HbA1C). The study was carried out from March to June 2010.

### Participants

A total of 6965 primary care assistants, diabetes specialised nurses and doctors from the database of the Langerhans Medical Research Group were invited by e-mail to participate in this survey. Furthermore, a message containing a link to the survey was placed on the website of the Dutch Association of Diabetes Care Professionals (EADV).

### Data collection

Participants anonymously completed a self-report questionnaire containing a maximum of 33 questions. The questionnaire included three questions about the profession, the province and the number of patients with T1DM and patients with T2DM in their practice. The items of the questionnaire were derived from the SMBG guidelines. The surveys were then checked for clarity, length and inappropriate use of jargon by four diabetes specialised nurses, who did this independently from one another.

Ten subcategories of patients were created, based on the type of diabetes and the kind of insulin therapy. Patients with T1DM were categorised into three groups: (1) patients on 4 insulin injections a day (multiple daily injections, MDI), including short-acting human insulin, (2) MDI, including rapid-acting insulin analogue, and (3) patients with a continuous subcutaneous insulin infusion (CSII). Insulin-treated patients with T2DM were divided into 7 groups: (1) 1 injection with long-acting insulin a day, (2) 2 injections with long-acting insulin a day, (3) 2 injections with premixed insulin a day, including short-acting human insulin, (4) 2 injections with premixed insulin a day, including rapid-acting insulin analogue, (5) MDI, including short-acting human insulin, (6) MDI, including rapid-acting insulin analogue, and (7) CSII.

In the Netherlands, patients with T1DM are almost always treated with MDI or with CSII. Therefore, the recommendations given to patients with T1DM who are using a non-intensive insulin regimen are not included in this study. The same three questions were asked for each category: in general, what advice do you give to insulin-treated patients with diabetes, who are in stable good glycaemic control, regarding:

1. The frequency of SMBG
2. The number of measurements per day
3. The timing of SMBG

In the Netherlands, stable good glycaemic control generally corresponds with an HbA1C < 53 mmol/mol (7.0%).<sup>12</sup>

### Data analysis

The questionnaires were analysed using frequency distributions. SPSS software (version 15.0) was used for the analyses.

## RESULTS

A total of 980 professionals (14%) returned the questionnaire, including 531 (54%) primary care assistants,

**Table 2.** Recommendations regarding frequency of self-monitoring of blood glucose

Insulin therapy	Every day	1 day a week	2-3 days a week	1 day in 2 weeks	Every month	Before visiting healthcare provider
<b>T1DM</b>						
4 injections with RA/LA; n=171	108 (63)	22 (13)	23 (14)	9 (5)	9 (5)	-
CSII; n=98	94 (96)	2 (2)	1 (1)	1 (1)	-	-
<b>T2DM</b>						
1 injection with LA; n=546	20 (4)	113 (21)	39 (7)	204 (37)	140 (26)	30 (5)
2 injections with LA; n=194	9 (5)	52 (27)	13 (7)	73 (37)	41 (21)	6 (3)
2 injections with PM; n=427	20 (5)	116 (27)	51 (12)	139 (32)	94 (22)	7 (2)
4 injections with RA/LA; n=298	73 (25)	86 (29)	68 (23)	48 (16)	20 (6)	3 (1)
CSII; n= 67	64 (96)	-	3 (4)	-	-	-

Data in n (%); n is the number of professionals. LA = long-acting insulin; PM = premixed insulin with rapid-acting insulin analogue and long-acting insulin; RA/LA = rapid-acting insulin analogue (3 times a day), long-acting insulin (once every day).

168 (17%) diabetes specialised nurses working in a general practice, 166 (17%) diabetes specialised nurses working in an outpatient clinic, 81 (8%) general practitioners, and 34 (4%) other professionals.

An overview of the different recommendations regarding the frequency, number of measurements per day and timing of SMBG given by professionals is presented in tables 2 to 4. There were no relevant differences between recommendations that were given to patients who used short-acting human insulin as part of an MDI regimen, and the patients who used rapid-acting insulin analogue. Therefore, the recommendations to patients using short-acting human insulin were not presented in this paper.

In general, there is agreement among professionals with respect to recommendations to patients with either T1DM or T2DM who use CSII to measure their

glucose concentration daily. However, about two thirds of the professionals advised these patients to do 3-4 measurements per day, and most of the other professionals advised 5-6 measurements per day. There was less agreement on the timing of SMBG. Alternating pre- or postprandial and pre- and postprandial measurements (about 37%) and preprandial measurements (about 30%) were most frequently advised.

We observed more variation in the recommendations with less intensive insulin regimens. The majority (63%) of the healthcare providers advised patients with T1DM on an MDI regimen to perform SMBG daily, compared with 25% of the patients with T2DM on such a regimen. In both MDI groups, the recommendations on the number of measurements a day were (almost) similar to those in the CSII group. However, the variation in the timing of measurements was greater.

Concerning the frequency of SMBG in patients with T2DM on 1 or 2 insulin injections a day, once every two weeks was most frequently reported (32-37%), followed by one day a week (21-27%) and one day a month (21-26%). Just over 50% of the professionals advised these patients to perform SMBG 3-4 times on the specified days. Preprandial measurements were most frequently advised (29-37%).

## DISCUSSION

The majority of the professionals in the Netherlands advised patients using CSII (both T1DM and T2DM) and patients with T1DM on an MDI regimen to measure the blood glucose concentration 3-4 times a day. However, there is less agreement on the timing (pre- and/or postprandial with or without alternation) of SMBG. Patients with T2DM were advised to test their blood glucose less frequently, even when they used a similar insulin regimen. Furthermore, our study shows there is a wide variation in

**Table 3.** Recommendations regarding the number of measurements per day

Insulin therapy	1-2 a day	3-4 a day	5-7 a day
<b>T1DM</b>			
4 injections with RA/LA; n=171	14 (8)	119 (70)	38 (22)
CSII; n=99	4 (4)	69 (70)	26 (26)
<b>T2DM</b>			
1 injection with LA; n=546	157 (29)	281 (51)	108 (20)
2 injections with LA; n=194	29 (15)	116 (60)	49 (25)
2 injections with PM; n=427	38 (9)	248 (58)	141 (33)
4 injections with RA/LA; n=298	17 (6)	162 (54)	119 (40)
CSII; n=67	7 (10)	43 (64)	17 (26)

Data in n (%); n is the number of professionals. CSII = continuous subcutaneous insulin infusion; LA = long-acting insulin; PM = premixed insulin with rapid-acting insulin analogue and long-acting insulin; RA/LA = rapid-acting insulin analogue (3 times a day), long-acting insulin (once every day); T1DM – type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

**Table 4.** Recommendations regarding the timing of self-monitoring of blood glucose

Insulin therapy	1 <sup>†</sup>	2	3	4	5	6	7	8	9
<b>T1DM</b>									
4 injections with RA/LA; n=171	3 (2)	-	-	64 (37)	10 (6)	19 (11)	28 (16)	28 (16)	19 (12)
CSII; n=99	2 (2)	-	-	29 (29)	1 (1)	12 (12)	12 (12)	39 (40)	4 (4)
<b>T2DM</b>									
1 injection with LA; n=546	55 (10)	32 (6)	45 (8)	168 (31)	80 (14)	33 (6)	53 (10)	10 (2)	70 (13)
2 injections with LA; n=194	2 (1)	11 (6)	15 (8)	72 (37)	33 (17)	13 (7)	22 (11)	7 (3)	21 (10)
2 injections with PM; n=427	2 (1)	19 (5)	31 (7)	124 (29)	89 (21)	39 (9)	65 (15)	19 (4)	39 (9)
4 injections with RA/LA; n=298	0	3 (1)	22 (7)	88 (30)	41 (14)	59 (20)	45 (15)	25 (8)	15 (5)
CSII; n=67	0	0	0	20 (30)	2 (3)	3 (5)	12 (18)	23 (34)	7 (10)

Data in n (%): n is the number of professionals. LA = long-acting insulin; PM = premixed insulin with rapid-acting insulin analogue and long-acting insulin; RA/LA = rapid-acting insulin analogue (3 times a day); long-acting insulin (once every day); <sup>†</sup>1) fasting; 2) fasting and before evening meal or bed time; 3) alternating fasting and pre- and/or postprandial; 4) preprandial; 5) postprandial; 6) pre- and postprandial (7 measurements); 7) alternating pre- and postprandial; 8) alternating pre- or postprandial and pre- and postprandial; 9) other.

the recommendations that are given to patients with T2DM on 1 or 2 injections a day with respect to the frequency, the number of measurements per day and the timing of blood glucose testing.

Only a minority of the professionals advised patients with T1DM to perform SMBG 2–3 days a week, as recommended in the Dutch guideline (1–14%).<sup>5</sup> Most of the professionals advised to perform SMBG daily, which is in accordance with the recommendations of the Diabetes UK, the ADA and the Canadian Diabetes Association.<sup>4,6,7</sup> In the guidelines, no distinction is made between the recommendations to patients with T1DM using an intensive insulin regime or CSII, and patients with T2DM with the same insulin regimen. In daily practice, however, patients with T1DM using an intensive insulin regimen were advised to measure more frequently than patients with T2DM with the same insulin regimen. A higher number of professionals (but still only 23%) advised these patients with T2DM to perform SMBG 2–3 days a week, as recommended in the Dutch guideline. Just a quarter of the professionals advised them to test daily. As for patients with T2DM on 1 or 2 insulin injections per day, 58 to 64% of the professionals reported that they recommend to measure the blood glucose concentration 1 day each week or 1 day every two weeks, as recommended in the Dutch guidelines. However, nearly a quarter of the professionals advised to perform SMBG on a monthly basis. In the Netherlands, there are other guidelines (clinical practice guidelines for general practitioners) for the treatment of diabetes in which patients with T2DM are advised to perform SMBG less frequently. For example, it is stated that patients on 1 injection a day, who are in stable good glycaemic control, do not have to measure their glucose concentration several times a day. Measuring a fasting glucose concentration and an HbA1C once every 3 or 6 months is sufficient.<sup>12</sup>

Perceptions of the healthcare providers, based on their experiences regarding the basic frequency and timing of SMBG sufficient to maintain the glycaemic goals, could be the explanation for the differences between daily practice and the guideline recommendations. Another possibility may be that the healthcare providers just do not know what the guidelines recommend.

Yet, advice on SMBG can have great consequences for patients. Studies among patients with diabetes on oral medication and insulin-treated patients with diabetes show that performing SMBG can lead to a decreased quality of life.<sup>13–17</sup> Complexity of the treatment is one of the factors leading to inconvenience for patients, which in turn leads to non-adherence to SMBG (e.g. alternating the timing of measurements and postprandial measurements).<sup>17</sup> Furthermore, there is a debate over the need to test the postprandial blood glucose. Although there are arguments that postprandial levels need to be considered important for the long-term complication risk, the verdict on this assumption is still out.<sup>18,19</sup> Therefore, routinely advising postprandial controls might be superfluous. This advice could be given to patients who show good preprandial glucose levels, but still have an unsatisfactorily high HbA1C, or to patients with special conditions, for example in case of pregnancy. Unnecessary measurements will also lead to unnecessary costs.

We conclude that it is important for studies that investigate the adherence to SMBG guidelines to take into account the variation in recommendations that are given to patients by healthcare professionals. When non-adherence to a specific guideline is observed, it may well be that this is due to the advice they received from their healthcare provider. Therefore, the results of studies that investigated SMBG from a patient's perspective or by using databases on the dispensing of blood glucose strips, should be interpreted with caution.

The aim of SMBG should be to reach the glycaemic goals with the least amount of inconvenience and complexity. However, more research is necessary in order to give a more evidence-based advice on the basic frequency and timing of SMBG, taking into account the glycaemic goals, quality of life and costs.

A limitation of our study is the limited response to the internet survey. One reason might be that the number of inactive e-mail addresses was unknown. The limited response may have led to a non-response bias. Unfortunately, we do not have data on the characteristics of the non-respondents. However, because we were able to use large databases, the total number of respondents is still considerable.

Finally, we have initiated a new study to investigate the effect of a specific frequency of SMBG on glycaemic control and quality of life in patients with T2DM who are on 1 injection a day ([www.register.clinicaltrials.gov, NCT01460459](http://www.register.clinicaltrials.gov/NCT01460459)).

## CONCLUSION

This study investigated SMBG from a professional's perspective, providing a different view of blood glucose testing. It is an important and neglected aspect of SMBG in clinical practice. We observed a considerable and relevant variation in the recommendations about the number and timing of SMBG. The most striking differences were found for patients with T2DM on less intensive insulin regimens, also with respect to the frequency of SMBG. Hopefully, the results of this study will lead to an increased awareness among professionals about the recommendations they give. Well-designed studies are necessary in order to obtain more knowledge on the basic frequency and timing of SMBG, taking into account the glycaemic goals, quality of life and costs.

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# Vitamin D, or wait and see?

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Dear Editor,

In March 2011, a previously healthy 50-year-old woman underwent an apicotomy (#36) and extraction of two elements (#15, 47) because of progressive mandibular bone resorption and radix fractures. Orthopantomogram (figure 1A) and dental X-ray (figures 1B and C) showed radiolucent spots and loss of the lamina dura, suggesting bone resorption and/or inflammation. Histopathological examination was consistent with undermining bone resorption, showing polynuclear osteoclast-like giant cells and mononuclear fibroblast-like cells, findings associated with either a giant cell granuloma or hyperparathyroidism. As endocrine work-up revealed a parathyroid hormone (PTH) serum level of 88.4 pmol/l (reference 0.6 to 6.7 pmol/l) and a normal calcium level of 2.46 mmol/l (reference 2.20 to 2.60 mmol/l, albumin 43 g/l), the patient was referred to the Outpatient Clinic of Endocrinology. Further analysis showed low 25-hydroxy-vitamin D (25-OHD) of 23 nmol/l (reference 75 to 250 nmol/l), elevated serum creatinine compared with a measurement in 2009 (122 and 74  $\mu$ mol/l, respectively), and a normal phosphate level of 0.76 mmol/l. We concluded primary hyperparathyroidism (PHP) and concomitant vitamin D deficiency, and hypothesised mandibular osteitis fibrosa cystica. In accordance with the current recommendations to initiate 25-OHD supplementation in patients with serum levels below 50 nmol/l,<sup>1</sup> we started treatment with 50,000 IU (1.25 mg) colestiferol orally once every two weeks. Six days later, the patient had developed severe hypercalcaemia (Ca 3.83 mmol/l, albumin 45 g/l), requiring admission to the Medium Care Unit for treatment with intravenous fluid and pamidronate. Parathyroid scintigraphy with tetrofosmin (99m)Tc and ultrasound of the neck were suggestive of a parathyroid adenoma on the right side, which was surgically extirpated one week later. The postoperative course was complicated by severe and persistent hypocalcaemia for which the patient needed intravenous treatment. Pathological examination of the extirpated parathyroid gland confirmed an adenoma.

In our patient, hypercalcaemia in the context of primary hyperparathyroidism had obviously been masked by concomitant 25-OHD deficiency. The underlying mechanism of the massive calcium increase after administration of vitamin D is unclear. Although a number of vitamin D receptor polymorphisms are associated with the risk of primary hyperparathyroidism, further research is needed to elucidate their role in the calcium response to administration of vitamin D.<sup>2</sup> Vitamin D deficiency is a relatively frequent phenomenon in patients with PHP, as it has been reported to occur in 81% of patients with PHP compared with 60% in a carefully defined control group. The current guidelines, recommending 25-OHD supplementation in PHP, are based on studies reporting safe administration of 25-OHD.<sup>3,5</sup> However, these studies did not have a randomised and controlled design and included patients with mild PHP exclusively, mean PTH values ranging from 11.9 ( $\pm$  7.5) to 16.5 ( $\pm$  9.9) pmol/l.<sup>4,5</sup> In addition to safety issues, an equally important question is whether vitamin D supplementation is beneficial. A decrease in PTH levels was seen in one prospective study,<sup>3</sup> but not in another<sup>5</sup> after 53 and 8 weeks of 25-OHD repletion, respectively. Of note, one study reported significantly lower serum alkaline phosphatase,<sup>3</sup> but no differences in urinary *N*-telopeptide excretion or in bone mineral density.<sup>3,5</sup> Fracture risk was not assessed. In addition to its effects on calcium and bone homeostasis, vitamin D treatment has been suggested to have beneficial effects in other (patho)physiological domains, including metabolism, immune function and atherosclerosis.<sup>6</sup> More clinical studies will be needed, however, before definitive conclusions can be drawn on the role of vitamin D in these areas.

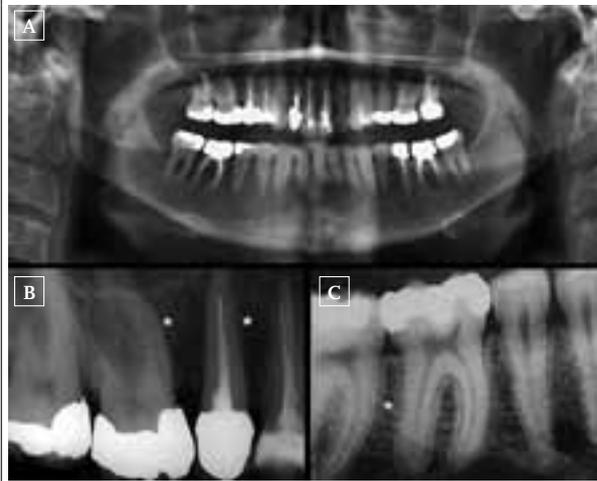
Our case illustrates that 25-OHD repletion can induce severe hypercalcaemia in a patient with vitamin D deficiency and concomitant PHP, although this type of management is considered safe by current recommendations. The clinical benefit of 25-OHD repletion in this setting can be questioned. Until better

data are available, we suggest that 25-OHD deficiency should be treated cautiously in patients with mildly elevated PTH. In patients with severe PHP and 25-OHD deficiency, the possible benefit of 25-OHD prior to parathyroidectomy does not seem to outweigh the risk of the rapid development of severe hypercalcaemia.

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**Figure 1A-C.** (A) Patient's orthopantomogram with periapical bone loss at the first left lower molar (#36) and severe periodontal bone loss at the right lower molar region. (B) One of the patient's dental X-rays (right upper premolars and molars) showing loss of the lamina dura (white asterisk), if compared to the dental X-ray of a normal situation (figure 1C, white asterisk). Loss of lamina dura is a manifestation of hyperparathyroidism



# Vinorelbine chemotherapy-induced blistering

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Dear Editor,

We read with interest the paper by Heijmen *et al.*<sup>1</sup> in which the authors describe a case of blistering after administration of vinorelbine, a second-generation semi-synthetic vinca alkaloid antitumour drug employed in advanced lung and breast cancers and generally well tolerated. We wish to report a further case of skin blisters after the infusion of vinorelbine to provide a further contribution to the knowledge on the various clinical aspects.

In August 2011, a 74-year-old Caucasian woman was referred to the Dermatology Department for blisters on the hand. She was diagnosed with breast cancer in 2007 and treated with a mastectomy, right axillary dissection (pT1aN3M0) and adjuvant chemotherapy (fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel). In 2010, lymph node recurrence was treated with radiotherapy. In July 2011, she developed bone metastases: vinorelbine therapy was suggested. During the chemotherapeutic infusion, no apparent extravasations were detected and she did not complain of pain. After three days, big blisters appeared. The clinical examination revealed a large erythematous area with tense fluid-filled blistering associated with mild oedema on the dorsal side of the wrist and hand (*figure 1*). We suggested washing with saline, applying topical antibiotic and impregnated gauze. The patient recovered well within a week, with dyschromia appearing at the site of the lesion.

Vinca-alkaloids are classified as irritants or vesicants. Tissue injury may arise immediately or appear after several days, as mild erythema, itching or swelling, pain or local burning at the infusion site. Symptoms may later increase and skin indurations, desquamation or blistering develop, as happened in our patient. The direct toxic effect of the agent and amount and concentration of the extravasated fluid might influence the severity of tissue injury. In our case, a skin reaction and vessel irritation appeared, despite the correct administration.<sup>2</sup> Dilution of the drugs with saline or hyaluronidase (150 to 1500 U subcutaneously

**Figure 1.** Vinorelbine-induced blistering of the dorsal side of the hand



in surrounding tissues) in combination with hot packs might limit skin damage. Oral or topical antibiotics may prevent eventual superinfection. On the contrary, cold packs increase toxicity and calcium leucovorin, diphenhydramine, hydrocortisone, isoproterenol, sodium bicarbonate, and vitamin A cream seem to be ineffective.<sup>3,4</sup> In our opinion, these two cases are interesting because they show that erythema, mild swelling, pain or blistering can appear days after the vinorelbine infusion. We think that this presentation highlights the importance of being aware of early symptoms and signs of this possible complication.

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