PHOTO QUIZ: Fever, diffuse rash and arthralgia, see page 80

Value judgements in oncology guidelines

- Microscopic colitis
- Vascular liver disorders
- Prognostic markers in IgA nephropathy
- Unexpected INRs
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Beyond the evidence of guidelines

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INTRODUCTION

Clinical guidelines should support health care providers and patients with appropriate recommendations for daily practice to enable both to make better informed decisions. Preferably, the recommendations are based on the best available evidence, supplemented with clinical expertise. In former days guidelines were often developed by the so-called ‘Good Old Boys Sat Around the Table’ (GOBSAT) method. Nowadays, this expression refers to the unstructured manner by which a group of self-selected experts discuss their (often subjective) opinions, which are written down by one of them. Gradually it became clear that this informal procedure has major limitations. The scientific basis of the resulting guideline may be poor. Dominant and influential persons may push through their preferences or limit ideas about optimal care by considerations of what they suppose is achievable in daily practice (required skills, instruments, money, time, staff, patient preferences). The group often tried to draw attention to themselves to strengthen their position within a clinical area. There was a lack of uniformity in the guidelines developed by the ‘GOBSAT method’. They were not updated on a regular basis and as most professionals and their representing bodies were not involved in the end product, wide acceptation was lacking, resulting in poor compliance. Because of these flaws, guideline development was gradually professionalised. The development procedures were standardised. The recommendations were provided with a sound scientific basis and developed in a rigorous systemic way by a balanced working group which incorporates clinical and methodological expertise, adequate technical support to carry out searches and health economic analyses and an agreed work plan with well-organised meetings. First a representative and multidisciplinary group of six to 15 experts from relevant organisations are invited. Besides clinical and methodological experts, patient representatives, policy makers, insurers and managers should be involved. The skills of the chairman are crucial, to stimulate discussion while ensuring an effective and efficient group process. Existing (international) guidelines on websites and systematic reviews or meta-analyses (for example within the Cochrane library) are identified. Subsequently a literature analysis (search and a qualitative analysis of the findings) and a formal group process with structured consensus discussion according to the Delphi methodology should be started. Formulation of recommendations with their evidence grading has to be performed by a democratic voting procedure after extensive discussions of all the information obtained.

FORMAL CONSSENSUS METHODS

The RAND-modified Delphi procedure is a formal consensus method that is derived from the Delphi method. It is especially suitable to select recommendations for problems where evidence is scarce. A panel of experts forms opinions about the appropriateness of different treatments in a large number of cases. These cases are paper patients with certain diagnostic characteristics (for example disease or disease stage, age, complaints, abnormal findings) that have been shown to influence treatment decisions. The judgement of appropriateness is determined by the advantages (effectiveness, rapidity and duration of the treatment response) and disadvantages (invasiveness, side effects and complications) and is scored by all panel members on a 0-9 scale. In a plenary session all scores are compared and differences discussed. Subsequently the scoring is repeated and a treatment is considered appropriate if the median score is in the 7-9 scale.

BEYOND EVIDENCE

Weak or absent evidence is not exceptional as for more than half of the questions or choices there will be no or
conflicting evidence. Even if an explicit search strategy is used guideline groups may end up with different evidence findings due to a different search strategy and inclusion and exclusion criteria. For example, less than 11% of the evidence was shared between Dutch and German guidelines for breast cancer.\textsuperscript{7}

Even if evidence is found, the relevance and quality of the studies may be disputed or the findings may be in selected populations that differ from those seen in routine care. Especially in the elderly, comorbidity may lead to conflicting evidence.

If controversies occur, normative and cultural opinions about the risk-benefit ratio of a recommendation play an important role.\textsuperscript{8,9} This is all right, as long as these implicit norms and values are made explicit and are in agreement with those within the target groups, especially the health care providers and patients involved.

**DECISION-MAKING**

Medical decision-making in individual patients uses the findings of population-based evidence in guidelines, but the recommendations should be translated to an individual patient with unique needs and preferences. Moreover, personal experiences and interests of the health care provider and ethical principles together with economic and political considerations influence the ultimate decision. These factors cannot be quantified against each other, as they are difficult to balance. The World Health Organisation recognises this dilemma\textsuperscript{10} and advises that value judgements should be explicit and be influenced by patients in particular.

**HIDDEN ETHICAL VALUES**

In the article by de Kort et al. in this number of the Journal, hidden value judgements in the formulation of recommendations in palliative oncology care were found.\textsuperscript{11} These value judgements may account for many of the variations between guidelines. For example, a preference to prolong life without considering the quality of life that can be expected when no curative options are available or for doing something instead of watchful waiting was found.

As patient’s and doctor’s value judgements may differ and these judgements are not made explicit in the guideline report, they may be taken as evidence. Instead they should be a tool to discuss the pros and cons of an option with the patient. To support these discussions they suggest a meaningful checklist of potential values that may support the decision process. I feel that the suggestion to imagine that one of your parents is sitting in front of you is the most important.

**REFERENCES**

ABSTRACT

Chronic diarrhoea is a frequent complaint in clinical practice. Microscopic colitis is the cause of this symptom in 10% of these cases and the prevalence is rising. To exclude microscopic colitis a colonoscopy with multiple biopsies of different regions of the colon is mandatory. A sigmoidoscopy alone is insufficient. Two histopathological types of microscopic colitis can be distinguished: collagenous colitis and lymphocytic colitis. Nowadays, there is sufficient evidence to recommend budesonide as the first-choice treatment. Bismuth can also be recommended, but this drug is not easily available in the Netherlands. Evidence of efficacy of other drugs is scant.

KEYWORDS

Bismuth, budesonide, collagenous colitis, lymphocytic colitis, microscopic colitis

INTRODUCTION

Chronic diarrhoea is a common complaint in the daily practice of the general practitioner, internist and gastroenterologist. While the exact prevalence of chronic diarrhoea in the general population is unknown, epidemiological data from the United States of America estimate it at 5%. Chronic diarrhoea can be defined in a number of different ways. First, the diarrhoea must be present for longer than four weeks. Additionally, depending on the definition used, defecation frequency must be increased (more than three times daily), consistency must be decreased (porridge-like to watery) and/or the mass of stool must increase (more than 200 grams a day). Chronic diarrhoea must be distinguished from irritable bowel syndrome and faecal incontinence. In irritable bowel syndrome, chronic abdominal pain is predominant, accompanied by an altered defecation pattern that may be dominated by diarrhoea. Patients with faecal incontinence often initially present their complaints as diarrhoea, making careful history-taking essential in these cases. The differential diagnosis of chronic diarrhoea is very extensive, and includes chronic bowel infections, inflammatory bowel disease, and malabsorption syndromes (such as coeliac disease and lactose intolerance). A less well-known cause of chronic diarrhoea is microscopic colitis. However, making this diagnosis remains difficult, and watchfulness is required from the internist, gastroenterologist and pathologist. Additionally, the prevalence of this condition is rising and its treatment has recently become clearer. Therefore, we will present four patients with microscopic colitis and discuss the diagnosis and treatment of this disease.

CASE REPORTS

Patient A, a 44-year-old woman, presented in 1999 with a history of diarrhoea lasting for a number of years. Other than chronic back pain and pyrosis due to reflux oesophagitis, she had no significant past medical history. She only took loperamide as needed. She reported passing porridge-like to watery stools six to eight times daily, without blood or mucus. She had also lost a number of kilograms of weight. Additionally, she was sometimes incontinent, which was socially disabling. Physical examination and preliminary laboratory investigations did not reveal any abnormalities. Colonoscopy did not show any
visible abnormalities. However, randomly taken biopsies of macroscopically normal mucosa showed collagenous colitis. Treatment with mesalazine and bismuth subcitrate did not lead to any improvement in her symptoms. Initially, her complaints improved somewhat following treatment with beclomethasone enemas and loperamide, with porridge-like stools two to three times daily without incontinence. Four years later, however, her symptoms increased, with watery stools six to eight times daily. She was now treated with 9 mg of budesonide a day, which resolved her symptoms, with normal stools once to twice daily. Unfortunately, the budesonide could not be completely tapered off, and she continued maintenance therapy of 3 mg of budesonide a day. She was symptom-free during her last check-up in April 2007.

Patient B is a 40-year-old man who presented to our hospital in 2001 for a second opinion for chronic unexplained diarrhoea. His past medical history included trauma with a clavicle and pelvic fracture and a stomach perforation. He also had a history of gout complicated by a urate nephropathy, with a creatinine clearance of 70 ml/minute. He also had psoriasis. He was taking a variety of drugs, but stopping these medications did not lead to any improvement in his symptoms. His chronic diarrhoea had been investigated in various hospitals. Extensive diagnostic procedures had been performed: exhaustive laboratory examinations, a gastroduodenoscopy with small bowel biopsies, a lactose breath test, and repeated colonoscopies with biopsies, none of which had resulted in a diagnosis. One colonoscopy, however, did reveal a number of nonspecific lesions in the distal colon, upon which treatment with mesalazine and 10 mg of prednisone was initiated. When his symptoms failed to significantly improve, he was referred to our hospital. He reported watery stools six to eight times daily, without blood or mucus, and having lost a number of kilograms. Physical examination and laboratory investigations did not reveal any abnormalities. Colonoscopy revealed normal mucosa everywhere, although randomly taken biopsies showed collagenous colitis. Treatment with 9 mg of budesonide had a positive effect on his symptoms. Unfortunately, tapering off the budesonide quickly resulted in a relapse of his symptoms. He ultimately received maintenance therapy of 6 mg budesonide daily for a number of years. In early 2005, the decision was made to initiate an eight-week test treatment with bismuth subcitrate. He subsequently became symptom-free and budesonide treatment was stopped. During his last check-up in November 2005, he was still passing normal stools once to twice daily.

A 37-year-old man, patient D, was referred due to chronic diarrhoea in 2002. Other than asthma, and arthroscopies of both his left and right knee, he had no past medical history. He used salmeterol and salbutamol inhalers. Other than the chronic diarrhoea, which consisted of porridge-like stools without blood or mucus several times a day, he had no other symptoms. Physical examination and preliminary laboratory investigations did not point to any diagnosis. A gastroduodenoscopy revealed mild reflux oesophagitis, but pathology showed normal small bowel biopsies. Colonoscopy showed normal mucosa. Randomly sampled colon biopsies, however, showed a lymphocytic colitis (figure 2). He was treated with 9 mg of budesonide daily, upon which his symptoms disappeared. His symptoms quickly returned upon tapering off the budesonide. He was therefore treated with the lowest effective dose of budesonide: 3 mg every other day. As he remained steroid-dependent, an attempt was made to switch treatment to loperamide.
and cholestyramine in 2003, but this did not result in sufficient symptom alleviation. Treatment with bismuth subcitrate in 2004 was curtailed by the patient due to a lack of effectiveness. He has since been taking 3 mg of budesonide every other day alongside psyllium fibres, and remains symptom-free.

**Clinical Presentation**

Patients with microscopic colitis typically have chronic porridge-like or watery diarrhoea without blood or mucus. Defecation frequency generally lies somewhere between four and nine times daily, with a faecal mass of between 300 and 1700 grams a day. Abdominal cramps, weight loss and faecal incontinence can also occur. Patients may present with dehydration, but this is uncommon. The clinical course is variable, with episodes of spontaneous improvement and exacerbation. Complications do not arise. Microscopic colitis occurs at all ages in both men and women, but is slightly more common in middle-aged women. Both Spanish as well as Swedish epidemiological studies estimated prevalence at around 10% of all patients with chronic diarrhoea. Additionally, various studies indicate the prevalence is rising, although it cannot be excluded that the observed rising prevalence in these studies is due to an increased awareness by clinicians and does not reflect a true rise in incidence. Laboratory investigations do not contribute to the diagnosis. Endoscopic investigations also practically never show macroscopic abnormalities, although minimal oedema and a few atypical ulcers of the mucosa have been described (patient B). The microscopic abnormalities are diffuse and variably located in the colon, making it necessary to take multiple biopsies from various regions in the colon during endoscopic investigations. Performing a sigmoidoscopy with biopsies alone would lead to a missed diagnosis in 40% of cases.

**Pathology**

Pathological examination distinguishes two forms of microscopic colitis: collagenous colitis and lymphocytic colitis. Both forms may occur independently as well as concurrently. The basal membrane or basal lamina is thickened in collagenous colitis, which is microscopically visible as a varying wide sub-epithelial collagenous band (figure 1, patient A). The basal lamina is normally thinner than 7 μm; in collagenous colitis, it is more than 10 μm, and usually between 20 and 60 μm, thick. Lymphocytic colitis is defined as an increase in the number of intra-epithelial located mononuclear inflammatory cells to more than 20 per 100 epithelial cells (figure 2, patient C). Slight flattening of the epithelial cells, a decrease in the number of goblet cells and an increase in the number of paneth cells may occur in both forms of the disease. Mild cryptitis is also possible. For the microscopic diagnosis of microscopic colitis the haematoxylin and eosin stain is sufficient in most cases. However, the Masson stain or trichrome stain can be used to highlight the sub-epithelial collagenous band in collagenous colitis and a CD3 immunostain is available to show the intraepithelial lymphocytes in lymphocytic colitis (figures 1 and 2).

**Aetiology and Differential Diagnosis**

The cause of microscopic colitis remains unclear. It is thought to be the result of an abnormal immune response to bowel contents (bacterial toxins, medicinal products, food) or of abnormal collagen metabolism. There is an association between autoimmune disease and microscopic colitis. Additionally, there seems to be an association between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and collagenous colitis, as a result of which use of these medicinal products is discouraged in patients with this condition. Recently, an association between selective serotonin reuptake inhibitors and statins and microscopic colitis has been described and patients using these drugs may benefit from an attempt of drug withdrawal. An increased production of nitrogen oxide (NO) seems to play a role in the diarrhoea. Administration of a nitrogen oxide synthase inhibitor decreases net secretion, while administration of the substrate L-arginine leads to an increase in secretion. The differential diagnosis should distinguish the microscopic pathology of microscopic colitis from inflammatory bowel disease (specifically, Crohn’s disease). However, the distinction between inflammatory...
bowel disease and microscopic colitis can generally be made on clinical grounds. A number of case studies and small patient series showed an association between coeliac disease and lymphocytic colitis. Ruling out coeliac disease is thus recommended in this patient population.16

**TREATMENT**

Since the first description of microscopic colitis by Lindstrom in 1976, single uncontrolled case studies have been published describing various therapies for treating the condition.17 These treatment modalities include steroids (systemic and topical), 5-amino-salicylic acid preparations, cyclosporin, 5-mercaptopyrurine, azathioprine, fibre compounds, spasmolytic agents, loperamide, probiotics, and surgery.18 These publications have led to placebo-controlled studies with probiotics, a plant extract, bismuth and budesonide. These studies were recently summarised in a meta-analysis.18 Only one small study examining the use of probiotics was included. In this study, 21 patients used a combination of *Lactobacillus acidophilus* and *Bifidobacterium animalis* subspecies *Lactis* and eight patients were treated with placebo. No statistically significant difference was found between the two groups: 6/21 vs 3/8 noticed some effect, but this may have been due to a type 2 error.19 Another small placebo-controlled study with a plant extract was also negative.20

**Bismuth**

Bismuth preparations are commonly prescribed for diarrhoea in the United States. Indications for the effectiveness of bismuth in the treatment of microscopic colitis were found in numerous case studies and one uncontrolled study.21-24 In the uncontrolled study, 12 patients were treated with eight 262 mg tablets of bismuth subsalicylate a day for eight weeks. Complete remission was achieved in 11 patients. No significant side effects were noted.23 This was confirmed by a small placebo-controlled study. This study was included in the cited meta-analysis.18

In this study, bismuth subsalicylate was given to four patients at a dose of three 262 mg tablets a day for eight weeks, while five patients received placebo tablets. Only the actively treated group responded to therapy. No notable side effects were found in this study, either.24 However, bismuth subsalicylate is not available in the Netherlands. Bismuth subcitrate, as used in the cases described above, is also no longer authorised or available in the Netherlands. However, bismuth subcitrate is still available via pharmaceutical wholesalers and the production of capsules can be performed easily by every pharmacy in the Netherlands. The equivalent dose of bismuth subcitrate is 600 mg thrice daily for eight weeks. Bismuth is hardly absorbed when administered orally. However, a treatment duration of no longer than eight weeks is recommended to prevent accumulation in the body. The most important side effect of bismuth is black stools.

**Steroids**

The use of systemic steroids for the treatment of microscopic colitis has been described in numerous case studies and small patients series.18 However, only a single, very small, placebo-controlled study with systemic steroids has been published and described in the above-mentioned meta-analysis. Improvements were noted in seven of the nine patients treated with prednisolone 50 mg once daily for two weeks. By comparison, only one of the three patients treated with a placebo showed improvement. However, this was not statistically significant in this small study.26 The significant disadvantage of systemic steroids is the well-known side-effect profile, which does not seem to outweigh the benefits for a ‘benign’ condition such as microscopic colitis. Budesonide is a glucocorticoid that is quickly absorbed after oral administration, but is quickly and effectively metabolised by the liver, so it barely enters systemic circulation. Delayed release preparations have been proven to be effective in patients with Crohn’s disease in administering a local dose in the bowel with minimal systemic side effects.27 This compound has been used in a variety of uncontrolled studies and case reports of microscopic colitis.18 However, three randomised, double-blind, placebo-controlled studies have also since been published and analysed in the meta-analysis.18 A total of 94 patients were included in these studies. A total of 38 of the 47 patients (81%, 95% confidence interval 70 to 92%) responded to budesonide, compared with eight out of the 47 (17%, 95% confidence interval 6 to 28%) treated with placebo. The number needed to treat was determined to be only two. Additionally, there were significant histological and quality of life improvements.18 The dose of budesonide used was, depending on the brand of medicinal products used, three 3 mg tablets once daily (Entocort®) or one 3 mg tablet thrice daily (Budenofalk®) for six weeks, after which the dose was slowly tapered off by 3 mg per four to six weeks. The natural history of microscopic colitis is variable and recurrences are frequent. Unfortunately, exacerbation during the tapering-off period or after stopping budesonide treatment is, therefore, common, so many patients remain dependent on a low dose of budesonide.28

**CONCLUSION**

Microscopic colitis is the cause of chronic diarrhoea in 10% of all cases, and its prevalence is rising. Microscopic colitis is a distinct clinical-pathological entity that includes both lymphocytic colitis and collagenous colitis. As the mucosa appears normal at colonoscopy, the analysis of chronic
diarrhoea should include active searching for this condition by performing multiple biopsies from various regions of the colon. As diagnostic yield may be higher from the right side of the colon, sigmoidoscopy alone is not sufficient. Most of the data regarding the treatment of microscopic colitis favour the use of budesonide. There are now also sufficient indications for the effectiveness of bismuth to justify its use. However, the use of bismuth preparations is complicated by the practical difficulties of its availability in the Netherlands. There is limited evidence for the use of other drugs. Given their side-effect profiles, loperamide, spasmolytic agents and fibre preparations are the prime contenders in this category. Finally, the use of NSAIDs should be avoided in patients with microscopic colitis.

REFERENCES

A B S T R A C T

Portal vein thrombosis (PVT) is a rare disorder that is associated with a variety of underlying conditions, of which liver cirrhosis, malignancy and myeloproliferative disorders are the most common. Based on clinical presentation and results of imaging, two different entities can be identified, acute and chronic PVT. Anticoagulation therapy is recommended for all patients with acute PVT in an attempt to prevent further thrombosis and to promote recanalisation of the obstructed veins. Chronic PVT is characterised by the presence of a portal cavernoma and development of portal hypertension. Bleeding from ruptured oesophageal or gastric varices is the main complication of portal hypertension in these patients. Both endoscopic therapy and β-adrenergic blockade are used for the prevention and treatment of gastrointestinal bleeding. In the absence of bleeding, continuous anticoagulant therapy should be considered for the group of chronic PVT patients in whom an underlying prothrombotic factor can be identified. With adequate management of complications and concurrent diseases, prognosis of PVT is good in patients without underlying cirrhosis or malignancies.

K E Y W O R D S

Anticoagulation, myeloproliferative disorder, portal hypertension, portal vein, thrombosis

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

The portal vein forms the backbone of the portal venous system that allows for blood from the digestive organs to flow towards the liver. Thrombosis of the portal vein can occur both in children and adults and results in significant haemodynamic changes. As with other forms of venous thrombosis, portal vein thrombosis (PVT) is associated with a number of different precipitating factors, both inherited and acquired. Though it is considered a rare disorder, a recent autopsy study showed the life-time risk of PVT in the general population to be 1%. In adults, clinical presentation is highly variable but depending on the duration of symptoms and results of imaging, PVT can usually be classified as either acute or chronic. In the past decade a number of, mainly retrospective, studies have been performed in patients with PVT. Results from these studies have significantly contributed to the current understanding of this vascular liver disorder. However, many questions remain unanswered and there is still much debate concerning the optimal treatment strategy for both acute and chronic PVT. In this review we will discuss the aetiology and clinical characteristics of PVT, with special attention for the management of this disorder.

A E T I O L O G Y

Both local (hepatobiliary) and systemic (thrombophilic) risk factors have been associated with thrombosis of the portal vein (table 1). In children, infectious causes of PVT, such as sepsis or omphalitis, are frequently present. Specifically in neonates, catheterisation of the umbilical vein is an important risk factor for development of PVT. In the adult population, liver cirrhosis and hepatobiliary malignancies are the most common local precipitating factors that together account for a large proportion of cases of PVT. Patients with liver cirrhosis, the reported incidence of PVT varies from 6 to 17%. Patients with more advanced stages of cirrhosis have a higher risk of PVT than patients with compensated liver disease. Development of thrombosis in cirrhotic patients is thought to be caused by both reduced portal blood flow.
and the effects of periportal fibrosis. Thrombus formation in patients with a local malignancy is usually related to direct compression or invasion of the portal vein by tumour mass. The incidence of PVT in patients with hepatocellular carcinoma (HCC) is 10 to 44% and appears to increase even further when concurrent cirrhosis is present. For this reason, diagnosis of PVT in a patient with liver cirrhosis should raise awareness for the presence of HCC. Other known local risk factors, such as pancreatitis, abdominal surgery and inflammatory bowel disease, are associated with a lower risk of PVT and are only encountered in a minority of patients. In contrast, it is now clear that in many patients with noncirrhotic nonmalignant PVT, a systemic, thrombophilic risk factor is present. Over the past two decades, a number of systemic conditions, either inherited or acquired, that result in a thrombogenic phenotype have been identified as risk factors for the development of PVT. Of these factors, myeloproliferative disorders (i.e. polycythaemia vera, essential thrombocythaemia and myelofibrosis) are by far the most common. In a recent study, a myeloproliferative disorder (MPD) was found in 37% of patients with noncirrhotic nonmalignant PVT. Less frequent systemic risk factors associated with PVT are factor V Leiden mutation, prothrombin gene mutation and inherited deficiencies of protein C, protein S and antithrombin. Moreover, in concordance with venous thrombosis at other sites, the aetiology of PVT is often multifactorial, as in many patients a combination of underlying risk factors can be identified. This was not only demonstrated in patients with noncirrhotic nonmalignant PVT, but also in cirrhotic patients with PVT. In a cohort of patients with liver cirrhosis and PVT, a concurrent systemic risk factor was present in 70% of patients. Furthermore, patients with PVT also seem to be at an increased risk of developing other venous thromboembolic events.

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<th>Table 1. Risk factors for the development of portal vein thrombosis</th>
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<td><strong>Local (hepatobiliary) factors</strong></td>
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<td>Liver cirrhosis</td>
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<td>(Hepatobiliary) malignancy</td>
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<td>Intra-abdominal infection/inflammation:</td>
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<td>• Omphalitis</td>
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<td>• Splenectomy</td>
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<td>• Abdominal surgery</td>
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<td>• Umbilical vein catheterisation</td>
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**Clinical Manifestations and Diagnosis**

**Acute PVT**

An acute obstruction of the portal vein usually manifests itself as a sudden onset of abdominal pain, which may be very severe. Other symptoms that can occur are nausea, fever and diarrhoea. Whereas in the past, very few patients were diagnosed with acute PVT, due to increased awareness and improved imaging this disease entity is increasingly being recognised. On physical examination the majority of patients will exhibit splenomegaly, but ascites is usually absent. Laboratory investigations provide few clues and unless an underlying liver disease is present liver function tests are usually (near) normal. However, using noninvasive imaging techniques the diagnosis of PVT can easily be established. Doppler ultrasound, computerised tomography (CT) or magnetic resonance imaging (MRI) can all be applied to demonstrate either the absence of flow or the presence of a thrombus in the portal vein (figure 1). Additionally, with these imaging modalities it is possible to visualise the extent of the thrombosis. If apart from the portal vein, the mesenteric veins are also obstructed, there is a substantial risk of intestinal ischaemia and subsequent bowel infarction. This is the most severe complication of acute portal vein thrombosis and often requires immediate surgical intervention. Fortunately, intestinal infarction occurs very infrequently; in a recent study less than 5% of patients with acute PVT suffered from this complication.

Once PVT is diagnosed, patients should be screened for underlying aetiological factors. Identification of a single...
risk factor does not diminish the need for a further search because multiple risk factors may be present. Of interest, in patients with PVT or underlying liver disease the diagnosis of certain thrombogenic factors may be impaired. Firstly, decreased hepatic synthetic function may result in lower plasma levels of protein C, protein S and antithrombin, thereby potentially masking a true deficiency or leading to an incorrect diagnosis of natural anticoagulant deficiency.36 Secondly, characteristic features of an MPD (e.g. elevated platelets or haemoglobin) may be absent due to splenomegaly or haemodilution.37 The latter diagnostic problem can be solved by performing a bone marrow biopsy or by assessing the presence of endogenous erythroid colony formation.38 Furthermore, the diagnosis of MPD has recently been facilitated by the discovery of the V617F mutation of the Janus Kinase 2 (JAK2), a tyrosine kinase.39 In patients with polycythaemia vera it has been shown that approximately 95% carry the JAK2 mutation; for essential thrombocythaemia and myelofibrosis this mutation is present in 50 to 60% of patients.40 Because the JAK2 mutation is not found in healthy controls, it has been applied as a screening marker for MPD. In several studies of patients with noncirrhotic nonmalignant PVT, 20 to 35% of the cases were JAK2 positive, underlining that MPDs are a major risk factor for the development of PVT.41-43

**Chronic PVT**

Whereas many patients will display some symptoms associated with PVT, a number of patients are completely asymptomatic.3,16 These patients are often only diagnosed by coincidence or later on when complications of chronic PVT occur. In response to thrombosis of the portal vein, portoportal and portosystemic collateral veins will develop to compensate for the decreased portal blood flow.44,45 These collaterals may be present within several days after the venous occlusion and are eventually found in nearly all patients with a complete obstruction of the portal vein.46 However, the amount, size and localisation of collaterals differ strongly between patients. On imaging, the presence of a network of collateral vessels around the portal vein, a so-called portal cavernoma, is a typical feature of chronic PVT.47 Moreover, in patients with long-standing thrombosis the portal vein itself often becomes a fibrotic cord and may be difficult to visualise (figure 2). Besides the development of collaterals, another compensatory mechanism that takes place is dilatation of the hepatic artery.3 Nevertheless, despite the fact that hepatic blood flow is only minimally decreased as a result of these haemodynamic changes, portal venous pressure is inevitably increased. Therefore, complications related to portal hypertension, such as splenomegaly and gastro-oesophageal varices, are the main features of patients with chronic PVT. At diagnosis of PVT, more than half of the patients will already have varices or signs of portal hypertensive gastropathy.48,49

Furthermore, in 20 to 40% of cases, an episode of gastrointestinal bleeding will be the presenting symptom of an underlying chronic PVT.3,16 In addition to complications of portal hypertension, two other potential consequences of chronic PVT are intestinal ischaemia and portal biliopathy. As in patients with acute PVT, there is also a minor risk of intestinal ischaemia and bowel infarction in chronic PVT if there is secondary extension of thrombosis into the superior mesenteric vein. The other complication, portal biliopathy, denotes structural abnormalities of the intrahepatic or extrahepatic biliary
risk factors. Although no controlled studies have been performed, there is convincing evidence that rapid initiation of anticoagulation therapy results in either complete or partial recanalisation in a significant number of patients. Several retrospective series and a recent prospective study have all shown a beneficial effect of anticoagulation in patients with noncirrhotic nonmalignant PVT, with recanalisation rates of approximately 45%.30,35,48 Spontaneous improvement of portal vein patency was rarely seen in these studies. Therefore, the current consensus indicates that all patients with acute PVT should be treated with anticoagulation when there are no contraindications.55 A minimal treatment duration of three months is advised but, as with venous thrombosis at other sites, this could be extended to six months. Moreover, in patients with proven systemic thrombophilia life-long anticoagulation therapy may be warranted due to the increased risk of new thrombotic events.28,48

Apart from anticoagulation, several other treatment modalities have also been employed to achieve

TREATMENT

Acute PVT

The management of patients with acute PVT is based on: (1) prevention of further thrombosis and therapy aimed at recanalisation, (2) treatment of complications (e.g. bowel infarction) and concurrent disease and (3) identification and, if possible, treatment of underlying (thrombophilic)
recanalisation of the obstructed portal vein. A number of case reports have successfully demonstrated the use of local thrombolysis in the early phase of PVT. Recanalisation has also been described after surgical thrombectomy or with percutaneous transhepatic angioplasty (PTA). Nevertheless, experience with these techniques is limited and the risk of procedure-related complications and mortality is high. Consequently, their role in the treatment of acute PVT is still highly controversial. In addition to its effect on recanalisation, anticoagulation should also be initiated in the acute phase of PVT to prevent extension of the thrombosis. Extensive thrombosis of the mesenteric veins is mostly symptomatic and carries a high risk of intestinal ischaemia. Symptoms that may be present are severe abdominal pain and bloody diarrhoea. When intestinal infarction is suspected, immediate surgical intervention is required to resect necrotic parts of the bowel. If left untreated, bowel ischaemia can lead to major complications such as intestinal perforation, shock, multi-organ failure and even death.

**Chronic PVT**

*Treatment and prevention of variceal bleeding*

For patients with chronic PVT, therapy is mainly aimed at the treatment and prevention of complications of portal hypertension. Bleeding from gastro-oesophageal or ectopic (e.g. duodenal or rectal) varices is the most important complication of PVT-induced portal hypertension. Around 50% of patients will already have signs of varices at diagnosis and for that reason endoscopic screening for the presence of varices should be part of the diagnostic work-up in all patients with (chronic) PVT. In the case of noncirrhotic nonmalignant PVT, approximately 30% of patients will experience one or more episodes of gastrointestinal bleeding during follow-up. When an underlying cirrhosis is present the incidence of variceal bleeding is even higher. The risk of bleeding is also increased in patients with large varices at diagnosis, especially for those who do not receive adequate prophylactic treatment. Despite the serious nature of complications, no controlled studies have been performed addressing the optimal management of variceal bleeding in patients with PVT. Therefore, current guidelines are mainly based on data from studies in patients with portal hypertension caused by liver cirrhosis, in the absence of PVT. As has become clear from these studies, primary prevention of bleeding is recommended in patients with large (>5 mm) varices. Treatment with nonselective β-blockers and endoscopic band ligation are equally effective and both significantly reduce the risk of a first bleeding episode. It has not been established which therapy should be preferred in patients with PVT, but pharmacological treatment with β-blockers is probably more cost-effective. Endoscopic treatment as primary prevention could then be reserved for those patients with intolerance or contraindications to β-blockers.

When prevention fails or when a patient presents with variceal haemorrhage, endoscopic therapy is the mainstay of treatment. Variceal band ligation is the preferred treatment modality for acute bleeding episodes but endoscopic sclerotherapy may also be applied. For acute bleeding from gastric fundal varices, endoscopic variceal obturation with tissue adhesives seems to be most effective to control bleeding. Other, more general, measures in patients with gastrointestinal haemorrhage may include volume resuscitation, blood transfusions and admission to an intensive care unit. Furthermore, it has been shown that additional treatment with vasoconstrictors and antibiotics also has a beneficial effect on complications and survival. After a first episode of variceal bleeding has been controlled, therapy is aimed at prevention of further events. In patients with cirrhosis and portal hypertension, treatment with β-blockers and endoscopic band ligation can both reduce the rate of rebleeding. Combined therapy of pharmacological treatment and endoscopy is even more effective in the secondary prevention of variceal bleeding. In patients with PVT there have been a few studies addressing the prevention of rebleeding, specifically with endoscopic therapy. It was shown that endoscopic eradication of varices in patients with noncirrhotic nonmalignant PVT significantly reduced the risk of rebleeding. The rate of rebleeding was reported to be 23% in the first year, which compares favourably with a rebleeding rate of approximately 31% in cirrhotic patients treated with endoscopic band ligation. Studies investigating the effect of β-blockers on the prevention of rebleeding in patients with PVT have not been performed and their role in the secondary prophylaxis of variceal bleeding in these patients is therefore still unclear.

Many patients with PVT-induced portal hypertension can be adequately managed with pharmacological or endoscopic treatment. However, when these therapeutic options fail and in patients with recurrent variceal bleeding, a shunting procedure could be considered. Surgical shunts, preferably a distal splenorenal shunt, have proven to give durable decompression of the portal venous system. Disadvantages that hamper the widespread application of these procedures are the considerable rates of morbidity and mortality and the high risk of shunt thrombosis. As a less invasive option, recent interest has gone out to the use of a transjugular intrahepatic portosystemic shunt (TIPS). Several studies have reported the successful use of TIPS in the management of patients with PVT. Nevertheless, a TIPS can only be performed in selected patients, as in many cases the procedure is technically not feasible due to extensive thrombosis (e.g. involving the splenic and mesenteric veins) or an inability to catheterise either the portal vein itself or collaterals forming the portal cavernoma. Future studies will have to determine the exact role of TIPS in the treatment of portal hypertension associated with PVT.
Other therapeutic measures

Treatment of portal biliopathy is only indicated in symptomatic patients. Endoscopic therapy with or without stent placement is effective in most cases of biliary obstruction or biliary stone formation. When symptoms persist, a surgical intervention may be needed, aimed at the management of portal hypertension. A few studies performed in patients with portal biliopathy as a result of PVT have illustrated that symptoms can be relieved with a portosystemic shunting procedure. This diminishes the need for a secondary surgical biliointestinal anastomosis, which is associated with a high morbidity and mortality in these patients due to the extensive network of collaterals frequently surrounding the biliary structures. Whereas the role of anticoagulation has been quite well established in the treatment of patients with acute PVT, there is still much debate concerning its place, if any, in the management of chronic PVT. The significant risk of bleeding complications from gastro-oesophageal varices is often seen as a contraindication. Nevertheless, the high prevalence of systemic thrombophilia would support treatment with anticoagulation, as it has been reported that patients with PVT and an underlying thrombogenic risk factor have an increased risk of developing further thrombotic events. Moreover, it was shown that anticoagulation therapy decreased the incidence of new thrombotic episodes in these patients whilst the risk and severity of variceal bleeding was not altered. This would support the use of anticoagulation in patients with chronic PVT and proven thrombophilia. Whether anticoagulation should be considered in patients with PVT and underlying liver cirrhosis is even less clear. One study has suggested that anticoagulation therapy may prove useful in a subgroup of patients with cirrhosis and PVT that are candidates for liver transplantation. The presence of PVT in patients undergoing liver transplantation is associated with more complex surgical procedures and an increased rate of complications. Treatment with anticoagulation in cirrhotic patients with PVT awaiting transplantation resulted in recanalisation in 42% of cases and successfully prevented extension of thrombosis. Still, despite these favourable results of anticoagulation, evidence is minimal and more studies are needed to define whether treatment with anticoagulation truly has a beneficial effect in patients with chronic PVT. Current consensus, solely based on expert opinion, indicates that life-long anticoagulation therapy should be considered in patients with PVT in whom an underlying thrombophilic risk factor has been identified.

Prognosis

The prognosis of patients with PVT is mainly determined by the underlying cause of thrombosis and not by the complications of portal hypertension. Whereas in earlier studies many patients died as a result of variceal bleeding, recent data suggest that mortality related to gastrointestinal haemorrhage is uncommon. In a large cohort of 172 patients with PVT, death due to variceal bleeding occurred in 2% of the patients. Furthermore, in a recent short-term prospective study in patients with noncirrhotic nonmalignant PVT, no deaths due to variceal bleeding were reported. The prognosis of PVT patients without underlying cirrhosis or malignancy can therefore be considered as good, with five- and ten-year survival rates of 90 and 80%, respectively. Outcome is worse in patients with liver cirrhosis because in this group liver function is already impaired and there is a higher risk of (liver-associated) complications and liver decompensation. Survival after liver transplantation was shown to be significantly lower in cirrhotic patients with concomitant PVT as compared with cirrhotic patients without PVT. Clearly, the presence of an underlying malignancy also substantially affects survival. It has been reported that patients with HCC who develop PVT during the course of the disease have a very poor prognosis. In one study, five-year survival of PVT patients with malignancy was only 8%. Another factor that has a negative impact on survival is intestinal ischaemia complicated by bowel infarction. In patients with mesenteric vein thrombosis mortality rates may vary between 20 and 50%. Conversely, underlying systemic risk factors do not seem to influence prognosis, although long-term follow-up data of patients with PVT and known thrombophilia are lacking. A recent study demonstrated that the presence of an MPD does not affect five-year survival rates.

Conclusion

Thrombosis of the portal vein often has a multifactorial aetiology. Presentation is highly variable and the clinical course is relatively benign, but dependent on the underlying cause. Acute and chronic PVT are two distinct disease entities that require a somewhat different treatment approach. Anticoagulation is the mainstay of treatment in acute PVT whereas therapy for chronic PVT is guided by the presence and severity of complications related to portal hypertension. Because controlled studies in patients with PVT are not available, gastro-oesophageal varices should be treated as in patients with liver cirrhosis-induced portal hypertension. Despite recent advances, many aspects of the (multifactorial) aetiology and management of PVT are still unclear. More studies are needed to further elucidate the role of anticoagulation in patients with chronic PVT and the role of different therapeutic options in the treatment and prevention of variceal bleeding.
REFERENCES


hoekstra, et al. portal vein thrombosis.
ABSTRACT

Background: Immunoglobulin A nephropathy (IgAN) is characterised by high variability in clinical course and outcome. Accurate prediction of prognosis is needed to optimise treatment. Urinary α1-microglobulin and β2-microglobulin are markers of tubulointerstitial injury and predict the risk of end-stage renal disease (ESRD) in idiopathic membranous nephropathy. We questioned the relevance of these markers in IgAN.

Methods: We included patients with biopsy proven IgAN, who were evaluated for proteinuria in our centre between 1995 and 2007. Data were analysed using univariate and multivariate Cox regression for the outcome variables ESRD and progression (rise in serum creatinine of >50% or start of immunosuppressive therapy).

Results: Seventy patients (71% men) were selected. Median age was 39 years, median serum creatinine 140 μmol/l, and median proteinuria 2.4 g/day. Median urinary α1-microglobulin excretion was 23.5 μg/min (range 3.5-275.3) and median urinary β2-microglobulin excretion was 0.4 μg/min (range 0.1-62.1). Both α1m and β2m correlated significantly with serum creatinine (r = 0.65, p<0.01 and r = 0.62, p<0.01) and total proteinuria (r = 0.35, p<0.01 and r = 0.28, p<0.05). During follow-up (median 75 months) 25 patients (36%) developed ESRD, and 46 patients (66%) showed progression. 19 patients (27%) were treated with immunosuppressive agents. In univariate analysis urinary α1- and β2-microglobulin predicted ESRD and progression. In multivariate analysis only serum creatinine and urinary protein were independent predictors of both outcomes.

Conclusion: Urinary excretion of low molecular weight proteins did not offer an advantage over total proteinuria and serum creatinine in predicting prognosis in patients with IgAN.

KEYWORDS

α1-microglobulin, β2-microglobulin, end-stage renal disease, IgA nephropathy, prognosis, progression

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis worldwide. The natural history is quite variable and published data must be interpreted with caution since many patients with mild disease may never come to clinical attention or undergo a renal biopsy. End-stage renal disease (ESRD) develops in 20 to 30% of patients with IgAN within 20 years after diagnosis.1-4 Although there is a lack of randomised controlled trials, data suggest that a minority of patients may benefit from immunosuppressive treatment.5-8 Ideally, such treatment should be restricted to patients who will progress to ESRD. Several variables have been identified as predictors of prognosis i.e. elevated serum creatinine concentration,3,9-13 severe proteinuria,9,14-17 arterial hypertension9,15,16 and histological characteristics.1,10,14-15 Few studies have showed that clinical features evaluated after one year of follow-up predicted prognosis more accurately than at the time of presentation.17,18 Recently Reich et al. reported that persistent proteinuria is the strongest predictor of poor renal outcome in IgAN and that sustained reduction of proteinuria to <1 g/24 hour is associated with a good prognosis.19 Unfortunately, most markers are not very accurate, with low sensitivity and specificity. In idiopathic membranous nephropathy, high-risk patients can be identified in an early stage by measuring low-molecular-weight proteins such as α1-microglobulin.
urine samples were obtained for measurement of 83% and a specificity of 97%. We aimed to determine whether the excretion of low-molecular-weight (LMW) proteins adds to predicting prognosis in patients with IgAN.

SUBJECTS AND METHODS

Population
Since 1995, we have performed standardised protein measurements in patients with proteinuria due to glomerular diseases. Patients are referred to our medical centre from hospitals located mainly in the south-eastern part of the Netherlands. For the present study we analysed the data of adult patients with biopsy-proven IgA nephropathy who were evaluated for proteinuria in our centre between 1995 and 2007, and followed thereafter. Patients with other causes of IgA-positive glomerular staining (systemic lupus erythematosus, Henoch-Schönlein purpura or liver disease) or a follow-up of less than 12 months, were excluded from analysis.

Baseline measurement
Gender, ethnicity, age, body weight and height were recorded at the time of measurement. Details of the measurements have been described. Two 24-hour urine samples were obtained for measurement of creatinine and total protein. The excretion of the low- and high-molecular-weight proteins was measured under standardised conditions. A urinary pH >6.0 is necessary to allow reliable measurements of urinary β2m. Therefore, patients took 4000 mg of oral sodium bicarbonate the evening before the measurement. On arrival at the ward, the patients took an additional 2000 to 4000 mg sodium bicarbonate and up to 500 ml of tap water was given to enforce diuresis. The patients remained supine for two hours except for voiding. Blood pressure measurements were taken using an automated device (DINAMAP, Criticon, Tampa FL) with six consecutive readings registered every five minutes after ten minutes rest; these readings were used to calculate the mean arterial pressure (MAP). Measurement of urinary pH, β2m, α1m, immunoglobulin G (IgG), transferrin, albumin, total protein and creatinine was performed. Beta-2-microglobulin excretion was only measured in urine with a pH >6.0. Laboratory parameters were measured in blood samples collected in the middle of the urine collection period.

The use of angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin II type 1 receptor antagonists (ARBs), calcium channel blockers, other antihypertensive agents, diuretics, and non-steroidal anti-inflammatory drugs (NSAIDs), as well as HMG-CoA-reductase inhibitors, was recorded. Current or previous use of corticosteroids, other immunosuppressive agents or fish oil was registered.

Serum creatinine, cholesterol, urinary total protein and creatinine were measured with standard automated techniques. Urinary proteins were measured as described before.

Follow-up
After baseline measurements, patients were commended to the care of their local physicians. Immunosuppressive therapy was advised to patients with progressive renal disease. We collected data on serum creatinine, albumin, cholesterol and urea, total urinary protein and creatinine levels, blood pressure, body weight and exposure to medication during follow-up from medical records.

Calculations and definitions
Body mass index (BMI) was calculated from body weight and height at baseline. MAP during follow-up was calculated as the diastolic pressure plus one third of the pulse pressure. The glomerular filtration rate at baseline and follow-up was estimated (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) equation. Start of follow-up was defined as the time of standardised measurement of proteinuria, regardless of the first assessment suggestive of renal disease. We defined the following two renal outcomes: ESRD and progression of renal disease. ESRD was defined as initiation of dialysis, renal transplantation or an eGFR  <15 ml/min per 1.73 m². Progression of renal disease was defined as an elevation in serum creatinine of 50% or more since the baseline measurement, the start of immunosuppressive therapy or the development of ESRD.

Statistical analysis
Missing values for urinary protein concentration in the 24-hour urine samples were imputed by using the urinary protein-creatinine ratio which was obtained from the two-hour sample, and by using serum albumin. Missing values for low-molecular-weight proteins were not imputed.

All baseline variables were compared for patient groups by χ²-test if dichotomous, one-way ANOVA if continuous and after log transformation if skewed. Each continuous baseline variable was divided into tertiles and plotted in a Kaplan-Meier curve for visual inspection.

Possible collinearity for univariate significant predictors was checked. Predictors that had a Spearman’s rho smaller than 0.800 were entered into a multivariate Cox model. A backward stepwise selection algorithm, criteria for exclusion being a likelihood ratio test with p-value greater than 0.05 and smaller than 0.10 for inclusion, was used.
Possible interactions, based on plausible mechanims, were entered and tested too. The most parsimonious model with the best fit, using generalised R², was considered most appropriate. Internal validation of the selected model was done with a bootstrapping procedure using 1000 samples. The predictive value of this model was investigated by the area under the receiver operating characteristics (ROC) curve.

RESULTS

Baseline characteristics and outcome variables

Initial demographic, clinical and laboratory data of 70 patients are listed in table 1. In the majority of patients (57%) proteinuria was >=2.0 g/day and the estimated GFR <60 ml/min/1.73 m². Eighty percent of the population were taking ACEIs or ARBs at the time of evaluation for proteinuria. Median duration of follow-up was 74 months. The time period between onset of renal disease or biopsy and subsequent referral to our centre varied. In 60% of patients the time between biopsy and referral was less than six months.

During follow-up all patients were treated with ACEIs and/or ARBs. Immunosuppressive therapy was initiated in 19 patients, the majority of them (74%) were treated with cyclophosphamide combined with prednisone. Twenty-five patients (36%) developed ESRD, with the shortest survival time being two months. Five- and eight-year renal survival rates from baseline were 78 and 66% (figure 1). In 46 (66%) patients progression of renal disease occurred based on an increase in serum creatinine of >=50% (n=35), or initiation of immunosuppressive therapy (n=11). Thus, of 19 patients who received immunosuppressive therapy during follow-up, eight patients were treated because of a rise in serum creatinine of more than 50%. In 11 patients, the time between biopsy and referral was less than six months.

### Table 1. Clinical and demographic characteristics at baseline

<table>
<thead>
<tr>
<th></th>
<th>Total group</th>
<th>Progression Rise in serum creatinine &gt;=50%</th>
<th>Therapy</th>
<th>No progression</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (% male)</td>
<td>70 (71.4%)</td>
<td>35 (74.3%)</td>
<td>11 (81.8%)</td>
<td>24 (62.5%)</td>
<td>0.436</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39 (17-70)</td>
<td>36.0 (17-70)</td>
<td>37 (25-59)</td>
<td>37 (35-59)</td>
<td>0.164</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.2 (19.4-41.0)</td>
<td>26.1 (20.4-31.1)</td>
<td>27.5 (21.2-32.4)</td>
<td>26.3 (19.4-41.0)</td>
<td>0.605</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>101.3 (73-131.7)</td>
<td>104 (83-133.7)</td>
<td>99.8 (73-112)</td>
<td>94.3 (80.0-133.2)</td>
<td>0.113</td>
</tr>
<tr>
<td>Urinary protein (g/d)</td>
<td>2.4 (0.4-24.4)</td>
<td>2.9 (0.5-12.6)</td>
<td>3.6 (0.4-24.3)</td>
<td>1.7 (0.4-9.6)</td>
<td>0.090</td>
</tr>
<tr>
<td>Protein-creatinine ratio (g/10 mmol)</td>
<td>2.9 (0.5-18.2)</td>
<td>3.5 (1.0-16.1)</td>
<td>4.5 (0.6-18.2)</td>
<td>1.2 (0.5-13.3)</td>
<td>0.093</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>139.5 (70-366)</td>
<td>149 (76-366)</td>
<td>186 (100-274)</td>
<td>112 (70-172)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum urea (μmol/l)</td>
<td>8.3 (4-36)</td>
<td>9.1 (4-36)</td>
<td>11.1 (6-22)</td>
<td>6.3 (4-14)</td>
<td>0.007</td>
</tr>
<tr>
<td>Use of ACEIs, ARBs before baseline</td>
<td>80.00%</td>
<td>80.00%</td>
<td>81.80%</td>
<td>79.20%</td>
<td>0.984</td>
</tr>
<tr>
<td>Use of diuretics before baseline</td>
<td>30.00%</td>
<td>34.30%</td>
<td>27.30%</td>
<td>25.00%</td>
<td>0.729</td>
</tr>
<tr>
<td>Use of other antihypertensives medication</td>
<td>34.30%</td>
<td>37.10%</td>
<td>45.30%</td>
<td>25.00%</td>
<td>0.437</td>
</tr>
<tr>
<td>Use of immunosuppressive treatment before baseline</td>
<td>4.30%</td>
<td>5.70%</td>
<td>9.10%</td>
<td>0.00%</td>
<td>0.393</td>
</tr>
<tr>
<td>Use of ACEIs, ARBs during follow-up</td>
<td>100.00%</td>
<td>100.00%</td>
<td>100.00%</td>
<td>100.00%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of diuretics during follow-up</td>
<td>68.60%</td>
<td>71.40%</td>
<td>90.90%</td>
<td>54.20%</td>
<td>0.082</td>
</tr>
<tr>
<td>Use of other antihypertensives during follow-up</td>
<td>54.30%</td>
<td>62.90%</td>
<td>63.60%</td>
<td>37.50%</td>
<td>0.126</td>
</tr>
<tr>
<td>Use of immunosuppressive drugs during follow-up</td>
<td>27.14%</td>
<td>22.86%</td>
<td>100.00%</td>
<td>0.00%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data expressed as median (range). In a few patients biopsy was performed after evaluation for proteinuria. BMI = body mass index; MAP = mean arterial blood pressure; MDRD4 = modification of diet in renal disease equation; ESRD = end-stage renal disease; ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II type 1 receptor antagonist.

P values are from χ²-test or ANOVA comparing the three groups: rise in serum creatinine, therapy and non-progressors.
patients treatment was started earlier. These patients were characterised by higher serum creatinine values at baseline and more severe proteinuria (table 1).

**Low-molecular-weight proteins**

Alpha-1-microglobulin levels were not available for two patients, while \( \beta_{2m} \) levels could not be measured in nine patients due to a urinary pH <6.0. The urinary excretion of both \( \alpha_{1m} \) and \( \beta_{2m} \) was increased in patients with IgAN, with median levels of 23.5 \( \mu \)g/min (reference value <10 \( \mu \)g/min) and 0.4 \( \mu \)g/min (reference value <0.2 \( \mu \)g/min). There was a high correlation between \( \alpha_{1m} \) and \( \beta_{2m} \) (\( r = 0.86, p<0.01 \)). Both \( \alpha_{1m} \) and \( \beta_{2m} \) correlated significantly with serum creatinine (\( r = 0.65, p<0.01 \) and \( r = 0.62, p<0.01 \)), IgG excretion (\( r = 0.59, p<0.01 \) and \( r = 0.58, p<0.01 \)), and total proteinuria (\( r = 0.35, p<0.01 \) and \( r = 0.28, p<0.05 \)).

**Predictors of outcome**

**End-stage renal disease**

Urinary \( \alpha_{1m} \)-microglobulin, \( \beta_{2m} \)-microglobulin and IgG excretion, serum creatinine and urea levels, total urinary protein, eGFR and the use of diuretics before baseline were all significantly associated with ESRD. When evaluating tertiles of \( \alpha_{1m} \), renal survival in the highest tertile was markedly lower compared with that in the lowest and middle tertiles (94% vs 63% at five years, 85% vs 44% after eight years, \( p=0.001 \)) (figure 2). Only one patient within the lowest tertile of urinary \( \beta_{2m} \) developed ESRD. Therefore, renal survival in the lowest tertile of \( \beta_{2m} \) was higher than in the middle and highest tertile (figure 3). After multivariate Cox regression analysis only baseline serum creatinine and total proteinuria proved significant predictors of ESRD when correcting for therapy (table 2). Thus, neither \( \alpha_{1m} \)-microglobulin nor \( \beta_{2m} \)-microglobulin
were independent predictors of ESRD. Of note, patients who were treated with immunosuppressive agents during follow-up were less likely to develop ESRD.

Progression of renal disease
Urinary $\alpha_1$-microglobulin, $\beta_2$-microglobulin and IgG excretion, serum creatinine and urea levels, total urinary protein, eGFR and age, were significant predictors of progression in univariate analysis. Multivariate Cox regression showed that only serum creatinine and total urinary protein were independent significant predictors of progression (table 2).

Discussion
Our data clearly indicate that the urinary excretion of low-molecular-weight proteins does not predict prognosis in IgAN more accurately than total proteinuria. To our knowledge we are the first to report on the prognostic value of urinary excretion of $\alpha_1$-microglobulin and $\beta_2$-microglobulin in IgAN. Others have found a highly significant relation between tubulointerstitial damage and the presence of unspecified, urinary LMW proteins, in a small cohort of patients with IgAN.$^{23}$ Woo et al. reported a higher incidence of chronic renal failure in 60 patients with IgAN who presented with LMW proteinuria and were followed for six years.$^{48}$ However, patients with LMW proteinuria had more severe proteinuria and higher serum creatinine levels.

In our patients with IgAN urinary excretion of $\alpha_1$m and $\beta_2$m exceeded normal values. Renal survival was significantly lower in patients with values of urinary $\alpha_1$m and $\beta_2$m in higher tertiles. We observed a difference when comparing renal survival curves for tertiles of urinary $\alpha_1$m and $\beta_2$m excretion. This apparent discrepancy can be explained by the fact that $\beta_2$m could not be measured in nine patients due to a low urinary pH. These patients were characterised by higher serum creatinine levels and more severe proteinuria. Thus, missing values are not at random but reflect an impairment of renal function and bicarbonate excretion. This illustrates the limitations of $\beta_2$m as a prognostic marker. Both urinary $\alpha_1$m and $\beta_2$m predicted ESRD and progression of renal disease in univariate analysis. However, in multivariate analysis they did not prove to be independent predictors of either outcome. These findings are in contrast with previous reports on the good performance of LMW proteins as prognostic markers in patients with idiopathic membranous nephropathy. Urinary $\alpha_1$m and $\beta_2$m are considered to reflect tubulo-interstitial injury. In general, the presence and extent of tubulo-interstitial injury determines renal outcome. From this perspective, the difference in the predictive value of LMW proteins between IgAN and idiopathic membranous nephropathy is remarkable.

Of note, the predictive value of LMW proteins (such as $\alpha_1$m) in idiopathic membranous nephropathy was validated in patients with no or moderate renal impairment, defined as a serum

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**Table 2.** Hazard ratios (HR) and confidence intervals (CI) of significant baseline predictors of ESRD or progression of renal disease after univariate and multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>ESRD</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysis</td>
<td>Multivariate analysis</td>
<td>Univariate analysis</td>
</tr>
<tr>
<td>ESRD</td>
<td>(HR)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>$\alpha_1$-microglobulin (μg/min)</td>
<td>1.015</td>
<td>(1.008 – 1.023)</td>
</tr>
<tr>
<td>$\beta_2$-microglobulin (μg/min)</td>
<td>1.060</td>
<td>(1.022 – 1.099)</td>
</tr>
<tr>
<td>IgG excretion (mg/d)</td>
<td>1.002</td>
<td>(1.001 – 1.004)</td>
</tr>
<tr>
<td>Use of diuretics before referral</td>
<td>2.922</td>
<td>(1.197 – 7.132)</td>
</tr>
<tr>
<td>MDRD 4 ml/min/1.73 m²</td>
<td>0.029</td>
<td>(0.897 – 0.962)</td>
</tr>
<tr>
<td>Protein-creatinine ratio (g/10 mmol)</td>
<td>1.133</td>
<td>(1.022 – 1.255)</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>1.161</td>
<td>(1.099 – 1.226)</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>1.018</td>
<td>(1.012 – 1.025)</td>
</tr>
<tr>
<td>Total urinary protein (g/d)</td>
<td>1.160</td>
<td>(1.061 – 1.268)</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td>0.843</td>
<td>(0.336 – 2.115)</td>
</tr>
</tbody>
</table>

Generalised $R^2 = 0.508$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Progression</th>
<th>ESRD</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysis</td>
<td>Multivariate analysis</td>
<td>Univariate analysis</td>
<td>Multivariate analysis</td>
</tr>
<tr>
<td>$\alpha_1$-microglobulin (μg/min)</td>
<td>1.013</td>
<td>(1.008 – 1.018)</td>
<td>1.013</td>
</tr>
<tr>
<td>$\beta_2$-microglobulin (μg/min)</td>
<td>1.033</td>
<td>(1.006 – 1.061)</td>
<td>1.033</td>
</tr>
<tr>
<td>IgG excretion (mg/d)</td>
<td>1.002</td>
<td>(1.001 – 1.003)</td>
<td>1.002</td>
</tr>
<tr>
<td>MDRD 4 ml/min/1.73 m²</td>
<td>0.972</td>
<td>(0.955 – 0.990)</td>
<td>0.972</td>
</tr>
<tr>
<td>Protein-creatinine ratio (g/10 mmol)</td>
<td>1.119</td>
<td>(1.039 – 1.205)</td>
<td>1.119</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>1.102</td>
<td>(1.055 – 1.151)</td>
<td>1.102</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>1.009</td>
<td>(1.005 – 1.013)</td>
<td>1.009</td>
</tr>
<tr>
<td>Total urinary protein (g/d)</td>
<td>1.216</td>
<td>(1.116 – 1.325)</td>
<td>1.216</td>
</tr>
</tbody>
</table>

Generalised $R^2 = 0.368$

ESRD = end-stage renal disease; MDRD = modification of diet in renal disease equation, IgG = immunoglobulin G.
creatinine <135 μmol/l. However, even within the subgroup of patients with IgAN and a serum creatinine level of <135 μmol/l, α1m does not allow identification of high-risk patients. This difference is illustrated in the panels of figure 4. From the figure it is evident that levels of α1m are higher in patients with idiopathic membranous nephropathy. These patients presented more frequently with nephrotic range proteinuria. Thus, the prognostic value of these LMW proteins may be confined to glomerulopathies characterised by nephrotic range proteinuria.

We found baseline serum creatinine and proteinuria to predict ESRD and progression of renal disease. The relation between serum creatinine and ESRD is to be expected, since a patient with a higher serum creatinine concentration will develop ESRD at an earlier time-point, even if the rate of renal function deterioration is similar. To overcome this problem we defined a 50% or more increase of serum creatinine concentration as progression. We chose a 50% rise to be sure that no patients who had a minor increase were marked as progressors. Since multivariate analysis regarding the outcome ESRD implied that the natural progression of IgAN is influenced by immunosuppressive therapy, this was considered an end-point. The use of initiation of immunosuppressive therapy as an end-point can be debated. In our study, 19 out of 70 patients received immunosuppressive therapy during follow-up. In eight patients, treatment was started after serum creatinine had increased by 50% or more. The remaining 11 patients received immunosuppressive treatment before reaching this 50% rise in serum creatinine. These patients were characterised by high serum creatinine and more severe proteinuria at baseline. Further delay of treatment was considered inappropriate by their physicians. As such, these patients reflect current treatment practice in our region. At the start of therapy, mean serum creatinine was 221 μmol/l, clearly pointing to the severity of IgAN. Even with progression as outcome, serum creatinine level and total urinary protein excretion remained significant, independent predictors.

The observation that serum creatinine concentration is a significant, independent predictor of progression of renal disease implies that an accelerated rather than a linear decline in renal function occurs in the course of the disease. In order to correct for the possible confounding effect of using initiation of immunosuppressive therapy as an end-point, we reanalysed the data using an increase of serum creatinine of >50% as only end-point. Serum creatinine concentration remained a significant predictor, which possibly reflects that patients with an increased serum creatinine are more likely to progress or progress at a faster rate than those with no renal impairment. Our findings support observations reported by others and are in line with the hypothesis that loss of nephrons gives rise to hyperfiltration of a reduced number of nephrons leading to further destruction of nephrons and an accelerated deterioration of renal function.29,30 Although data are scarce, immunosuppressive medication may be of benefit for patients failing a supportive approach.

**Figure 4A.** Correlation between α1-microglobulin and proteinuria in patients with iMN

**Figure 4B.** Correlation between α1-microglobulin and proteinuria in patients with IgAN
Urinary excretion of the low-molecular-weight proteins nowadays. Furthermore, we ruled out an effect of therapy with ACEIs and/or ARBs, an important element of therapy. This cohort is comprised of patients who were all treated with a comparable blood pressure. A large percentage of patients showed fast progression and many patients developed ESRD.

This may be due to a selection bias since patients with stable serum creatinine and moderate proteinuria are less likely to be biopsied and/or referred to our medical centre. Since many patients were biopsied in another hospital and material was unavailable, we were unable to correlate urinary α₁,m and β₂,m with histopathological characteristics. On the other hand, in contrary to earlier populations examined, this cohort is comprised of patients who were all treated with ACEIs and/or ARBs, an important element of therapy nowadays. Furthermore, we ruled out an effect of therapy while analysing data. Finally, the lack of a validation group, as in every other study evaluating the prognostic predictors for progression of IgAN, was corrected for by bootstrapping.

CONCLUSION

Urinary excretion of the low-molecular-weight proteins α₁-microglobulin and β₂-microglobulin does not add to predicting prognosis of IgAN. Serum creatinine concentration and urinary protein excretion are the most potent predictors of progression of IgAN nephropathy.

ACKNOWLEDGMENTS

H.P.E. Peters is supported by a grant from the Dutch Kidney Foundation.

We thank G. Feith and M. Den Hartog, Gelderse Vallei Hospital, Wageningen; J. Beutler, D. Hollander, J. Jansen and M. Koolen, Jeroen Bosch Hospital, ’s-Hertogenbosch; M. Ten Dam, I. Go and J. van de Leur, Canisius Wilhelmina Hospital, Nijmegen; A. van den Wall Bake, St Joseph Hospital, Veldhoven; R. van Leusen and L. Reichert, Rijnstate Hospital, Arnhem; W. van Kuijik and V. Verstappen, VieCurie Medical Center, Venlo; R. Smeets, St Anna Hospital, Geldrop; A. Lückers, Maas Hospital, Boxmeer; H. Krepel, Lievensberg Hospital, Bergen op Zoom, for their participation in this study.

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Value judgements that matter to patients remain implicit in oncology guidelines: an observational study

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ABSTRACT

Background: Clinical practice guidelines are often evidence-based. However, it is inevitable that there are value judgements in the practical recommendations contained in the guidelines. In order to see if patients are ultimately being supplied with sufficient information to help them make treatment decision, we determined 1) which value judgements influence the process of developing guidelines for palliative chemotherapy, and 2) whether these value judgements were made explicit in the final guideline report.

Methods: We studied the development process of six Dutch oncology guidelines in which palliative chemotherapy plays a substantial role. We observed the guideline development groups (GDGs), conducted semi-structured interviews with individual GDG members (including the chairs), and analysed the minutes of GDG meetings and subsequent versions of the guidelines. A value judgement was defined as a statement about the value of a patient outcome with regard to palliative chemotherapy.

Results: We identified the following value judgements in the process of guideline development: 1) consensus on what should be considered as valuable minimum patient outcomes, 2) preference for tailored treatment in situations where there is no evidence of treatment effect, 3) preference for ‘doing something’ even when there is sufficient evidence of no effect, and 4) the patient outcome of ‘prolonging life’. These value judgements, however, were not reported in the final guideline.

Conclusion: At least the last two value judgements mentioned are relevant for patients with incurable metastatic cancer in making decisions whether to undergo chemotherapy and what kind. Value judgements should be made explicit in guidelines, so that clinicians can transparently discuss treatment options with individual patients.

KEYWORDS

Chemotherapy, ethics, guidelines, qualitative research

INTRODUCTION

Based on the best available research evidence, clinical practice guidelines aim to standardise and improve the quality of health care by rendering medical action more ‘objective’. Clinicians use these guidelines in making decisions on the best treatment for their patients. In the Netherlands, guidelines are developed according to the principles of evidence-based medicine, often with methodological support from the Dutch Institute for Healthcare Improvement (CBO).

A guideline development process includes the following steps: 1) formulation of clinical questions based on an analysis of the most relevant problems in practice, 2) systematic collection, critical appraisal and grading of evidence, and 3) translation of evidence into practical recommendations. This third step includes considering factors other than evidence, such as safety issues, patient perspective, organisational barriers and cost.

When formulating a recommendation, developers determine whether a certain treatment will be recommended as a standard of care. It is inevitable that value judgements are used in this process. For example, recommendations need value judgements about the value of life when health is impaired, the meaningfulness of aggressive treatment, and the acceptability of side effects and risks. Although the same body of evidence is used both nationally and internationally, these value judgements account for many variations between clinical practice guidelines.
It is particularly important to take value judgements into consideration when developing guidelines for the treatment of metastatic cancer. Because no curative options are available, metastatic cancer patients are facing death. For these patients, guidelines may recommend offering chemotherapy as an option for prolonging life or reducing symptoms. Chemotherapy, however, can also cause serious side effects and may burden the patient with visits to the hospital. According to principles of shared decision-making, the patient and his or her physician need to weigh up the pros and cons of different treatment options, including the possibility of 'watchful waiting'. One patient’s value judgements may differ from those of another patient, which may differ from those of a physician, which may in turn differ from those of another physician. Nowadays, physicians tend to be less paternalistic and to share decision-making with their patients. Therefore, both physicians and patients should be aware of the value judgements in these cancer guidelines in making decisions on treatment.

It is unknown how value judgements are incorporated into guidelines for ‘optimal care’ for metastatic cancer patients. The purpose of our study was to answer the following questions: 1) Which value judgements were used in developing guidelines for palliative chemotherapy? and 2) Have these value judgements been made explicit in the final guideline report?

Methods

Between January 2005 and January 2008, we conducted a longitudinal observational study of the development process of six national oncology guidelines in the Netherlands. We selected cancer guidelines for areas in which palliative chemotherapy plays a substantial role: lung cancer, oesophageal cancer, breast cancer, prostate cancer, ‘cancer with pain,’ and colorectal cancer.

Data collection

Different methods were used to collect data: 1) observing guideline development group (GDG) meetings as an auditor; 2) in-depth, semi-structured interviews (of one hour in length) with the members of the GDGs; and 3) text analysis of meeting minutes, draft and final guideline documents. GDG meetings were observed at crucial stages in the guideline development process: at the start (scoping and defining clinical questions), halfway (formulation of recommendations), and the end (endorsement of the final guideline). In addition, meetings were observed when palliative chemotherapy was on the agenda. At the start of our study, one guideline (lung cancer) had already been completed and another guideline (oesophageal cancer) was nearly ready. For these guidelines we could not observe their GDG meetings (table 1). One guideline meeting concerned the update of a guideline (just one meeting). We observed three to five meetings for the other three guidelines. In total, 14 meetings were selected for observation.

All chairs of the GDGs were asked for an interview. Key members of all GDGs were identified and asked for an interview, also if they were involved in metastatic cancer care. In total we selected 20 professionals (including chairs) from different disciplines, including medical oncologists, a palliative care physician, a radiotherapist, a urologist, methodologists and also a patient representative (see also table 1). Two professionals, one chair and one radiotherapist, declined due to time constraints.

The results of text analysis were used as input for the GDG observations and interviews. If available, GDG observations were also used as input for interviews. Analysing the next versions of guideline documents allowed us to trace the changes that resulted from the GDG meetings we observed.

Observations and interviews were recorded on tape and transcribed. The interviews included open questions related to the specific guideline documents and relevant events during observations (table 2).
Based on the findings from other studies,\textsuperscript{3,22} we defined a value judgement as a statement about the value of a patient outcome with regard to palliative chemotherapy. As an example, the aim of prolonging life with two months could be considered as a value judgement in recommending a treatment for patients with metastatic cancer. The research questions were guiding in the analysing process. MAXqda\textsuperscript{®} software was used for open coding and identifying themes in the transcripts of observations and interviews.\textsuperscript{14} The codes were categorised by sorting the data by theme. Text analysis of draft and final guideline documents supported refining the categories. We compared categories of different value judgements with the guideline text\textsuperscript{15} and examined the presence or absence of arguments supporting the value judgements. We excluded judgements on the availability of resources, cost and organisational issues.

**Results**

Nine out of fourteen observed GDG meetings had palliative chemotherapy on the agenda, but the subject was discussed at only five meetings. During these meetings, most discussions about palliative chemotherapy dealt with patient quality of the individually evaluated studies related to the overall evidence. We seldom encountered explicit statements on the value of a certain patient outcome. Table 3 illustrates how we identified a small number of value judgements while observing the prostate cancer GDG. In the interviews, the 20 respondents did not spontaneously mention value judgements as being important to the guideline development process. Evidence-based medicine and guidelines were primarily associated with scientific research and empirical studies. Most of them also assumed that the strength of the recommendations is determined by the strength of the evidence. According to respondents, the GDG’s expert opinion would only be needed if there was non-inclusive evidence or inconsistent findings. The meeting minutes mentioned organisational issues but no value judgements. Drafts and final guideline texts included a few statements about the perceived value of evidence-based outcomes. However, no details were provided about the background of these statements. For example, no motivation or further specification was provided for the recommendation ‘Benefits and burdens of docetaxel in metastatic hormone-refractory prostate carcinoma should be considered.’ Based on observations and interviews, it appeared that GDG members were in doubt about the best moment to start docetaxel and about whether to offer this palliative chemotherapy to frail, elderly men.

**Value judgements in developing guidelines for palliative chemotherapy**

We identified four value judgements in the guideline development process that influenced final recommendations.

**Consensus on what should be considered as minimum patient outcomes**

If there is sufficient evidence available on the effectiveness of palliative chemotherapy, the GDGs often agreed on a ‘valuable minimum’ for deciding whether the treatment should be recommended. There seemed to be consensus about the minimum results on certain patient outcomes:

**Table 3. Examples of observational notes and implicit value judgements**

<table>
<thead>
<tr>
<th>Observational notes</th>
<th>Value judgements</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the discussion on the value of docetaxel, one GDG member questioned whether docetaxel should become the standard treatment, because prolonging life by two months could be considered to be a very marginal outcome in patients who have had this disease for years.</td>
<td>Considering disease-specific patient outcomes is important.</td>
</tr>
<tr>
<td>Another GDG member replied that the studies were the first to show a significant increase in survival time. Obviously, the benefits of the treatment should be weighed against the burdens.</td>
<td>Prolonging life is important.</td>
</tr>
<tr>
<td>The treatment could be offered to younger patients who are in good condition, have an aggressive tumour, and want to be treated.</td>
<td>Tailored treatment is important.</td>
</tr>
</tbody>
</table>
I believe that palliative chemotherapy can only be considered a standard if the response rate is at least 30%. Some people would say 20%, but, obviously, if the response rate is lower you cannot recommend this as standard therapy. (respondent Breast 4)

Some respondents referred to the PASKWIL criteria developed by the Medicines Evaluation Board in the Netherlands (Beoordeling Oncologische Middelen in Dutch) (table 4). For example, for the outcome ‘survival’ in metastatic disease, these criteria set a minimum of prolonging life by at least six weeks. A valuable minimum patient outcome specified per disease (rather than a consensus on what should be considered as valuable minimum for all diseases) was rarely used. However, some respondents highlighted the specific disease context:

Patients with metastatic prostate cancer are often frail and elderly and have known for years that they have cancer. For them, a few extra months would not be as important as for patients with colorectal cancer who are younger and asymptomatic. (respondent Colorectal 1).

<table>
<thead>
<tr>
<th>Table 4. PASKWIL criteria for metastatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria</td>
</tr>
<tr>
<td>Palliative:</td>
</tr>
<tr>
<td>• Response rate</td>
</tr>
<tr>
<td>• Time to treatment failure</td>
</tr>
<tr>
<td>• Time to progression</td>
</tr>
<tr>
<td>• Survival (median, after 1 year)</td>
</tr>
<tr>
<td>Side effects:</td>
</tr>
<tr>
<td>• Lethal</td>
</tr>
<tr>
<td>• Acute, serious (admission)</td>
</tr>
<tr>
<td>• Chronic (restrictive)</td>
</tr>
<tr>
<td>Impact of treatment:</td>
</tr>
<tr>
<td>• Clinics</td>
</tr>
<tr>
<td>• Outpatient</td>
</tr>
<tr>
<td>Quality of life:</td>
</tr>
<tr>
<td>• Performance status (PS), WHO/Karnofski</td>
</tr>
<tr>
<td>• Stable PS, Time to progression to PS</td>
</tr>
<tr>
<td>Level of evidence</td>
</tr>
<tr>
<td>Costs</td>
</tr>
</tbody>
</table>

Preference for tailored treatment
In situations without evidence of treatment effect (which should be distinguished from ‘evidence of no effect’) or in the case of equal treatment options, GDGs preferred to tailor the treatment to the individual patient, weighing up the benefits and harms. For example, one member of the prostate cancer GDG proposed during an observed GDG meeting only offering palliative chemotherapy (docetaxel) to young patients who had an aggressive tumour and an explicit preference for treatment. Respondents in the interviews mentioned different criteria used in practice, such as a drop in haemoglobin or a rise in lactate dehydrogenase or prostate specific antigen (PSA) (respondents Prostate 2 and Prostate 3). However, these criteria were not mentioned in the guideline because of lack of evidence. Nevertheless, the strong conclusion in the prostate guideline (level 1, two randomised controlled trials (RCTs) with positive results) was translated into a weak recommendation (‘...might be offered to patients’, instead of: ‘... should be offered’) because the GDG wanted to allow professional freedom in tailoring the treatment to the individual patient.

In the colorectal guideline, the GDG decided to describe different treatment options and leave the actual treatment decision to the physicians, for instance whether to use mono-chemotherapy or combination-chemotherapy, or choosing between oxaliplatin and irinotecan. One of the respondents explained how he tailored the therapy for certain patients (and groups of patients):

…you can make a ‘tailored decision’. If the patient needs to be progression-free in six months, it would be better to give combination chemotherapy, and if the patient doesn’t want to go bald you shouldn’t give irinotecan. (respondent Colorectal 2) However, only options were provided in the guideline text. Considerations how to weigh these options were not mentioned.

Preference for ‘doing something’
We found that physicians in the GDGs preferred to offer at least some kind of intervention to patients with metastatic cancer, even if there was sufficient evidence of no effect. For example, estramustine was a standard therapy for patients with metastatic, hormone-resistant prostate cancer (HRPC) before docetaxel became a standard therapy (in an earlier guideline that is not evaluated in this study). At that time estramustine was the only drug available and therefore at least ‘something’ could be offered. (respondent Prostate 1)

Physicians also believed patients attached value to ‘doing something’. One guideline developer told about patients’ preferences with regard to the best moment in time to start docetaxel:

The patient wants to start as soon as possible because he finds it hard to do nothing. (respondent Prostate 2)

However, there was no evidence available that showed that an early start in patients with raised PSA but no other symptoms was better than a later start once other symptoms of metastasis had occurred. The recommendations of the final guideline just mentioned that: 1) Patients with HRPC can be offered docetaxel, and 2) in asymptomatic HRPC patients who do not prefer...
docetaxel, a symptomatic treatment is recommended. No background information was given to support decision making. We found one clear exception to the tendency to value ‘something’ over ‘nothing’. The oesophageal carcinoma guideline (2005) clearly stated in the conclusion that: (…), chemotherapy cannot be considered to be a standard of care. It is preferable to use chemotherapy exclusively in studies.

Although chemotherapy was not considered to be a standard of care, in fact again ‘something’ was offered in the form of chemotherapy in the context of research.

**Prolonging life**
We found that GDGs often considered prolonging life to be the most important patient outcome:

*What you notice is that a working group is focused on ‘curing’ the disease, with quality of life getting less attention. Apart from those treatments, the side effects of treatments could be a focus too, to see how you could treat them and what evidence there is for this.* (respondent Oesophagus 5)

Several respondents stated that this tendency could be explained by the difficulty in measuring quality of life and also the average patient’s preference to live as long as possible. For example, prolonging life was the only decisive patient outcome when docetaxel became the standard of care. Palliative chemotherapy was considered for potential chemotherapy-sensitive tumours in the ‘cancer with pain’ GDG. Although two respondents emphasised that palliative chemotherapy would never be administered only for pain reduction, prolonging life should also be attempted if possible (respondents Pain 1 and Pain 2). The fact that prolonging life is mentioned even in an area where pain reduction is the main goal underlines how highly this is valued.

**Value judgements in the final guideline report**
Although we encountered different value judgements during guideline development, often they were not reflected in the final guideline text. In the interviews, respondents gave several reasons for the lack of explicitness:

1. The treatment of a metastatic disease depends to a great extent on the preferences of the individual patient. This conflicts with a guideline that should be applicable for all patients. Therefore, respondents said that GDGs limited their job to summarising the statistically significant effects.

2. The section in the guidelines about palliative chemotherapy was often drafted by medical oncologists. As the interest of GDG members is often limited to their own field of expertise, the value of chemotherapy was not always discussed in detail in the GDG meetings: *Although surgeons might think that chemotherapy is terrible for the patient, they will leave the decision up to medical oncologists because it is our profession* (respondent Breast 4)

3. The GDGs aimed to limit the length of the guideline. Detailed considerations were not included for reasons of readability.

**Discussion**
In this study, we determined several value judgements used in developing guidelines for palliative chemotherapy. However, often these value judgements were not explicitly mentioned in the final guideline report. As a consequence, patients with incurable metastatic disease may not be aware of relevant value judgements. We believe that for patients in the process of making decisions about their treatment, at least two of the four encountered value judgements are important: the preference for ‘doing something’ and for prolonging life. A patient should know that chemotherapy could be offered because physicians find it hard to ‘do nothing’ and believe that patients value ‘doing something’ and prolonging life above ‘watchful waiting’. Such value judgements are not mentioned in the guideline but play an important role in determining the standard of care as expressed in the final recommendations in oncology guidelines.

We believe that the lack of explicitness about value judgements may be due to broad consensus between medical oncologists about routine care and the widespread association of evidence-based clinical practice guidelines with objectivity, thus excluding value judgements. However, value judgements about patient outcomes are inevitable in guideline development. These value judgements distinguish a guideline from a review of literature. In the guideline text the conclusions are based on scientific literature, which are graded using a scale from level 1 (one systematic review or two or more RCTs) to level 4 (expert opinion). Beyond the evidence, ‘other considerations’, including the value judgements that we found, can play an important role in translating the conclusion to recommendations. The wording of recommendations (for instance using terms as ‘must’, ‘should’, ‘could’) reflects both the level of the conclusion and the weight of the other considerations. One might argue that if the considerations and value judgements were more explicitly described, the length of the guideline could hamper the implementation of the guideline. This would not be a problem, however, if summary guides and tools for application (such as patient leaflets) are provided to facilitate the guideline’s use in practice.

As far as we know, this is the first study on value judgements in oncology guidelines. We studied the process of the development of six oncology guidelines in the Netherlands. Our analysis of a sample of evidence-based
The quality of guidelines for the treatment of metastatic cancer is rarely explained and value judgements have not been made explicit in these guidelines. Berg et al. studied value judgements in guidelines on depression and angina pectoris and came to the same conclusion. Strength of our study is the use of three different methods of data collection. We know from the literature that the process of guideline development is influenced by group dynamics and the composition of the GDG. By using semi-structured interviews as a data source (in addition to observations and text analysis), we used ‘triangulation’ to increase the consistency of findings.

A limitation of our study is that we observed plenary GDG meetings and might have missed small group discussions and discussions via email. Even if we did miss certain value judgements, these were not reflected in the final guideline reports. Furthermore, we excluded costs and other organisational issues. We report on different opinions for including/excluding cost issues in guidelines in another paper from this project. We also excluded value judgements that had already been made in evaluated studies during guideline development. In a separate paper for this project, we report on the importance of prolonging life compared with quality of life in interpreting randomised controlled trial results on palliative chemotherapy.

The quality of guidelines for the treatment of metastatic cancer could be improved by making value judgements explicit and by providing tools for weighing up the pros and cons of different treatment options. Then, the guideline user (the physician) will be able to discuss the relevant value judgements with his or her patient. A checklist of potential values could support this process (Appendix 1). Both physicians and patient representatives involved in the development of guidelines should be trained in making value judgements more explicit. Guidelines should ultimately focus on improving individual patient care, and being explicit about value judgements is essential to this.

Acknowledgements

This study was supported by the Dutch Cancer Society (Koningin Wilhelmina Fonds). There are no conflicts of interest. We would like to thank the guideline development groups for their consent to do observations and interviews. We also would like to thank members of the Netherlands School for Research in Practical Philosophy (NSRPP) Ethics and Health Care group, Pax Willemsen, Bert Schadé and Debby Keuken for their comments on a draft version of this manuscript. We would like to thank Pax Willemsen for providing materials for the study as well.

References


Appendix 1. Checklist to support explicit use of value judgements in guidelines (for example, in considering a palliative chemotherapy for metastatic, hormone-refractory prostate cancer)

What are preferable outcome measures?
Is (are) the main outcome(s) large enough to consider the treatment as standard? Yes/No. Why?
Does (Do) the main outcome(s) involve a representative part of the patient population?
What would be the best moment in time to start the treatment?
Have other (non)-treatment options been proposed?
Imagine that your father/partner has metastatic cancer.


Given the lack of evidence, we will be accused of GOBSAT if we do not invite some women!
Pylephlebitis after a duodenal ulcer in a patient with metastasised colon carcinoma treated with chemotherapy and bevacizumab: a case report

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ABSTRACT

Pylephlebitis or septic thrombophlebitis of the portal vein is a rare entity with a high mortality rate. It is often a complication of intra-abdominal infection most commonly caused by diverticulitis and appendicitis. Diagnosis is often delayed since clinical signs and symptoms are nonspecific. Pylephlebitis should be considered in patients with sepsis due to gut-associated organisms without a clear focus of infection. We describe a patient with metastasised colon carcinoma treated with chemotherapy and bevacizumab who was diagnosed with pylephlebitis after a duodenal ulcer and responded well to antibiotic treatment.

KEYWORDS
Chemotherapy, colon carcinoma, duodenal ulcer, pylephlebitis

INTRODUCTION

Pylephlebitis or septic thrombophlebitis of the portal vein is a serious condition with significant morbidity and mortality. It is a rare complication of intra-abdominal infection that occurs in the region drained by the portal venous system.² It has only been described once before in relation to a duodenal ulcer.³ The diagnosis of pylephlebitis requires the demonstration of a portal vein thrombosis usually accompanied by bacteraemia in a febrile patient.¹ Diagnosis is often difficult since no specific clinical signs, symptoms and laboratory parameters are involved. This may lead to a delay in treatment.⁴ We made a diagnosis of pylephlebitis in a patient treated for metastatic colon carcinoma, which occurred after a bleeding duodenal ulcer.

CASE REPORT

A 68-year-old male developed recurrence of liver metastases from colon carcinoma after hemicolectomy and a hemihepatectomy. Two months after systemic treatment was initiated with capecitabine, oxaliplatin and bevacizumab (CAIRO-2 Trial of the Dutch Colorectal Cancer Group, DCCG) he developed upper gastrointestinal bleeding due to a severe duodenal ulcer. There was no history of use of nonsteroidal anti-inflammatory drugs. Treatment with pantoprazol was started. Chemotherapy and bevacizumab were temporarily discontinued. One week later this patient presented with general malaise, fever, chills and abdominal pain in the upper right quadrant. There were no complaints of nausea or vomiting. At physical examination his blood pressure was 100/65 mmHg, heart rate was 110 beats/min. and his temperature was 39.4°C. His abdomen was tender upon palpation without signs of peritoneal involvement. Hepatomegaly was noted but appeared to be unchanged. Initial laboratory findings revealed a white blood cell count of 6.3 x 10⁹/l (normal 3.5 to 11.0 x 10⁹/l), haemoglobin 6.6 mmol/l (8.1 to 10.7), platelet count 82 x 10⁹/l (120 to 350 x 10⁹/l), CRP 118 mg/l (<5), total bilirubin 22 μmol/l (<10), direct bilirubin 7 μmol/l (<5), alkaline phosphatase 142 U/l (<120), aspartate aminotransferase 46 U/l (<40), alanine aminotransferase 28 U/l (<45), lactate dehydrogenase 378 U/l (<450) and gamma glutamyltransferase 76 U/l (<50).

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An intra-abdominal focus of the infection was suspected and treatment with piperacillin and tazobactam was initiated. Blood cultures showed *Staphylococcus aureus*, *Lactobacillus* spp, anaerobe gram negative rods, viridans group *Streptococci* and *Fusobacterium nucleatum*. This suggested an origin of infection in the upper gastrointestinal tract. Urine cultures were negative. Serological tests for *H. pylori* taken before, appeared to be positive.

A CT scan still showed a deep duodenal ulcer with a close relation to the hepatic portal vein (figure 1A). The gas formation in the liver was at first interpreted as air in the biliary tract, which could be related to the hepatectomy. Signs of portal vein thrombosis were not seen. The patient recovered, his temperature normalised and after one week intravenous antimicrobial therapy was stopped. The patient continued oral antibiotic therapy with clarithromycin for *H. pylori* eradication and for treatment of *Staphylococcus aureus*, although for the last indication clarithromycin was not the first choice. However, within 24 hours the fever and chills recurred. Treatment with piperacillin/tazobactam was resumed.

A FDG-PET scan was performed and showed an increased FDG uptake at the liver hilus. Evaluation by CT scan was repeated, which now showed a thrombus in the portal vein (figure 1B). With this combination, the high FDG uptake at the liver hilus and the thrombus in the portal vein, the diagnosis of pylephlebitis was made. After six weeks of antimicrobial treatment (two weeks piperacillin/tazobactam intravenously and four weeks amoxicillin/clavulanic acid orally) the patient made a full recovery.

**DISCUSSION**

Pylephlebitis is a complication of intra-abdominal infection, most commonly caused by diverticulitis or appendicitis. Other causes have been described including cholangitis, pancreatitis and inflammatory bowel disease. In some of the patients, an underlying cause is not found. Portal vein thrombosis due to a duodenal ulcer has been reported once before. In our patient pylephlebitis may have been related to the duodenal ulcer, since the micro-organisms that were cultured indicated a source of infection in the upper gastrointestinal tract and no other underlying cause was found. There were no signs of local recurrence of the colon carcinoma neither on CT scan nor on FDG-PET that may cause this pylephlebitis.

Recently, it has been suggested that duodenal ulcers may be involved in the pathogenesis of bevacizumab-related bowel perforations, although in our patient *H. pylori* infection may also have contributed to the development of the duodenal ulcer.

The diagnosis of pylephlebitis is frequently delayed due to the nonspecific clinical signs. Symptoms with which patients can present are fever, chills and abdominal pain often without jaundice. Leucocytosis is a common finding and bacteraemia has been reported in most patients (50 to 80%). The infection is, as in our patient, usually polymicrobial.

The demonstration of portal vein thrombosis in a febrile patient with bacteraemia is indicative for the diagnosis pylephlebitis. Imaging techniques such as CT scan, ultrasonography, magnetic resonance imaging (MRI) and angiography are all considered appropriate to detect thrombosis of the portal vein. However, as demonstrated...
in our patient, thrombosis may not always be visualised on CT scan and this may lead to a delay in diagnosis and treatment. The finding of gas formation in the portal vein has also been implicated in pylephlebitis, but the diagnosis of pylephlebitis is not proven by this.7 Another helpful imaging technique to diagnose pylephlebitis is the FDG-PET.8 Sensitivity and specificity of FDG-PET varies in different studies. A small study in diagnosing septic thrombophlebitis in patients with haematological malignancy showed a sensitivity and specificity of 100%. In a few cases diagnosis was made with FDG-PET even when thrombosis could not be visualised with duplex scan or venography.9 In other studies concerning FDG-PET investigation in patients with fever of unknown origin, sensitivity and specificity of FDG-PET are lower.10,11 In our patient there was an increased FDG activity near the liver hilus. In combination with the CT scan results, both the gas formation in the beginning and the thrombus in the portal vein finally confirmed the diagnosis of pylephlebitis. Prolonged administration of broad-spectrum antibiotics and eradication of the underlying cause are the most important in treatment of pylephlebitis. The optimal duration of antibiotic therapy varies in the literature from four to six weeks.12 The role of anticoagulation therapy remains controversial. Limited data suggest a benefit for patients with hypercoagulable state or mesenteric vein involvement.13 Other studies have noted no benefit from anticoagulation.14 In a review Falagas et al. suggest that early administration of heparin in the management of septic thrombophlebitis might be useful and seems to be safe regarding the low complication rates, but the authors also stated that there are too few data to make a definite conclusion about the effectiveness and toxicity of heparin in patients with septic thrombophlebitis.14 Treatment with thrombolytic therapy in pylephlebitis has been described in a few case reports but there is no conclusive evidence of efficacy.9 Although in our patient a hypercoagulable state due to the advanced cancer may have contributed to the development of pylephlebitis, we did not apply anticoagulation therapy because of its dubious role in the treatment of pylephlebitis and the high risk of serious bleeding due to the duodenal ulcer. Although the incidence of pylephlebitis has decreased upon the availability of antibiotic drugs, it still carries a high mortality rate of 11 to 32%.4,5 Pylephlebitis may be complicated by severe therapy-resistant sepsis, which is responsible for the high mortality rates.4 Other complications include hepatic abscess formation, and less commonly progression of the thrombus into the mesenteric vein and portal hypertension.6,7 In conclusion, pylephlebitis is a rare but serious condition, which may be difficult to diagnose even with imaging techniques such as CT scan. It should be considered in patients with sepsis due to gut-associated organisms without a clear source of infection. FDG-PET seems to be a useful additional method for diagnosing septic thrombophlebitis.

REFERENCES

Ceftriaxone-induced acute reversible encephalopathy in a patient treated for a urinary tract infection

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ABSTRACT

Encephalopathy is a rare side effect of third- and fourth-generation cephalosporins. Renal failure and previous disease of the central nervous system predispose to this neurotoxicity. We describe a case of encephalopathy with generalised triphasic waves in a patient with pre-existent cerebrovascular disease who was treated with ceftriaxone for a urinary tract infection. Early recognition of this complication is relevant given that ceftriaxone discontinuation reverted the neurological syndrome.

KEYWORDS

Ceftriaxone, encephalopathy, neurotoxicity, triphasic waves

INTRODUCTION

Encephalopathy is a rare side effect of third- and fourth-generation cephalosporins. Renal failure and previous central nervous system (CNS) disease have been shown to predispose to this neurotoxicity. We present a case of acute reversible encephalopathy with generalised triphasic waves (TWs) in a patient with pre-existent cerebrovascular disease who was treated with ceftriaxone for a urinary tract infection. The present case illustrates the diagnostic challenges and management of this rare but potentially severe side effect of one of the most commonly prescribed parenteral antibiotics.

CASE REPORT

A 60-year-old Caucasian female with a chronic urinary catheter presented to our hospital with a four-day history of hypogastric pain and fever. One month earlier, the patient had been diagnosed with acute urinary tract infection and treated with ciprofloxacin. Her medical history included type 2 diabetes mellitus, hypertension, dyslipidaemia and established atherosclerosis (cerebrovascular disease, revascularised coronary heart disease and peripheral artery disease). She was on biphasic isophane insulin (12 IU + 6 IU), amlodipine (10 mg/day), furosemide (20 mg/day), ramipril (10 mg/day), pravastatin (20 mg/day), acetylsalicylic acid (100 mg/day), nitroglycerine (5 mg/day), amitriptyline (25 mg/day) and esomeprazole (20 mg/day). The patient had also been medicated with carbamazepine (400 mg/day) after a single partial seizure occurring six months earlier. An EEG performed then showed slow background activity, with no epileptiform discharges.

In the emergency department the patient was not in acute distress, had no fever, was haemodynamically stable, but dehydrated. C-reactive protein (22.6 mg/l; normal range <3.0) was elevated and acute renal failure (serum creatinine 177 μmol/l [normal range 53.0 to 88.4] and serum blood urea nitrogen (BUN) 10.9 mmol/l; normal range 1.8 to 8.9) was present. Urinalysis revealed bacteriuria and pyuria. The patient was started on ceftriaxone (2 g IV daily) and intravenous fluids. The patient was then admitted to the internal medicine ward. Furosemide and ramipril were suspended. The urine culture was positive for a quinolone-resistant but third-generation cephalosporin-sensitive strain of Klebsiella pneumoniae.

After four days of antibiotic coverage, the patient presented altered mental status with progressive apathy and somnolence. No focal neurological signs or convulsive movements were observed. No myoclonic jerks were present. She had no fever and the C-reactive protein
(14.9 mg/l) and serum creatinine levels (114 μmol/l) were declining. An EEG was performed (figure 1) showing high amplitude (200 μV), 1 to 1.6 Hz periodic generalised triphasic waves (TWs), maximally localised over the frontal areas of both hemispheres, although predominantly on the left. The head CT scan did not reveal acute stroke. No abnormalities of liver function tests or in serum electrolytes were present.

It was unlikely that alcohol withdrawal contributed to the clinical picture given that the patient had no history of alcohol abuse, no seizures, hallucinations or agitation were present, and the symptoms appeared four days after admission. Hypoglycaemia was not detected in capillary glucose monitoring and hyperglycaemia was controlled with insulin administration. Acidosis was absent in repeated arterial blood gas sample analysis. Cerebral hypoxaemia was also unlikely, given normal oxygen saturation in pulse oxymetry and the absence of acute ischaemic lesions in the head CT scan.

A toxic encephalopathy was then considered and ceftriaxone discontinued. The patient's neurological status improved and three days later she was again alert and oriented. A control EEG (figure 2) was performed five days later that showed no TWs. A gross asymmetry with respect to the right hemisphere was also noted, possibly related to the cerebrovascular disease. The patient was discharged three days later.

**DISCUSSION**

Neurotoxicity has been reported with both third-generation and fourth-generation cephalosporins. The proposed mechanisms include a decrease in γ-aminobutyric acid (GABA)-mediated inhibition and cephalosporin-mediated release of cytokines. In fact, cephalosporins may decrease GABA release from nerve terminals, increase excitatory amino acid release, and exert a competitive antagonism with GABA. Alternatively, cephalosporin treatment has been proposed to induce endotoxin release, which generates cytokines liberation, such as tumour necrosis factor-α, a proinflammatory cytokine implicated in septic encephalopathy.
Pre-existing CNS abnormalities have been indicated as a risk factor for β-lactams encephalopathy. The patient had a history of cerebrovascular disease and a prior symptomatic partial seizure, which probably accounted for the increased risk of drug-induced encephalopathy. In most published cases of cephalosporin-induced encephalopathy, renal impairment was present. This was also the case in our patient, who presented with acute renal failure, progressively corrected with intravenous fluids and treatment of the urinary tract infection. Excessive dosage has also been shown to be an important determinant of cephalosporin neurotoxicity. Given that no dose-adjustment is required for ceftriaxone in the presence of renal failure with the dose used (2 g IV daily), excessive dosage did not seem to play a role in this case.

Different EEG patterns have been described in association with cephalosporin encephalopathy. Both encephalopathy with TWs and nonconvulsive status epilepticus have been reported and the differential diagnosis between the two conditions may at times be difficult. In this case, several EEG features favoured the assumed pattern of TWs, namely the frequency of discharges lower than 2 Hz, the amplitude predominance of phase 2 wave component, the anterior-posterior lag of phase 2, the absence of associated extra spiky components and the persistence of background activity.

Metabolic encephalopathy, especially hepatic and uraemic, is known to be frequently associated with TWs on EEG. Our patient did not present evidence of liver failure and had only mild and reversible acute renal dysfunction that could not account for the observed encephalopathy. In fact, the temporal association of the encephalopathy induction and resolution with ceftriaxone administration and withdrawal makes this antibiotic highly likely to be responsible for the encephalopathy. Moreover, the temporal pattern is in accordance with previous publications reporting cephalosporin neurotoxicity, with a latency of one to ten days after drug initiation and regression of all neurological symptoms within two to seven days following ceftriaxone treatment suspension.

The use of amitriptyline and carbamazepine most probably did not cause this clinical picture given that the patient

A gross asymmetry with respect to the right hemisphere is also noted, possibly related to the cerebrovascular disease. Time base 30 mm/sec, amplitude 7 μV/mm.
had been taking these medications for a long time and that clinical improvement was observed without its discontinuation.

**CONCLUSION**

We describe a case of acute ceftriaxone-induced acute reversible encephalopathy in a patient treated for a urinary tract infection. Although this potential side effect of cephalosporin treatment is increasingly recognised, the diagnosis is hampered by the broad differential diagnosis of altered mental state in patients with ongoing infection and multiple medical conditions. This neurotoxicity should be specially considered when the patient has pre-existing CNS abnormalities or renal impairment and an EEG should be performed for diagnosis confirmation. Early recognition of this complication is particularly relevant given that discontinuation of ceftriaxone reverted the neurological syndrome.

**ACKNOWLEDGMENTS**

We are grateful to our medical students, Sofia Alves and Alina Rosinha, for their extraordinary work on this case.

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ABSTRACT

Treatment with coumarin derivatives is highly individualized due to high intra- and inter-individual variation in dose response and risks of severe bleeding or thromboembolic complications. Treatment focuses on reaching and maintaining a stable target international normalized ratio (INR). However, unexpected INRs that are not explained by noncompliance or vitamin K intake may occur. Here we describe seven cases of unexpected INRs, and provide clues that clarify the underlying mechanism.

KEYWORDS

Coumarin, CYP2C9, INR, superwarfarin, VKORC1

INTRODUCTION

Coumarin derivatives are known to have a small therapeutic range, with many factors implicated in this range.1,2 Coumarins act as competitive inhibitors of the vitamin-K-epoxide-reductase (VKOR), which is essential in recycling vitamin K.2,3 Inhibiting VKOR results in decreased production of vitamin K-dependent coagulation factors. In this article, we present seven cases of unexpected international normalized ratio (INR). These cases show that beside the traditional factors such as vitamin K intake, intercurrent comorbidity, and nonadherence, one should consider other factors such as comedication, genetic factors and superwarfarins.

CASE REPORTS

Patient A, a 79-year-old man, was treated with acenocoumarol. However, his target INR was not achieved.4 Both raising the dosage to 8 mg/day and eventually changing to phenprocoumon 9 mg/day did not result in INR above 1.1. Nonadherence and absorption problems were excluded since serum concentration of phenprocoumon was 11 mg/l – the therapeutic range for elevation of INR is 1 to 3 mg/l – and vitamin K in serum was low, 0.6 nmol/l (reference 0.8 to 5.3 nmol/l). DNA prepared from blood was analysed for mutations in the vitamin K epoxide reductase C1 (VKORC1) coding region. We found a novel missense mutation leading to partial resistance to acenocoumarol and phenprocoumon.6 Eventually, the patient’s INR reached its target (2.5 to 3.5) with a daily dosage of 18 to 21 mg phenprocoumon.

Patient B, a 68-year-old man, was admitted to the intensive care unit with recurrent pulmonary embolism. He had been treated with phenprocoumon for a few years. It was not possible to find the correct dose in spite of dose adjustments. The INR showed fluctuating values. He was screened for mutations in cytochrome P450 enzyme subunit C9 (CYP2C9) and VKORC1. CYP2C9 is known to be involved in metabolism of coumarins.7 No abnormalities were found in CYP2C9 but a heterozygous mutation was found in the VKORC1 gene (C1173T), resulting in increased sensitivity to coumarins. Such patients need prudent dosing.8

Patient C, an 87-year-old female, was prescribed acenocoumarol after the diagnosis atrial fibrillation. INR values were stable within the therapeutic range with a daily
dose of 1.7 to 1.8 mg acenocoumarol. After starting tube feeding for a deglutition complication, her INR was lower than before (<1.5). Target INR was reached by prescribing a higher dose of 3 mg acenocoumarol a day. The effect of tube feeding is known from the literature.\textsuperscript{9,10}

Patient D, a 43-year-old female treated with acenocoumarol, showed strongly fluctuating INR values. During hospital admission she was treated with a list of drugs of which carbamazepine is known to cause induction of the hepatic metabolism of anticoagulants. Comedication with carbamazepine has been reported to cause decreased anticoagulant effects by inducing cytochrome P450 activity.\textsuperscript{11,12}

Achenocoumarol is then quickly metabolised and the effect on coagulation is lowered. In this case, serum concentration of acenocoumarol was beneath the lower limit of detection of 20 μg/l (the therapeutic concentration is 30 to 90 μg/l). Changing carbamazepine into valproate did not resolve the problem. Finally, intake under supervision resulted in target INR.

Patient E, a female, 63-year-old, was admitted to the hospital with anaemia and gastrointestinal bleeding with high INRs. Intoxication with coumarin derivatives was suspected and blood was analysed. However, acenocoumarol, phenprocoumon, and warfarin were all absent in her serum. Subsequently, a blood sample was sent to the Leiden University Medical Centre for superwarfarin screening. Both difenacoum and difethialone were detected in her blood. The patient was treated with vitamin K (10 mg per os per day) for several months until her INR returned to normal. Superwarfarins are rodenticides, which have a long-lasting effect and a high volume of distribution, even at low concentrations. In this case it is likely an autointoxication; in superwarfarin intoxications unintentional intake should be excluded. High dosages of vitamin K for a long period are the antidote.\textsuperscript{13}

Patient F, an 18-year-old boy, was seen at the emergency room. He said he had taken 6 to 7 spoons of a brodifacoum containing rodenticide, which is equivalent to 0.007 g of brodifacoum. Treatment with activated charcoal was started immediately (4 x 50 g). Oral vitamin K (10 mg/day on first three days after intake) was prescribed. INR showed no elevations and the serum concentration of brodifacoum was 3 μg/l. Even a week after the suspected date of ingestion the INR was normal. Calculations on the basis of the suspected intake and 100% biological availability, however, would result in a much higher serum concentration of 100 μg/l. The patient had pervasive developmental disorder not otherwise specified (PDD NOS), thus we think that he strongly exaggerated the amount of poison he took. Because brodifacoum has a long half-life of elimination (40 to 60 days, half lives of acenocoumarol and phenprocoumon are 10 and 160 hours, respectively), in serious intoxications INR values have to be checked regularly, and long-lasting administration of vitamin K is needed.\textsuperscript{14}

Patient G, a 38-year-old man, started phenprocoumon after a pulmonary embolism. INR values ranged from 1.1 to 2.4, while target INR was 2.5 to 4.0. His serum phenprocoumon concentration was 0.3 mg/l (therapeutic concentration 1.0 to 3.0 mg/l). He was switched to acenocoumarol. Two weeks later we found acenocoumarol and phenprocoumon simultaneously in his blood. The acenocoumarol concentration was >180 μg/l, and the phenprocoumon concentration was 1.5 mg/l. It is peculiar, however, that the patient declared at that time he was not taking any coumarins at all.

**DISCUSSION**

When an unexpected high, low or strongly fluctuating INR is found, first of all technical failure in blood sampling, storage, or INR determination have to be excluded. We then advise to discuss compliance with the patient. Tablet intake under supervision and eventually measurement of serum concentrations may clear this issue. In addition, it is important to enquire about vitamin K intake, comorbidity, and check the patient’s medication list for inducing or inhibiting drugs. A global blood screening is needed to confirm normal kidney and liver function. Finally, visually examine the tablets to rule out exchange of medication. A structured summary of potential causes and actions, in order of clinical relevance, is given in table 1. Factitious behaviour is not easily diagnosed. In cases of sustained INR, we advise measuring blood concentrations of phenprocoumon and acenocoumarol, which can confirm intake. Detecting superwarfarins is possible, but relatively rare. The number of anticoagulant rodenticide intoxications registered at the Dutch Poison and Information Centre (NVIC) was 196 in 2006, and 224 in 2005. Coagulation defects are outside the scope of this article.

When all options mentioned above are excluded, we recommend screening for variations in CYP2C9 and the VKORC1 gene. VKORC1 and CYP2C9 genotype explain half of the inter-individual variability in anticoagulant maintenance dosages.\textsuperscript{5,8} The CYP2C9*2 and CYP2C9*3 alleles, for instance, confer higher susceptibility to coumarins, with pharmacokinetic consequences. Lower dosages than in CYP2C9 wild-type patients will give normal serum concentrations of the anticoagulant in patients carrying CYP2C9*2 or CYP2C9*3. Allelic frequencies of CYP2C9 *1, *2, and *3 in the Netherlands are 80%, 10 to 13%, and 7 to 10%, respectively.\textsuperscript{5,8} Most VKORC1 genetic variants correspond to an increased effect (prescribe lower dosages) of coumarins. The most abundant of these variations is 1173C>T, present in 40% of VKORC1 alleles.\textsuperscript{5,8} However, VKORC1 variants exist that cause partial resistance, requiring very high dosages for therapeutic effect. In cases of partial resistance,
Genes do not change during a lifetime, so genetic analysis of CYP2C9 and VKORC1 only needs to be done once. The role of nonadherence in coumarin therapy is generally thought to be of great importance, although this could not be confirmed in adherence studies. The influence of nonadherence is probably lower than genetic variation.

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A 36-year-old woman was sent to the emergency department because of fever, rash and arthralgia, which started two days ago. Her medical record was negative. She was the mother of three healthy children, and reported no exotic travelling. She reported a negative parvo-B19 serology tested two years earlier during her last pregnancy. At physical examination the patient was rather ill, febrile (38.4°C) and haemodynamically stable. Her cheeks were markedly red (figure 1) and there was a maculopapular rash on trunk and extremities, with visible arthritis of the small joints of both hands (figure 2) and feet, wrists and knees. Laboratory examination analysis revealed: haemoglobin 7.2 mmol/l, leucocyte count 11.1 x 10^9/l, thrombocyte count 287 x 10^9/l, C-reactive protein 115 mg/l, aspartate aminotransferase 108 U/l, alanine aminotransferase 213 U/l, alkaline phosphatase 167 U/l and gamma-glutamyl transpeptidase 197 U/l.

**Figure 1. Red cheeks**

**Figure 2. Arthritis of the small joints**

**What is your diagnosis?**

See page 81 for the answer to this photo quiz.
The differential diagnosis of fever, rash and arthralgia is broad and contains autoimmune disorders, and viral and bacterial infections. Because the medical history was completely negative and signs and symptoms developed within two days, an infectious origin was suspected. The bacterial diseases considered were meningococcosis, group A streptococcal infections and leptospirosis. For that reason treatment with ceftriaxone and acetylsalicylic acid was started. Possible viral infections included Rubella virus, hepatitis B virus, CMV and human parvovirus B-19 (HPV-B19).

Further laboratory analysis showed a positive IgM and polymerase chain reaction (PCR) for parvo-B19 virus. Blood cultures were negative and the antistreptolysin titre remained 320. The fever normalised and the arthritis disappeared within four days, the rash remained visible for three days, and the arthralgia persisted for two to three weeks.

The fifth erythematous exanthema of childhood, also called ‘slapped-cheek syndrome’ was first described in 1905. In 1983 HPV-B19 was found to be the causative agent. The target of the virus is the blood group P-antigen, which is present on red cell membranes, but also on platelets, heart, liver, lung kidney, endothelial and gastrointestinal smooth muscle and synovial cells. Classically, infections occur during outbreaks at schools and may be asymptomatic in children. The frequency of positive serology increases with age; 50% are positive at the age of 15 and 80 to 100% at the age of 70 years. The clinical features of HPV-B19 are: (1) Erythema infectiosum characterised by erythema of the cheeks (slapped cheeks, see figure 1), followed by a maculopapular rash on trunk and limbs; (2) Anaemia due to infection of erythroid precursor cells in the bone marrow; (3) Arthralgia and arthritis characterised by a symmetrical pain, swelling and stiffness of mainly the small joints of hands, knees and feet. This feature is more often seen in adults then in children. Women are more commonly affected than men (60 vs 30%); (4) Increased foetal death rate (9%) after maternal infection during pregnancy.

Under normal circumstances the disease is self-limiting and requires no therapy, unless anaemia is severe.

REFERENCES

A 58-year-old woman with a history of type-2 diabetes, hypertension, and myocardial infarction, presented with acute onset of severe continuous pain of her right lower and upper abdomen, and vomiting. The pain started at 3 o’clock in the night, during sleep. Physical examination revealed a moderately obese woman with a normal pulse, blood pressure and body temperature. There was tenderness of the right upper abdomen and costovertebral angle. Blood and urinalysis revealed no abnormalities except an elevated C-reactive protein (CRP) of 12 mg/l (normal <10 mg/l). An echography of the abdomen and a nonenhanced CT scan (figure 1) were normal. The following day the pain increased and blood analysis showed a white blood cell count of 13.3 x 10^9/l and a lactate dehydrogenase (LDH) of 494 U/l (normal 110 to 200 U/l). CRP 17.3 mg/l. Urinalysis demonstrated microscopic haematuria. The surgical consultant, unaware of the first CT scan, ordered a contrast-enhanced CT scan (figure 2).

**Figure 1. Nonenhanced CT scan of the abdomen**

**Figure 2. Contrast-enhanced CT scan of the abdomen**

**WHAT IS YOUR DIAGNOSIS?**

See page 83 for the answer to this photo quiz.
The contrast-enhanced CT scan revealed a wedge-shaped perfusion defect in the lower pole of the right kidney (arrow, figure 2), consistent with a renal infarction. The patient was treated with heparin and acenocoumarol. The pain resolved after one week.

Acute renal infarction is often an overlooked or delayed diagnosis.\(^1\) Because its presentation is nonspecific, it is frequently mistaken for more commonly encountered diseases such as ureterolithiasis, pyelonephritis, appendicitis, diverticulitis, biliary obstruction and torsion of pelvic masses. Patients with acute renal infarction typically present with nonspecific symptoms of acute onset of low back pain, abdominal pain or flank pain with nausea, vomiting, hypertension and sometimes fever. Physical examination reveals costovertebral angle tenderness, which is a characteristic sign of acute renal infarction. About 90% of patients have increased LDH levels. Other common laboratory findings include leukocytosis, haematuria and proteinuria. Aspartate aminotransferase, alkaline phosphatase and CRP are also useful markers, but less specific.\(^4\) These laboratory abnormalities may be absent in case of very early presentation after onset of the pain.\(^4\) The major causes of an acute renal infarction are atrial fibrillation, and valvular or ischaemic heart disease. Additionally, other causes of acute renal infarction include trauma, hereditary or acquired clotting disorders, both intravenous and nasal cocaine abuse,\(^4\) vessel anomalies, medical interventions such as surgery for valve replacements, kidney transplantation, endovascular catheterisation and application of intraluminal stents, sickle cell disease or sickle cell trait and malignant disease.\(^4\) None of these diseases were observed in this patient and a magnetic resonance angiogram did not show arterial vessel disease.

Spiral (helical) computed tomography without contrast is usually the preferred initial test for flank pain, being the imaging technique of choice for the diagnosis of kidney and ureteral stones, which are more common than renal infarction. However, contrast enhancement is required when unenhanced CT reveals no abnormalities because the diagnosis renal infarction will be missed as happened in this case. The triad of acute flank pain, high serum LDH and microscopic haematuria should make the physician aware of a possible renal infarction.

**REFERENCES**


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