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The Journal of Medicine
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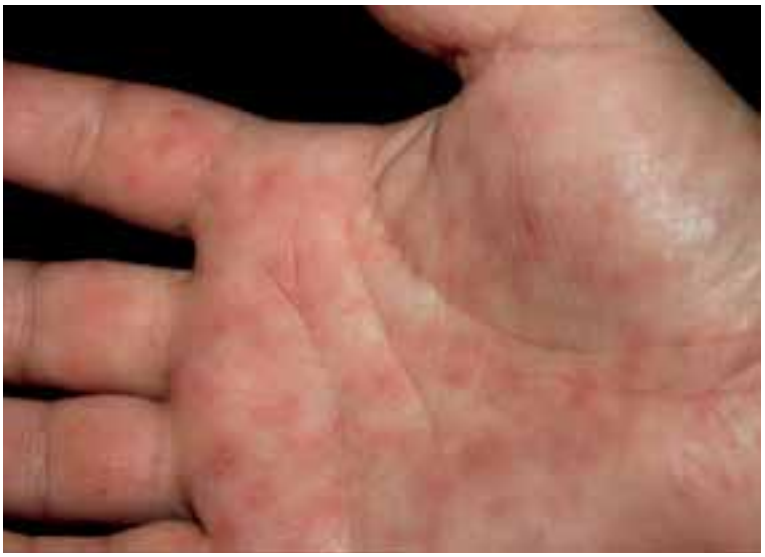

"Pythons and a palmar rash: what is your diagnosis?"

June 2012, VOL. 70. No. 5, ISSN 0300-2977

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ISSN: 0300-2977

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EDITORIAL

Predictions of the past, prepared for the future?

P. Fockens

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The famous scientist and Nobel Prize winner Niels Bohr (1885-1962) is quoted to have said, 'Prediction is very difficult, especially about the future'. The interesting article from the Gastroenterology group from Zaandam, the Netherlands, in this issue of the Netherlands Journal of Medicine, illustrates nicely that it is also quite difficult to predict the past when trying to analyse a large database with data from two decades of an upper gastrointestinal endoscopy service.[1] The article is a retrospective analysis of a prospective database that the first author initiated when he started his practice in a medium-sized city in the Netherlands. With almost 30,000 endoscopies in the database, this provides a wealth of information; however we also miss a lot of data. Understandably but unfortunately no data about the population from which these patients were referred are presented. Did the population age, was there a change in ethnic background and more importantly: were there changes in the referral pattern of the general practitioners? All these questions are very interesting and probably important to put their findings into the right perspective.

In the 20 years the authors report on, there have been many changes in medicine as well. In the period described in this study we have seen, for instance, the rise of evidence-based medicine, the increasing use of proton pump inhibitors, the possibility of cure in *Helicobacter pylori*-related peptic ulcer disease, the dramatic improvements in the quality of diagnostic endoscopy etcetera, etcetera. The rise of evidence-based medicine led to standards of practice being published by the Royal Dutch Medical Association and undoubtedly these have changed the referral pattern for 'open access' endoscopy. In these guidelines a therapeutic trial with acid-reducing medication was advised and the remarkably stable total number of endoscopies per year should therefore be interpreted with caution. With an overall growth of the population and a higher threshold for referral, the stable number of endoscopies in this unit may actually represent a significantly reduced use of open access endoscopy in the population. This trend was described earlier by another group in the Netherlands.[2]

The authors briefly describe the improvements in their equipment; however, it seems to be worth discussing this a little further. In the early 1990s, most endoscopies were still done with fibre-optic endoscopes. Although the quality was considered excellent at that time, our current fellows in training would be devastated if they ever had to use such an instrument. The optical resolution was at least a tenfold lower than that of our current systems. Besides that, the ergonomics were markedly inferior to our current standards. A full day of endoscopy was a much more tiring activity at that time than it is today. Recent studies looking into the relationship of the time of the day and the finding of relevant pathology have shown us that endoscopists tire during the day and their performance decreases, although other studies were not all able to confirm this phenomenon.[3] Trying to translate those findings to the poor ergonomics of the equipment at the start of this study, one could speculate (predict?) that actually more lesions per patient should have been detected in the second half of this study, purely based on the improved ergonomics. Figure 3 of the article shows an increase in endoscopic findings which will probably also be related to the dramatically improved resolution. The endoscopy system the authors currently use is a high-definition system with very fine detail, which must have played an important role in this increasing number of relevant findings.

The cause of peptic ulcer disease was still not completely unravelled at the start of the current study, but *H. pylori* had already been described. In the early 1990s, it became clear that eradication of *H. pylori* opened the way to cure for most patients with chronic *H. pylori*-related peptic ulcer disease with a subsequent three to fourfold decrease in the rate of finding ulcers during the study period. It is interesting and to some extent maybe even worrisome that the endoscopic diagnosis of metaplastic gastric epithelium has not changed. During the study period many things

changed regarding the endoscopic diagnosis of Barrett's oesophagus. One change was that the original diagnosis of Barrett's oesophagus was reserved for a minimum of 3 cm metaplastic epithelium in the oesophagus. This definition changed over the years and a minimum length was abandoned, which one would expect to lead to a higher incidence figure for Barrett's. Secondly, the higher resolution of the equipment, as described above, could be expected to lead to an increased diagnosis of Barrett's oesophagus. Thirdly we now know that the incidence of squamous cancers of the oesophagus is decreasing whereas the incidence of oesophageal adenocarcinoma is rising rather steeply (as also demonstrated in one of the graphs of the current study). As Barrett's oesophagus is a known precursor of oesophageal adenocarcinoma, this would be another argument to expect a rise in the endoscopic diagnosis of Barrett's oesophagus in the population under study.[1]

So what do we learn from this study? In my opinion, first and foremost the study shows that well-structured reporting of endoscopic procedures provides an excellent opportunity to critically look back at one's performance. In this day and age, prospective collection of endoscopic data allows benchmarking within and among hospitals. Quality assurance is the new buzzword in medicine. Our patients want to know that the doctors they visit are not only qualified but also deliver quality.[4] For gastrointestinal endoscopy and specifically for colonoscopy, this means that in the coming year each endoscopist in the Netherlands will have to be able to provide data on the efficacy of their bowel preparation regimens, on the percentage of patients in which they successfully reached the caecum, on the number of adenomas they detected, on the amount of sedation they used and on many other variables.[5] Data that far exceed the data that Loffeld and others collected, but it still shows us that they were ahead of their time when they initiated the database reported on in this article.

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REVIEW

Podoconiosis, a neglected tropical disease

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ABSTRACT

Podoconiosis or 'endemic non-filarial elephantiasis' is a tropical disease caused by exposure of bare feet to irritant alkaline clay soils. This causes an asymmetrical swelling of the feet and lower limbs due to lymphoedema. Podoconiosis has a curable pre-elephantiasic phase. However, once elephantiasis is established, podoconiosis persists and may cause lifelong disability. The disease is associated with living in low-income countries in the tropics in regions with high altitude and high seasonal rainfall. It is found in areas of tropical Africa, Central and South America and north-west India. In endemic areas, podoconiosis is a considerable public health problem. Social stigmatisation of patients is widespread and economic losses are enormous since it mainly affects the most productive people, sustaining the disease-poverty-disease cycle. Podoconiosis is unique in being an entirely preventable, non-communicable tropical disease with the potential for eradication. Low-cost preventive measures are a simple but effective solution. However, so far it has received little attention from health care policy makers and, until recently, research into the disease has been scarce and the pathogenesis and genetic basis are partly unclear. A better understanding of these aspects may lead to new prevention and treatment opportunities. In the past few years, several projects fighting podoconiosis have been started by non-governmental organisations. In February 2011, the World Health Organisation designated podoconiosis as one of the 20 neglected tropical diseases, marking an important step in the fight against the disease.

KEYWORDS

Elephantiasis, mossy foot disease, neglected tropical disease, non-filarial elephantiasis, podoconiosis

INTRODUCTION

Podoconiosis is a tropical disease characterised by an asymmetrical swelling of the feet and lower limbs due to lymphoedema. This swelling is called 'elephantiasis'. Although the most common cause of elephantiasis in the tropics is infection with filarial worms (*box 1*),

Box 1. Lymphatic filariasis

Lymphatic filariasis is a tropical disease caused by roundworms (nematodes). Three species of these worms are known to cause filariasis, of which the most important is *Wucheria bancrofti*. It is endemic in countries in the tropics and 1.39 billion people live in areas of risk. Approximately 40 million people have stigmatising and disabling clinical manifestations of the infection, of whom 15 million have elephantiasis.[20] More than 60% of those affected live in South-East Asia and over 30% live in Africa.

It is a communicable disease transmitted by many different mosquito vectors, including *Anopheles*, *Culex* and *Mansonia* species. Humans are definitive hosts. The transmission cycle begins with a bite of a mosquito which is infected with larvae. The larvae enter the body and mature into adult threadlike worms that inhabit the lymphatic vessels of the groin and scrotum or sometimes those of the arm. They produce thousands of microfilariae daily that circulate in the blood. Once a mosquito bites an infected person, the cycle begins again. Although many infections are asymptomatic, some patients suffer acute or chronic illness, including lymphoedema or elephantiasis. Various antihelminthic agents are effective, such as diethylcarbamazine (DEC), albendazole and ivermectin.[21]

In 2000, the WHO launched the 'Global Programme to Eliminate Lymphatic Filariasis'. Since then, considerable progress has been made, eliminating the disease in China (2007) and Korea (2008).

Figure 1. *Podoconiosis is also called 'mossy foot disease'*

Photo's: J. van der Zee (Expertise Centre Lymphology, Drachten, the Netherlands), with permission.

podoconiosis occurs in the absence of parasitic infection and is therefore also known as 'endemic non-filarial elephantiasis'. Podoconiosis (from the Greek word for foot: *podos*, and dust: *konos*) is unique in being an entirely preventable non-communicable tropical disease. In local communities, it is often called 'mossy foot disease', because the skin becomes rough and bumpy and its appearance resembles moss (*figure 1*). In February 2011, the World Health Organisation designated podoconiosis as one of the 20 neglected tropical diseases (*table 1*). Despite being widespread, so far research into the disease has been scarce and the pathogenesis is partly unclear.[1] In the 1980s Ernest Price, a British surgeon, discovered that podoconiosis is caused by an abnormal inflammatory reaction to persistent contact with irritant soils, especially red clays derived from alkaline volcanic rock.[2] The disease is associated with living and walking barefoot in low-income countries in the tropics in regions located higher than 1000 m (3300 ft) above sea level with an annual rainfall of more than 1000 mm, the climatic factors necessary for producing these irritant soils.[1] Mineral particles from these soils penetrate through the skin of the foot and are phagocytised by macrophages in the lymphatic vessels.[2,3] Here, they induce an inflammatory reaction leading to fibrosis and blockage of the vessel lumen, causing lymphoedema. However, the pathogenic events through which the particles provoke inflammation are unclear and only a minority of the people exposed to the irritant soils develop clinical symptoms. Evidence for a genetic basis of podoconiosis is emerging. There is familial clustering of the disease and the heritability is estimated to be 63%.[4] Siblings of patients have a five times higher risk of developing podoconiosis than people in general. A recent study, using a genome-wide approach, found an association of podoconiosis with genetic variants in the HLA class II loci, suggesting that it may be a T-cell-mediated inflammatory disease.[5] However, other genes involved have not yet been identified[4] and there has not been any research into the possible role of co-factors contributing to podoconiosis, such as chronic infection or micronutrient deficiencies.[1]

Table 1. *WHO neglected tropical diseases*

Buruli ulcer
Chagas diseases (American Trypanosomiasis)
Cysticericosis
Dengue
Dracunculiasis (Guinea-worm disease)
Echinococcosis
Fascioliasis
Human African trypanosomiasis
Leishmaniasis
Leprosy
Lymphatic filariasis (elephantiasis)
Onchocerciasis
Rabies
Schistosomiasis
Soil transmitted helminths
Trachoma
Yaws
Podoconiosis
Snakebite
Strongyloidiasis

More than one billion people are affected by one or more of the 20 neglected tropical diseases identified by the World Health Organisation. These diseases are neglected because they have been largely eliminated elsewhere and are often forgotten in wealthier places. Further information: http://www.who.int/neglected_diseases/.

PREVALENCE

It is estimated that 4 million people are affected by podoconiosis worldwide,[5] and 5 to 10% of the population in endemic areas where the use of footwear is uncommon.[6] In these areas, it can be even more prevalent than HIV/AIDS, tuberculosis or malaria. It is found in highland areas of tropical Africa, Central and South America and north-west

India. High prevalence has been documented in Ethiopia, Tanzania, Kenya, Uganda, Rwanda, Burundi, Sudan, Cameroon and Equatorial Guinea.[7] In these countries, podoconiosis is a considerable public health problem. The total number of cases seems to be highest in Ethiopia. Here, 11 million people, which is 18% of the population, are at risk through exposure to the irritant soils and estimates suggest that between 500,000 and 1 million people are affected countrywide.[6] Podoconiosis has been present in Ethiopia for centuries but has so far received little attention from health care policy makers, either because it is not an immediate threat to life, or because of a lack of information on the socioeconomic impact of the problem.[8] Men and women are usually equally affected. In the past, podoconiosis was also common in North Africa and European countries such as France, Ireland and Scotland.[9] However, the disease disappeared in these areas when the usage of footwear became standard.

CLINICAL FEATURES AND DIAGNOSIS

Early symptoms of podoconiosis include itching of the skin of the forefoot and recurrent episodes of burning and oedema of the foot or lower leg, especially after periods of intense physical activity.[10] As lymphatic vessel obstruction progresses, established lymphoedema sets in and elephantiasis occurs. This can clinically vary from soft subdermal lymphoedema to hard or leathery leg elephantiasis, consisting of fibrosis of the skin and subcutis which becomes remarkably thickened.[10] Over the years, the increase in the diameter of the leg persists and can progress to severe elephantiasis. The skin often shows hyperkeratosis, moss-like papillomas, and hard nodules.[11] Podoconiosis has a curable pre-elephantiasic phase. However, once elephantiasis is established, podoconiosis persists.[12]

Podoconiosis must clinically be distinguished from filarial and leprotic lymphoedema.[1] In contrast to lymphatic filariasis, podoconiosis is ascending, starting in the foot and progressing to the knee but rarely involving the upper leg or the groin. Furthermore, it is commonly bilateral yet asymmetric and occurs at altitudes higher than 1500 m (5000 ft), which exceeds that at which filarial transmission occurs. Research in a highland endemic area in southern Ethiopia demonstrated that these specific clinical features combined with establishing that a patient has not migrated from a lowland area is a valid way of ruling out filarial disease.[13] If doubt remains, blood tests such as the filariasis *in vitro* immunodiagnostic essay for the detection of *Wucheria bancrofti* antigen can be used to rapidly distinguish podoconiosis from filariasis. In contrast to leprosy lymphoedema, sensation in the toes and foot is maintained, tropic ulcers are absent and there is no hand involvement.[1]

IMPLICATIONS

Podoconiosis has enormous social, psychological and economic implications for affected individuals. Social stigmatisation of people with the disease is widespread and patients are banned from schools, local meetings and churches, and not allowed to marry into unaffected families.[14] Patients going to non-specialist health services often encounter a lack of expertise and prejudicial attitudes among health workers.[6] A study among 275 health professionals in public and private health institutions in southern Ethiopia showed that nearly all held at least one significant misconception about the cause of podoconiosis.[15] Furthermore, around half incorrectly considered podoconiosis to be an infectious disease and were afraid of acquiring podoconiosis while providing care. All of the health professionals held at least one stigmatising attitude towards affected persons.

The stiffness of the skin and the increased diameter of the legs result in severe disability of the patient. Therefore, podoconiosis threatens economic development because it mainly affects the most productive people (16 to 45 years of age),[7] sustaining the disease-poverty-disease cycle. Research has demonstrated a loss of productivity equivalent to 45% of working days per patient annually.[8] This costs a single zone of 1.5 million inhabitants more than US$ 16 million per year, significantly contributing to poverty. The annual economic losses for Ethiopia are estimated to exceed US$ 200 million in lost productivity and medical costs.

PREVENTION AND MANAGEMENT

European history has shown that podoconiosis has the potential for eradication. Theoretically, the disease can be completely prevented by simple and low-cost measures. In endemic areas, the majority of the community hold significant misconceptions about causation, care, treatment and prevention of the disease.[16] Therefore, primary prevention should consist of education on the aetiology and how to avoid prolonged exposure to irritant soils, most importantly by using appropriate and protective footwear, covering floor surfaces and applying skincare. Early stages of podoconiosis are reversible and secondary prevention consists, again, of encouraging shoe wearing and daily foot-washing with soap, water and, if possible, antiseptics in order to prevent bacterial infection. Wound care is important and infections should be treated with antibiotics. Furthermore, compression therapy by bandaging and hosiery is essential to prevent further swelling (*figure 2*). In compliant patients, these measures are able to completely avert progression.[10] The tertiary prevention of podoconiosis is similar to the management

of patients with lymphoedema due to another cause. It is an extension of the secondary preventive measures and also includes elevation of the limb above hip level. This leads to reduction in limb size by improving venous and lymphatic return. A recent study showed that these measures in patients with podoconiosis have a considerable impact both on clinical progression and self-reported quality of life.[17] However, since many patients live far from a treatment centre, educating them on how to apply these measures is a fundamental part of the treatment. Although long-term results of more radical surgery are disappointing, prominent nodules can be removed in selected cases.[1] Most of these treatments seem simple but in the majority of the endemic areas shoes, socks and soap, let alone bandages, antibiotics and surgeons, are unaffordable luxuries.

In the past few years, several projects fighting podoconiosis have been started by non-governmental organisations. For example, in 1997 the 'Mossy Foot Project' was established in Ethiopia. This organisation aims to raise awareness of the disease in the Western World and works towards its treatment and eradication in affected countries. The main strategy of this program consists of prevention, for example by providing shoes and socks. Special oversized shoes are distributed among patients. Furthermore, microfinance initiatives have been created to assist patients to start their own business and become economically independent. The launch of 'Foot*work*', the International Podoconiosis Initiative, in March 2012 marks the next step in the increasing advocacy and awareness of podoconiosis.[18,19] The aims of this organisation include bringing together private and public partners to prevent and treat podoconiosis.

CONCLUSION

In endemic areas, podoconiosis is a considerable public health problem with severe social, psychological and economic implications. Despite being widespread and the lifelong disability it causes in affected individuals, research into the disease has been scarce and the pathogenesis is partly unclear. A better understanding of the pathogenesis might lead to new prevention and treatment opportunities. Low-cost preventive measures, especially raising awareness on the aetiology and prevention of podoconiosis, are a simple but effective solution and therefore must be promoted by health care policy makers. History has shown that podoconiosis has

Figure 2. *Secondary preventive measures include foot-washing and bandaging*

Photo's: J. van der Zee (Expertise Centre Lymphology, Drachten, the Netherlands), with permission.

the potential for eradication. Perhaps the largest challenge for the future will be to fight misconceptions and social stigmatisation in endemic areas.

ACKNOWLEDGEMENT

Thanks to Dr. M. van Vugt (internist, infectious diseases expert) for her comments on the manuscript and to Mrs. J. van der Zee (skin and oedema therapist) for her photos and remarks on the prevention and treatment of podoconiosis.

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REVIEW

Severe pulmonary manifestation of leptospirosis

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ABSTRACT

Based on increasing incidence and the occurrence of worldwide outbreaks, leptospirosis is recognised as an emerging zoonosis. Severe manifestations are associated with high morbidity and mortality rates and may therefore pose an important risk to public health, especially in certain high prevalence areas. A considerable number of infections progress to a severe form, which can present as the well-known triad of jaundice, impaired renal function and haemorrhage, known as Weil's disease. The severe pulmonary form of leptospirosis (SPFL) is a less known entity and is characterised by intra-alveolar haemorrhage and can lead to acute respiratory failure and death when adequate treatment fails. Prognostic factors correlating with severity and survival of leptospirosis include indicators of renal failure, pulmonary involvement and electrolyte imbalances. We report an imported case of SPFL in a returning traveller, and review the literature discussing epidemiology, clinical manifestations, prognostic factors and treatment of this resurgent disease.

KEYWORDS

Leptospirosis, lung, pulmonary manifestation, epidemiology, emerging infection

INTRODUCTION

Recent incidence estimates, combined with an increasing number of outbreaks in virtually every continent, have indicated leptospirosis as an emerging zoonosis with increasing numbers worldwide.[1-3] The disease has been identified as a potential threat for public health and can cause significant morbidity.[1] In recent years the severe pulmonary form of leptospirosis (SPFL), characterised by respiratory failure and haemorrhage with a mortality of >50%, is emerging and presents a cause for concern even in Western countries.[4]

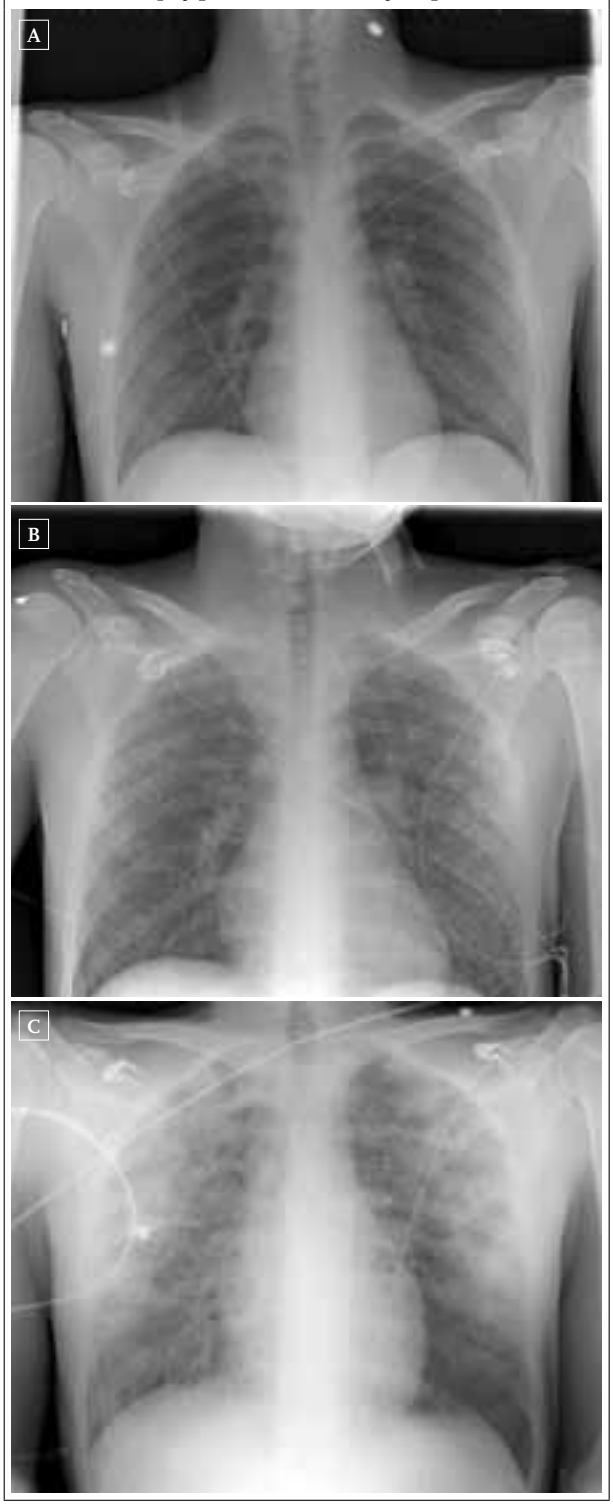
Leptospirosis is caused by spirochetes of the genus *Leptospira*. This dynamic group of bacteria consists of over 250 known serovars, surviving in warm and moist conditions. *Leptospira* can be carried and excreted by a wide range of mammalian species, which can serve as vectors. Infection can be acquired either through direct contact with animals, or through environmental contamination by animal urine. Consumption of contaminated food or water and exposure of mucosa or abraded skin to fresh surface water are the most important routes of infection.[5] Illness usually begins one to two weeks after infection and presents with fever accompanied by a broad spectrum of possible symptoms. In severe cases the disease can cause extensive tissue damage, vasculitis and, eventually, multi-organ failure. Worldwide incidence rates of leptospirosis seem to fluctuate annually, although a rising trend has been observed over the last years,[6] due to an increase in global flooding, which is driven by changes in climate, land use and socio-demographic factors.[5] Severe cases are estimated to occur >350,000 times each year throughout the world, with reported case fatality rates from about 5 to 30%.[1,2,7,8] However, reported numbers are likely to be a strong underestimation of the true incidence due to unawareness and neglect.[7] In the Netherlands, approximately 30 cases were reported per year over the last decade. However, the actual number of infections may be higher, as it is estimated that at least 30% of severe cases are missed.[2] In industrialised countries, recreational exposure and international travel have emerged as

increasingly important sources of infection over the past decades.[5,9-12] In our centre alone, we diagnosed 35 cases over the last 15 years. Only five cases (14%) were interpreted as locally acquired infections, and the remaining 30 infections were imported from another continent, of which 15 (43%) were from Thailand. Eighteen patients were hospitalised and four showed SPFL (haemoptysis, dyspnoea), which necessitated treatment on the intensive care unit (ICU). Of these four patients, serotype testing confirmed Icterohaemorrhagiae as the responsible serovar in three patients. The remaining patient is a case of SPFL from Thailand, imported to the Netherlands, and is discussed below. The aim of this manuscript is to elaborate on leptospirosis, and in particular the severe pulmonary form of leptospirosis, as a potential life-threatening disease.

CASE DESCRIPTION

A 22-year-old man presented to the emergency department ten days after a three-week trip to Thailand. His medical history did not reveal any medical abnormalities. He visited Bangkok and the North of Thailand and travelled through the jungle. One week after rafting in the jungle rivers he developed diarrhoea, myalgia and arthralgia. These symptoms resolved after a couple of days. Four days before presentation he experienced fevers up to 40° C, a nonproductive cough, watery stools, arthralgia and myalgia with pain in his neck and behind his eyes. On physical examination his vital signs were normal. A peripheral vascular redness of both sclerae was observed. Laboratory investigation revealed a mild thrombocytopenia of 110 x 10^9 E/l (normal 150 to 350), leukocytosis of 18.1 x 10^9 E/l (normal 4.0 to 10.5), with marked elevation of neutrophils (90%), total bilirubin 14 µmol/l (normal 0 to 17), alanine aminotransferase (ALAT) 60 IU/l (normal 0 to 40), aspartate aminotransferase (ASAT) 36 IU/l (normal 0 to 40), creatinine 120 µmol/l (normal 75 to 110), C-reactive protein 252 mg/l (normal <5), and albumin 20 g/l (normal 35 to 50). Urine examination showed a mild albuminuria, leukocyturia and erythrocyturia. An initial chest radiograph showed no signs of pneumonia (*figure 1A*). Leptospirosis was suspected, and the patient was admitted and treated with oral amoxicillin 750 mg three times daily. During the night of admission he developed high fever, hypotension, dyspnoea and haemoptysis. A second chest X-ray showed signs suggestive of intrapulmonary bleeding (*figure 1B*), and the patient was transferred to the ICU to be monitored for further respiratory impairment. Subsequently, he was supported with oxygen administration and treated with broad-spectrum antibiotics. A thick smear revealed no malaria parasites and the dengue rapid test was negative. The next day a leptospirosis rapid test was positive and antibiotics were changed to penicillin G 1 million units intravenously four times a day. The pulmonary abnormalities initially progressed (*figure 1C*), but after three days, the patient was discharged to the ward, where the X-ray of the lungs

Figure 1 A. *Chest X-ray of patient at presentation. B. Chest X-ray of patient four hours after presentation. C. Chest X-ray of patient 12 hours after presentation.*



showed substantial improvement. Two days later he left the hospital in good condition. The initial microscopic agglutination test (MAT) performed on serum taken on the day of admission was negative. However, six days later the test was positive for *Leptospira* serovar Mini, strain Sari (titre 1:2560). Blood cultures remained negative for leptospirosis.

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Mortality of severe leptospirosis caused by cardiac and renal failure is roughly 5 to 15%, while SPFL and respiratory failure causes fatalities in >50%.[4,13-17] Pulmonary symptoms are found independently or concurrently with renal and hepatic manifestations. This suggests that SPFL is a different form of leptospirosis, rather than a form of Weil's disease with apparent pulmonary symptoms.[4,18,19] SPFL has now surpassed renal failure as cause of death among patients in Brazil and other parts of the world.[20] Although the serovars Icterohaemorrhagiae and Copenhageni are associated with more severe forms of leptospirosis, it is not possible to associate specific serovars with distinct manifestations of leptospirosis. Apart from the lungs, several other organ systems are generally involved in severe forms of leptospirosis.

Infection begins when leptospiral organisms invade the human body through skin abrasions and mucous membranes, in particular the oropharynx and nasopharynx. The pathogen multiplies and disseminates in blood, cerebral spinal fluid (CSF) and tissues. The mechanism through which *Leptospira* can cause illness has not yet been fully elucidated, although a systemic vasculitis, most commonly affecting the kidneys, liver and lungs, is thought to be responsible for the diverse sequelae described.[20-23]

After an incubation period of two to 30 days, the natural clinical course is typically biphasic. In the first spirochetemic phase, which lasts a week, the organisms cause a wide array of symptoms and can be cultured from blood. The production of antibodies heralds the second, or immune phase, in which the pathogen disappears from blood and CSF, but persists in tissues and is excreted in the urine. In the vast majority of patients a self-limiting subclinical flu-like illness occurs, which carries an excellent prognosis.[24,25] In patients who do develop symptoms, leptospirosis generally manifests as a mild anicteric form with low mortality. Symptoms may include fever, rigors, headache, myalgia, arthralgia, abdominal pain, nausea, vomiting, skin rash, and redness of the sclerae.[26,27] After roughly one week of illness, defervescence coincides with IgM emergence in peripheral blood and quick resolution of symptoms follows, while urinary excretion of spirochetes can persist for weeks or even months.[28] More severe forms of leptospiral infection comprise 5 to 10% of the cases, and can present as the triad of jaundice, impaired renal function and haemorrhage, known as Weil's disease. In contrast, SPFL is characterised by profuse intra-alveolar haemorrhage and seen in less than 5% of patients.[29] SPFL was not part of the original description by Weil, but is rather considered to be a complication occurring early in the course of the disease.[30] Commonly presenting symptoms in severe cases are listed in *table 1*.

Renal involvement manifests in 44 to 67% of patients.[31] Vasculitis may accompany interstitial haemorrhage, while decreased renal perfusion and hypotension facilitate further renal failure.[32] Renal function usually reflects the severity of infection and may require intravenous fluid therapy or even dialysis. Without supportive dialysis, mortality rates range up to 40%, although kidneys normally regain full function.

Lung involvement occurs in 20 to 70% of cases, and the clinical severity ranges from mild dyspnoea to SPFL.[33] Capillary injury in the lungs results in leakage and extravasation of blood cells. The inflammatory reaction, characterised by infiltration by monocytes and neutrophils, is surprisingly mild when compared with vascular damage. Pulmonary oedema, fibrin depositions and proliferative fibroblastic reactions are seen frequently and further hamper respiratory function.[33] These changes can lead to intra-alveolar haemorrhage and acute respiratory distress syndrome (ARDS), which is often fatal.[22,34,35] The initial symptoms of dyspnoea and haemoptysis, combined with auscultation anomalies, indicate severe lung involvement.[34-36] Imaging typically reveals bilateral patchy alveolar infiltrates, like large snow flakes, and areas of consolidation, as reported in the presented case.[37,38] Symptoms usually begin between the fourth and sixth day of disease, and may be fatal in less than 72 hours.[20,33,35] In addition to adequate antibiotic therapy, admission to the ICU and mechanical ventilation may be necessary to secure adequate blood oxygenation.

Although jaundice may be an apparent accompanying sign, liver involvement is usually transient, as it follows liver cell dysfunction rather than hepatocyte loss or apoptosis. Clinically, plasma bilirubin concentration levels are high, especially of conjugated bilirubin, with normal or slightly elevated transaminase plasma concentrations. In addition, thrombocytopenia is frequently observed during the acute stage, probably because of both diffuse intravascular coagulation and immune-mediated mechanisms.[22]

Table 1. *Characteristics, clinical manifestations and laboratory signs in severe forms of leptospirosis*

	Authors					
Variable	**Dupont[14]**	**Gouveia[4]**	**Herrmann-Storck[17]**	**Marotto[36]**	**Paganin[35]**	**Panaphut[15]**
Study population						
Patients	All cases	Hospitalised cases	Hospitalised cases	Hospitalised severe cases	Hospitalised cases	Hospitalised cases
Diagnosis (% of total)	MAT, IgM ELISA (100)	MAT (79), unconfirmed (21)	MAT (81), culture (19)	MAT (85), IgM ELISA (14), culture (1)	MAT (100)	MAT, IgM lepto stick (100)
Country	West Indies	Brazil	Guadelope	Brazil	Réunion	Thailand
Time period	1989-1993	2003-2005	2003-2004	1998-2004	1992-2003	1999
Sub group (% of total)	12 non survivors (18)	44 SPFL cases (9)	24 severe cases (14)	51 SPFL cases (25)	80 ICU admissions (54)	17 non survivors (14)
Mortality, %	18	40	74	31	20	14
Characteristics						
Mean age, y	57*	37.6	53*	39*	*31.3% >46**	38
Male sex, %	100	70*	75	90	-	94
Clinical signs						
Fever, %	42	-	43.5	80.9	-	100
Jaundice, %	100	85	75*	70.9	-	88.2*
Renal involvement						
Oligoanuria, %	75*	47*	43.5*	*1816 ml/24h*‡*	44.3*	76.5*
Urea nitrogen mean, mmol/l	37.7*	42.1	30.6	54.8*	*77.2% >15**	32.8*
Creatinine, µmol/l	550*	345	248*	433*	*83.3% >200**	690*
Cardiac involvement						
Hypotension, %	33	28	35*	82*	-	94.1*
Shock, %	-	-		17*	22.5*	-
Pulmonary involvement	67		47*		86.1	
Dyspnoea, %	58*	42*	31.2*	*31.4*§*	31.5*†	70.6*
Haemoptysis, %	-	15*	20.8*	39*	60	29.4
Neurological involvement	83					
GCS <15, %	-	-	30.8*	34*	-	-
Meningeal signs, %	-	-	16.7	-	-	-
Headache, %	-	-	71.4	-	-	88.2
Laboratory findings						
Mean no. leucocytes, x10^9	23.7*	15.3	*43.5% >12**	13.7*	*50.7% >13**	16.5*
Mean potassium, mmol/l	4.5*	-	3.8	3.9*	*12.5% >5.0*	4.7*
Mean no. thrombocytes, x10^9	71	*29% <100*	*34.8% <50**	63*	*36.9% <50**	56

– = not reported; * = p<0.05 when compared with survivors, non severe or non SPFL cases, values in italics are classified in deviating formats; † = mechanical ventilation needed; ‡ = mean diuresis (ml/24 h); § = mean respiratory rate (n/min); GCS = Glasgow Coma Scale; SPFL = severe pulmonary form of leptospirosis.

PROGNOSIS

Although renal deterioration may be rapid and severe, mortality rates have dropped significantly since the availability of renal replacement therapy. Studies on prognostic factors have been conducted on cohorts in Thailand, Guadeloupe and other countries, and are summarised in *table 2*.[4,14,15,17,25,35,39,40] Factors associated with an unfavourable outcome were pulmonary involvement, oligoanuria, hypotension, blood leucocyte counts above 12.9 x 10^9/l, impaired consciousness, and hyperkalaemia. Additionally, males, smokers and the elderly more often had adverse outcomes. In Sao Paolo, a cohort of 203 patients with SPFL was studied and prognostic factors were identified in a multivariate model. This model, including respiratory rate, serum creatinine, serum potassium, hypotension and Glasgow Coma Scale, was validated to predict the risk of SPFL.[36]

DIAGNOSIS AND DIFFERENTIATION FROM OTHER DISEASES

Given the nonspecific clinical manifestations and the low suspicion, the diagnosis of leptospirosis is often missed.[27,41] However, early recognition of leptospirosis

Table 2. *Odds ratios for different identified prognostic factors*

	Authors					
Variable	**Dupont[14]**	**Herrmann-Storck[17]**	**Marotto[36]**	**Paganin[35]**	**Panaphut[15]**	**Spichler[40]**
No. participants	68	168	203	134	121	370
Outcome	Death	Severity	SPFL	Death	Death	Death
Prognostic factor						
Older age	-	-	-	2.6 *	1.9	2.4 ***
Oligoanuria	9.0 *	5.6 **	-	2.8 **	8.8 **	7.1 ***
High creatinine	-	1.7 *	1.2 **	6.7 ***	6.0 **	4.2 ***
Pulmonary involvement	7.3 *¶	8.7 **#	1.1 ***†	85 ***‡	5.2 *#	9.1 ***
Hypotension / shock	3.0	3.3	69.2 ***	19.2 ***	10.3 *	-
Thrombocytopenia	-	1.0	-	2.8 **	1.0	2.6 ***
High potassium	-	-	2.6 *	1.5	5.9 **	-

SPFL = severe pulmonary form of leptospirosis, defined as massive pulmonary bleeding (haemoptysis >300 ml or aspiration of fresh blood after endotracheal intubation which did not clear with suctioning) and respiratory failure requiring mechanical ventilation, and mortality; * = p=<0.05; ** = p=<0.01; *** = p=<0.001; - = not reported; † = odds ratio for respiratory rate; # = odds ratio for abnormalities on chest auscultation; ‡ = odds ratio for mechanical ventilation needed; ¶ = odds ratio for alveolar infiltrates.

may be crucial, especially since acute respiratory distress in SPFL may progress swiftly. In tropical regions with a high prevalence of multiple serovars that cause mild disease, leptospirosis is often not distinguished from other causes of undifferentiated fevers, of which dengue is the most common.[19,41] Peripheral redness of the sclera may differentiate between dengue and leptospirosis. This redness is often referred to as 'conjunctival suffusion', but is actually an episcleritis that is not irritating or itching. The headache in leptospirosis is mainly occipital and may mimic meningismus whereas the headache in dengue is more frontal and retrobulbar. Myalgia is common in leptospirosis, classically in the lower legs, but also severe abdominal pain may occur. Nausea and vomiting are quite common in leptospirosis and rather rare in dengue.

During the spirochetemic phase the organism can be cultured from blood, CSF, and urine samples. A positive culture provides definite proof of infection, but it is too slow to contribute to an early diagnosis. Alternatively, PCR on blood, urine or CSF samples can rapidly confirm the diagnosis in the spirochetemic phase.

Serology is applicable after five to ten days post onset of symptoms, when antibodies against *Leptospira* reach detectable levels. The MAT is the gold standard due to its high specificity. A live panel of *Leptospira* representing all pathogenic serovars in the area is required to adequately perform this test. False-negative results can occur when the infecting serovar is not represented in the panel, as infection may be acquired in regions where other serovars are endemic.[42]

The IgM ELISA is a genus-specific test that is widely applicable, standardised and can detect infection slightly earlier than MAT.[1] However, low specificity and cross reactions warrant confirmation by MAT. Similar to dengue antibody tests, leptospira ELISA or MAT are often negative in the very early stage of disease. In contrast, dengue antigen tests are helpful in the very early stages of disease and could help to differentiate between dengue and leptospirosis.

TREATMENT

At present, there is no consensus on the most effective and safe antibiotic treatment for leptospirosis, as convincing evidence is still lacking.

In most mild cases, leptospirosis is self-limiting. Amoxicillin, ampicillin, doxycycline or erythromycin can reduce symptoms and prevent further progression. However, in a more severe manifestation, treatment with cephalosporins or high doses of penicillin intravenously is recommended and early administration is associated with more favourable outcomes.[1,43,44] Mortality can also be reduced by adequate monitoring, supportive therapy and correction of electrolyte balances by intravenous fluid administration or renal replacement therapy. There is only modest evidence that plasma exchange or immunosuppression may improve survival of patients with SPFL.[45-48] In Brazil, a randomised placebo-controlled trial is currently evaluating the efficacy of pulse methylprednisolone in SPFL patients.[45-48]

Prevention may be the most effective approach to control the zoonosis. Doxycycline as chemoprohylaxis may prevent further infection and reduce morbidity and mortality.[49,50] To date, vaccination is inadequate,[51] not widely available

and provides only limited protection for specific serovars.[1] Serovars are to a large extent associated with their chronic carriers and serovar information may therefore be important for effective control and prevention.

CONCLUSIONS

Leptospirosis is a zoonosis with a wide range of clinical manifestations that can cause severe morbidity and mortality if left untreated. The disease is endemic in tropical regions, but may be increasing in temperate regions because of global warming. While leptospirosis is predominantly an occupational disease at a global scale, it has been marked as an emerging recreational disease in travellers to tropical and subtropical countries, as illustrated by the presented case. In recent years, the severe pulmonary form of leptospirosis (SPFL) seems to emerge as a distinct manifestation with high mortality rates. The course of the disease should be carefully monitored as respiratory distress may progress rapidly and requires adequate work-up and intervention. Treatment consists of antibiotics and should certainly be considered when a severe (pulmonary) course is suspected.

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Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

The changing prevalence of upper gastrointestinal endoscopic diagnoses: a single-centre study

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ABSTRACT

Introduction: Upper gastrointestinal (GI) endoscopy is increasingly applied in daily practice. Not many data are available on yearly changes in diagnostic yield, nor on changes in morbidity.

Aim: To study the possible changes in occurrence of abnormalities in the oesophagus, stomach and duodenum.

Methods: All consecutive upper GI endoscopies performed over a period of 20 years were included. Important diagnoses were defined as: oesophagitis, metaplastic epithelium in the oesophagus, hiatal hernia or defective sphincter, ulcers, erosive or nodular gastritis, operated stomach, and cancer.

Results: In the 20-year period, 29,218 upper GI endoscopies were performed. 'Open-access' endoscopy, i.e. at the request of the general practitioner, showed a clear increase in the first ten years and remained stable thereafter. A trend towards an increase in macroscopic abnormalities was seen. The presence of hiatal hernia and defective sphincter showed a significant increase over 20 years, while the number of patients with reflux oesophagitis showed a less impressive, but still significant increase ($p<0.001$) in the first ten years and remained stable thereafter. There was an impressive decrease in the incidence of peptic ulcer disease. Prevalence of oesophageal cancer showed a gradual increase, although the numbers were very low.

Conclusions: In a period of 20 years the diagnostic yield of upper GI endoscopy showed significant changes. Reflux disease increased in prevalence while peptic ulcer disease decreased.

KEYWORDS

Upper GI endoscopy, diagnostic yield, oesophagitis, peptic ulcer disease, epidemiology, endoscopy

INTRODUCTION

Upper gastrointestinal (GI) endoscopy is widely used in normal daily practice. It is considered the investigation of choice in cases of dyspepsia, reflux symptoms or alarm symptoms and is mandatory for a precise diagnosis in cases of these upper abdominal complaints.[1]

The advantage of direct visual inspection of the oesophageal, gastric and duodenal mucosa is obvious. Biopsy specimens can be taken for histological or microbiological examination. From many epidemiological studies it is well known that morbidity patterns can show changes in the course of the years. This is known for cancer, cardiovascular diseases and diabetes. In Gastroenterology the incidence of distal gastric cancer and the presence of *H. pylori* is decreasing due to a lower acquisition of the micro-organism. Given these epidemiological data, it is surprising that little is known about the changes in the diagnostic yield of upper GI endoscopy.

In the past, a study was presented on the outcome of upper GI endoscopy in a period of ten years.[2] The present study is an extension of that study in which the period was doubled to 20 years. Changes in prevalence of important upper GI diagnoses in this period were studied.

MATERIAL AND METHODS

All consecutive diagnostic upper GI endoscopies performed in a period of 20 years in a prospective dataset (January 1992 to December 2011) in the Zaans Medical Centre, the community hospital of the Zaanstreek region, were included. Endoscopies were done at the request of internists, gastroenterologists, and sometimes paediatricians, cardiologists or surgeons. In addition, there is an open-access facility for general practitioners. The

number of inhabitants in the Zaanstreek region increased from 131,262 in 1992 to 146,937 in 2011.

From 1992 until 2006 two gastroenterologists performed all the endoscopies. In 2006 a third gastroenterologist was added to the team.

Endoscopy was performed with Olympus endoscopes (Olympus Nederland BV, Zoetermeer the Netherlands). In 1992 fibreoptic endoscopes were used, from 1993 the EVIS 100 video endoscopes were gradually introduced. Since the beginning of 2000, this system has been gradually replaced by the EXERA 160 and 180 system of Olympus.

The procedure was done without sedation or local anaesthesia in 99% of the cases.

The results of the procedure were noted in a written standardised report. From 2003 a custom-made computerised system was used (Endobase™ Olympus). Biopsy specimens were taken to confirm the macroscopic diagnosis if necessary.

Important endoscopic diagnoses were defined as oesophagitis, metaplastic epithelium in the oesophagus, hiatal hernia or defective sphincter closure, ulcer disease, erosive or nodular gastritis, and cancer. In addition, the operated stomach was scored.

Hiatal hernia was defined as a distance of more than 2 cm between the diaphragm and the Z line. Defective or insufficient lower oesophageal sphincter closure was defined as a widely open lower oesophageal sphincter during introduction as well as retrieval of the endoscope with the Z line at the level of the diaphragm. Oesophagitis was scored if erosions or ulceration was present in the oesophagus. Scoring of the oesophagitis was done with the old well-known Savary-Miller system. Endoscopic gastritis was only scored if nodularity or erosions were seen in the antrum.[3] Erythema, vascular pattern, rugal hypertrophy, atrophy, and reddish streaks were not taken into account because of the possible inter-observer variability. Barrett's oesophagus was defined as the presence of cylindrical epithelium in the oesophagus.

Each year all endoscopy reports were stored in a prospective computerised database system.

Statistical analysis was done with chi-square test for contingency tables. A value below 0.05 was considered statistically significant. Each table in the chi-square test consisted of the presence or absence of a specific abnormality.

The ethics committee of the Zaans Medical Centre approved the study.

RESULTS

In the 20 consecutive years 29,218 upper GI endoscopies were carried out in 13,937 men (48%) and 15,281 women (52%). The mean number of endoscopies per year was 1460 (range 1280-1631) (*figure 1*).

Figure 1. *Number of upper GI endoscopies each year in the last 30 years*

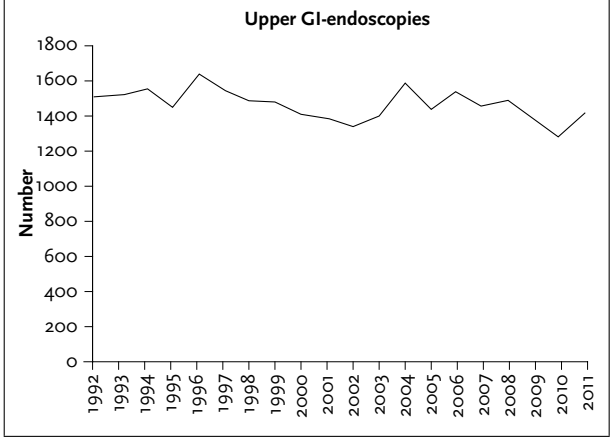
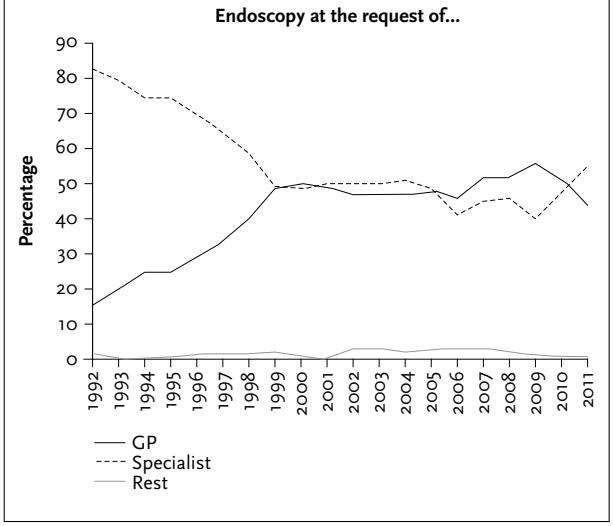


Figure 2 shows that 'open-access' endoscopy, at the direct request of the general practitioner, revealed a clear and significant increase in the first ten years and remained stable thereafter. Obviously, the relative number of procedures performed at the request of the internist and the gastroenterologist showed a parallel decrease in the first ten years.

Of all procedures, 1808 were done because of direct endoscopic follow-up of prior diagnosed abnormalities. This was due to upper GI bleeding or follow-up for gastric ulcer or cancer. The results of these endoscopies were excluded from the present analysis. However, these procedures were included in the analysis of the applicants for gastroscopy.

Figure 2. *Number of endoscopies each year at the request of general practitioners, and specialists; rest indicates endoscopies done at the request of surgeons, paediatricians or cardiologists*



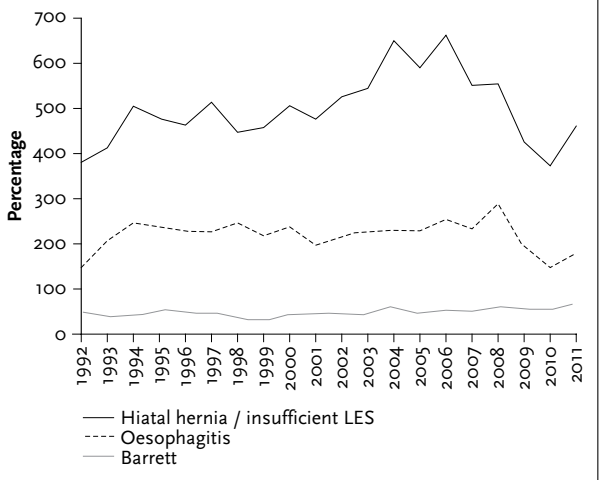
The overall yield of the upper GI endoscopy in the consecutive years showed a trend towards an increase in macroscopic abnormalities from 61% in 1992 to over 70% at the end of the study. The number of inconclusive endoscopies (i.e. the patient removed the endoscope before adequate inspection was possible or refused the procedure) was low and remained low (mean 15, range 6 to 26 procedures per year).

Hiatal hernia and/or defective lower sphincter closure was seen in a mean of 39% of the procedures (range 29 to 46%), oesophagitis in 16% (range 15 to 21%), Barrett's metaplasia in 3.9% (range 2.2 to 4.9%), gastric ulcer in 1.8% (range 1.3 to 5.6%), duodenal ulcer in 2.1% (range 1.3 to 5.6%), oesophageal cancer in 1.3% (range 0.2 to 1.8%), gastric cancer in 1.1% (range 0.6 to 2.3%), and finally erosive or nodular gastritis in 5.9% (range 2.4 to 10%).

The prevalence of hiatal hernia and insufficient lower oesophageal sphincter closure showed a statistically significant increase in 20 years ($p<0.001$), while the number of patients with reflux oesophagitis showed a less impressive but still significant increase ($p<0.001$), especially in the first ten years and remained stable thereafter (*figure 3*). The prevalence of metaplastic epithelium in the oesophagus did not change in the course of the years. Since 2006 the prevalence of these findings decreased, but this did not affect the trend lines.

Figure 4 shows a very impressive decrease in the prevalence of peptic ulcer disease. In *figure 5* the prevalence of oesophageal and stomach cancer in the 20-year period is presented. Prevalence of oesophageal showed a very gradual increase, although the numbers for cancer are low. *Figure 6* shows the presence of erosive and/or nodular gastritis.

Figure 3. *Relevant endoscopic findings seen in the oesophagus in the consecutive years*



LES = lower oesophageal sphincter.

Figure 4. *Prevalence of peptic ulcer disease in the consecutive years*

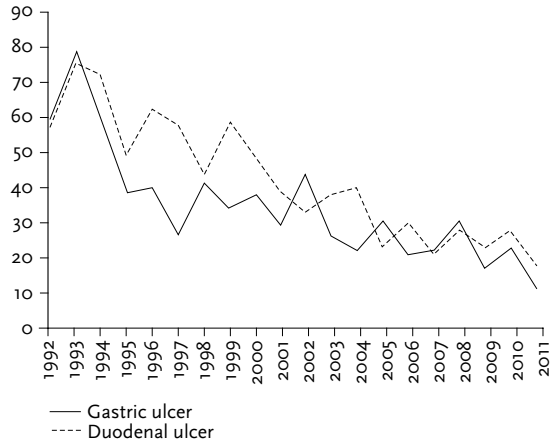


Figure 5. *Prevalence of oesophageal and stomach cancer in the consecutive years*

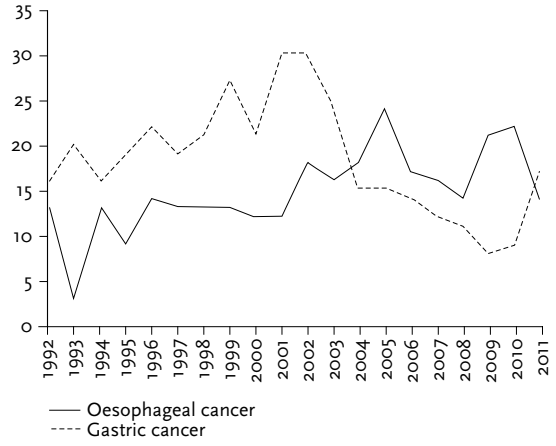
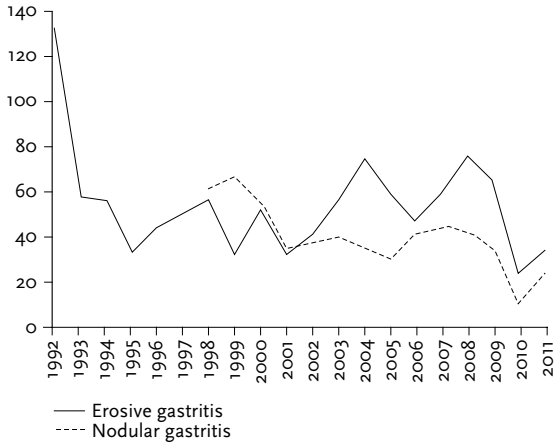


Figure 6. *Prevalence of endoscopic signs of gastritis in the consecutive years*



DISCUSSION

This study shows the diagnostic yield of upper GI endoscopy in a period of 20 years. It reflects the incidence and prevalence of findings in the oesophagus, stomach and duodenum in the Zaanstreek region. Patients with upper abdominal complaints in the Zaanstreek region are sent to their local regional hospital for diagnosis, i.e. endoscopy, and treatment. There is no waiting time for gastroscopy in the Zaanstreek region. The average time between the decision to do an endoscopy and the actual gastroscopy varies from one to ten days. Hence it can be assumed that not many patients move on to other hospitals in the vicinity, and that the results reflect the upper GI morbidity in the Zaanstreek region. Of course, the population under study shows selection bias because each patient was actually sent for upper GI endoscopy.

With the possibility of open-access upper GI endoscopy at the direct request of the general practitioner, the number of procedures showed a clear escalation in the 1990s.[4,5] This increasing number of upper GI endoscopies at the direct request of the general practitioner reflects the shift from diagnosis and management of dyspepsia and reflux disease from hospital-based medicine to primary care.

The number of endoscopies revealing no abnormalities is in accordance with the literature.[6,7] No abnormal macroscopically findings were detected in approximately 27% of cases.

In the first ten years a clear increase in the presence of reflux oesophagitis was noted. In the second period this finding remained rather constant. On the other hand, the trend line for hiatal hernia and defective lower sphincter closure showed an on-going increase in this period. However, the prevalence of hiatal hernia and defective sphincter closure shows a decrease in 2008, 2009, and 2010. In 2011 the prevalence increased. The explanation for this phenomenon is not obvious. But, there were some changes in endoscopists in these years and inter-observer variability could be responsible for the decrease.

Around 17% of the diagnostic procedures revealed oesophagitis. The possible explanation for the steadiness in reflux oesophagitis in the second period of ten years is the fact that according to guidelines in general practice, many patients are already being treated with acid-suppressive therapy before undergoing endoscopy. Since hiatal hernia is a clear and well recognised risk factor for reflux disease, the conclusion can be drawn that the incidence and prevalence of reflux disease has increased in 20 years.

The prevalence of Barrett's metaplasia in the oesophagus did not change in the course of the years. Since the development of metaplastic epithelium can be considered the consequence of long-standing reflux, this is surprising. The reason for the steady prevalence could be the fact that most patients with reflux disease are being treated adequately with acid-suppressive drugs thereby rendering the refluxate less deleterious and taking away the reason for the development of Barrett's metaplasia.

In the course of the 20 years, the prevalence of gastric and duodenal ulcer dramatically decreased. This can be explained by two phenomena. First: the decreasing acquisition of *H. pylori*, the major cause of peptic ulcer disease.[8-10] Secondly: the fact that patients on long-term NSAID therapy in the Netherlands receive standard gastric protection in accordance with local guidelines, i.e. proton pump inhibitor therapy.

Erosive and nodular gastritis are signs compatible with the presence of active *H. pylori* gastritis. Nodular gastritis was noticed for the first time in 1997 and scored separately, obviously due to the introduction of the video endoscopy. The macroscopic detection of gastritis has improved significantly. The visualisation of the gastric mucosa is much better with the video systems, and more details can be seen. But, in line with the decrease in prevalence of this gastric infection, these signs also decreased.

The diagnosis of Billroth I and II resection also showed a clear decrease in the consecutive years. The reason is very obvious. Since the discovery of *H. pylori* as the major cause of peptic ulcer disease, the reason for doing this anti-ulcer surgery has disappeared.

The number of cases of stomach cancer shows a gradual decrease in the second ten years of the study, while for oesophageal cancer there is a steady increase over 20 years. However, the numbers are too low to draw firm conclusions.

This single-centre study clearly shows major changes in the yield of upper GI endoscopy and hence in morbidity patterns. Especially, the increasing numbers of patients with reflux disease (reflux oesophagitis as well as hiatal hernia or defective lower oesophageal sphincter) implicate a rise in the use of acid-suppressive therapy. On the other hand the acquisition of *H. pylori* is decreasing resulting in a decrease of peptic ulcer disease.

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CASE REPORT

Severe hepatitis with coagulopathy due to HSV-1 in an immunocompetent man

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ABSTRACT

Severe hepatitis due to herpes simplex virus type 1 (HSV-1) in immunocompetent patients is a very rare event. The acute hepatitis may lead to fulminant deterioration of liver function and can be rapidly fatal. The diagnosis should be considered in case of severe hepatitis of unknown cause. Early consideration of HSV-1 hepatitis in the differential diagnosis in an adult patient, also with an apparently normal immune system, is important and early initiation of antiviral treatment may be lifesaving in this situation.

KEYWORDS

Herpes simplex infection, hepatitis, HSV-1, immunocompetent

What was known on this topic?

Systemic herpes simplex infection with acute severe hepatitis is a rare complication of HSV-1 infection, especially in immunocompetent patients. The diagnosis is often missed due to the absence of specific signs or symptoms. Severe HSV-1 hepatitis is usually marked by significant elevations in transaminases (ASAT higher than ALAT), and a mild or absent hyperbilirubinaemia and coagulopathy. The course of the disease is often rapid and frequently fatal. The mortality rates are high mainly because of delayed diagnoses and treatment with antiviral therapy.

What does this case add?

This report is interesting, since it involves an immunocompetent patient with severe HSV-1 hepatitis. This patient recovered completely with adequate antiviral treatment with acyclovir. In a sudden onset of severe hepatitis of unknown aetiology, rapid initiation of antiviral therapy should also be considered in immunocompetent patients, especially when acute liver failure is suspected.

INTRODUCTION

Herpes simplex infection (HSV-1 or HSV-2) is a common and usually benign, self-limiting disease, which normally presents with mucocutaneous lesions and mild viraemia, although the primary episode can cause rather severe local infection.[1,2] Systemic herpes simplex infection with acute hepatitis is a rare complication of HSV-1 infection, especially in immunocompetent patients.[2] HSV hepatitis is often missed due to the absence of specific signs or symptoms. Clinical manifestations are nonspecific, which include flu-like illness, fever and abdominal discomfort. Severe HSV-1 hepatitis is usually marked by significant elevations in transaminases (aspartate aminotransferase (ASAT) higher than alanine aminotransferase (ALAT)), a mild or absent hyperbilirubinaemia, coagulopathy, encephalopathy and skin rash. The course of the disease is often rapid and frequently fatal. The mortality rate can be as high as 90%, mainly because of delayed diagnosing and treatment with antiviral therapy.[2,3]
We describe a rare case of a very sudden onset of severe hepatitis in an immunocompetent male with coagulopathy due to herpes simplex infection (HSV-1). This case illustrates that awareness of HSV-1 hepatitis, though extremely rare in immunocompetent patients, is important, since timely recognition and early initiation of antiviral therapy improves survival considerably.

CASE REPORT

A 57-year-old man, who had been ill for three days with fever, sweating and chills, was referred to our hospital. Ten days after his return from a nine-day vacation to Gambia

he became ill. He had taken malaria prophylaxis and he was vaccinated for DTP, hepatitis A and B. He had stopped smoking eight months ago and he had an alcohol intake of one drink per day.

Physical examination showed a blood pressure of 99/62 mmHg, a pulse of 76 beats/min, an oxygen saturation of 96% and a temperature of 38.5 °C. He was noted to have a few small vesicles in his neck. Lung and heart sounds were normal. During abdominal examination, no abnormalities were found. Laboratory assessment revealed a high C-reactive protein of 75 mg/l (<5), a low platelet count (102 x 10^9/l) and a leucocyte count of 5.4 x 10^9/l. Kidney function was normal. The liver functions where not measured on day 1 of hospitalisation. Chest radiography showed no abnormalities. Because of progressive fever, intravenous amoxicillin/clavulanic acid was started. Intravenous acyclovir was also initiated because of a clinical suspicion of a disseminated varicella zoster virus infection, given the skin lesions in his neck.

On day 2, laboratory test results revealed elevated transaminases (ASAT 1348 U/l, ALAT 852 U/l) with normal bilirubin 12 mmol/l. Leukopenia (2.4 x 10^9/l) and a low platelet count (69 x 10^9/ l) were found. Ultrasound examination showed a normal aspect of the abdominal organs. Although hepatitis due to the malaria prophylaxis was a possibility, a serious bacterial or viral infection was thought to be far more probable.

Bacterial and fungal cultures, including cultures of blood, urine and sputum were unrevealing. Malaria testing by antigen testing and microscopy were repeatedly negative. Serological tests for hepatitis A, B and C viruses, cytomegalovirus (CMV), Ebstein-Barr virus (EBV), influenza and human immunodeficiency virus showed no evidence of a recent infection with any of these viruses.

The patient's condition worsened during hospitalisation. There were signs of disseminated intravascular coagulation (INR: 2.2, prothrombin time (PT) 21 sec, fibrinogen 1.6 g/l, D-dimer: 70649 mg/l) with spontaneous gastrointestinal and urinary tract haemorrhages and respiratory failure with pleural effusion. On day 3 he was admitted to the intensive care unit with melaena and haemodynamic instability. He had severe hepatitis with maximum levels of transaminases: ASAT 4530 U/l and ALAT 1978 U/l. Acute liver failure was suspected, but hyperbilirubinaemia was absent (*table 1*), which made acute liver failure less likely.

Liver biopsy was not performed because of a high risk of bleeding and the absence of hyperbilirubinaemia. CT scan, thoracentesis and gastroscopy did not reveal other pathology. A crista biopsy was performed which revealed no signs of myelodysplasia.

African viral haemorrhagic fevers (VHF) such as Dengue, Lassa, Marburg and Ebola where considered. Given the clinical picture, however, there was no immediate suspicion of VHF. The Dengue antigen test was negative.

Table 1. *Laboratory values in the patient*

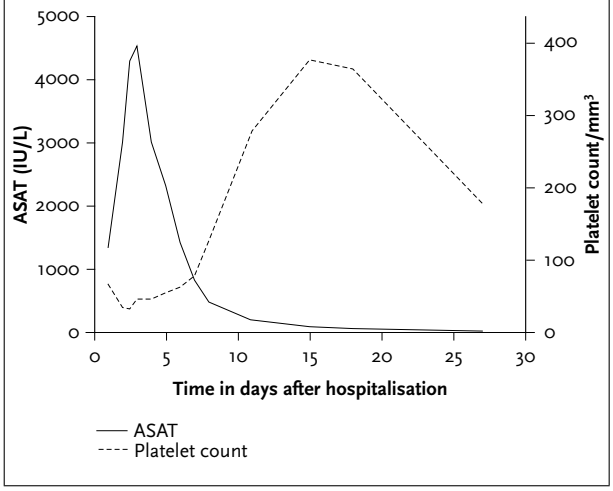
Time in days after hospital admission	1	2	3	18	Normal ranges
Haemoglobin	8.9	8.0	7.8	7.2	8.5-11.0
Leucocyte/mm³	5.4	2.4	2.0	4.0	4.0-10.0
Platelet/mm³	102	69	34	375	150-400
ALAT (IU/l)		852	2134	67	0-45
ASAT (IU/l)		1348	4292	40	0-40
LDH (IU/l)		1042	2134	331	0-250
Total bilirubin (µmol/l)		12	13	16	0-17
D-dimer (µg/l)			70649		0-500
Fibrinogen (g/l)		1.9	1.6		2.0-4.5
INR			2.2		0.8-1.2
APTT time/sec		21	59	31	26-34
Prothrombin time/sec		21		15	12-15
CRP (mg/l)	75	72	55	16	0-10

ALAT = alanine aminotransferase; APTT = activated partial thromboplastin time, ASAT = aspartate aminotransferase; CRP = C-reactive-protein; INR = international normalised ratio; LDH = lactate dehydrogenase.

The patient also developed a tremor and impaired consciousness, possibly caused by encephalitis.

On day 7 molecular analysis by polymerase chain reaction of EDTA blood revealed a high viral load (cycle value (CT): 17) of herpes simplex virus type I (HSV-1), which established the diagnosis of HSV hepatitis. Antibiotics were stopped and intravenous acyclovir (10 mg/kg of body weight every eight hours) was continued. On day 8 of intravenous acyclovir the patient started to improve clinically until full recovery, including normalisation of hepatic enzymes and coagulation (*table 1* and *figure 1*). HSV DNA was not measured over time, but a second EDTA-blood sample taken one day later than the first, analysed by a different laboratory, also revealed a high viral load (CT: 18.6) of HSV.

Figure 1. *Changes in serum aspartate aminotransferase (ASAT) and platelet count during hospital stay. Acyclovir is started on day 1*



DISCUSSION

In this report we present a case of an immunocompetent man with a very sudden onset of severe HSV-1 hepatitis with signs of disseminated intravascular coagulation (DIC).

HSV-1 is an uncommon cause of hepatitis. It is known that HSV-1 can induce hepatitis during pregnancy and in immunocompromised hosts.[4] To our knowledge, only eight cases of severe hepatitis due to HSV in immunocompetent adults have been reported.[2,5-7] HSV-1 hepatitis presents with nonspecific symptoms such as fever, headache, nausea, vomiting and abdominal pain. Diagnosis is often delayed because of absence of specific skin lesions. Previous reports have noted that mucocutaneous lesions are only present in up to 50% of cases.[2,8]

Strongly elevated liver enzymes, leukopenia, relatively low bilirubin level with DIC and mucosal herpetic lesions are clues to the diagnosis. The triad of fever, elevation of transaminases and presence of leukopenia is suggestive of a viral hepatitis such as herpes simplex hepatitis. The pathogenesis of fulminant HSV-1 hepatitis is unknown. Proposed mechanisms include an impaired immune system or infection with a particular virulent strain.[8,13]

The diagnosis of HSV-1 hepatitis should be considered in any patient with acute hepatitis, particularly with fever, leukopenia, and a negative hepatitis serology for hepatitis A, B, C, D, E,[9] EBV and CMV especially when DIC is present and liver failure is suspected.[11,12] A definitive diagnosis was made ante-mortem in only about one-third of the patients with a severe HSV hepatitis reported in the literature.[13]

Liver biopsy is the gold standard to diagnose HSV hepatitis, but is often contradicted in the context of coagulopathy.[4] Transjugular liver biopsy minimises the risk of bleeding and should be considered if DIC is present to accelerate the diagnosis, which could be lifesaving. Beersma *et al.* illustrated that quantification of HSV DNA levels by PCR in plasma or EDTA blood is a fast, sensitive and specific test to diagnose HSV hepatitis in patients with acute liver failure.[13] Rapid initiation of antiviral treatment is associated with improved outcomes in patients with HSV hepatitis.[12,13] This case underscores the need for early consideration of HSV-1 hepatitis in the differential diagnosis in an adult patient with an apparently normal immune system. Early initiation of acyclovir, although given because of a suspicion of generalised varicella-zoster virus infection, might have been lifesaving in this case.

CONCLUSION

In conclusion, severe hepatitis due to HSV in immunocompetent patients is a very rare event and is rapidly fatal, if unrecognised and not treated with intravenous acyclovir. This case illustrates that, in case of severe hepatitis of unknown cause, rapid initiation of antiviral therapy should be also considered in immunocompetent patients, especially when acute liver failure is suspected.

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PHOTO QUIZ

Pythons and a palmar rash

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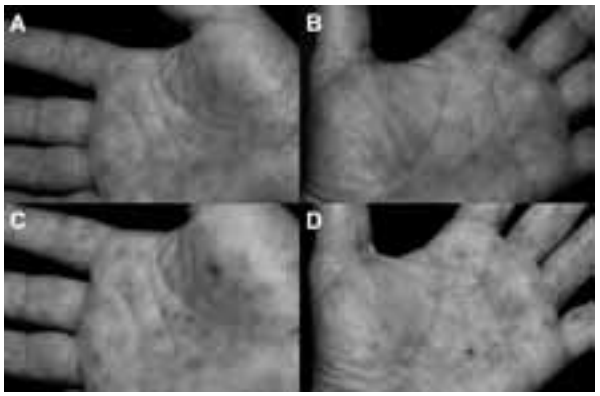
CASE REPORT

A 55-year-old woman with intravenous drug abuse in the past presented to our emergency department with a three-day history of fever with headaches, myalgia and neck pain. On the fourth day her fever resolved spontaneously and a non-itching, red spotted rash developed on both hand palms and foot soles. She also complained about nausea and joint pain of the wrists and fingers. She had not been sexually active for over eight years. On further questioning she told us she keeps pythons and boa constrictors as pets. For medication she takes pantoprazole, promethazine and acetaminophen. The last few days she had taken more than ten Ibuprofen tablets a day because of her wrist pain. On physical examination her blood pressure was 145/85 mmHg and temperature 37.9 °C. The left thenar eminence was enlarged and painful and a non-blanchable maculopapular rash was seen on both palms and both soles (*figure 1*). Some pustules were present and cultures were taken. She had no cardiac murmurs or lymphadenopathy. Her laboratory results showed a thrombocytopenia of 116 x 10^9/l, leucocytes of 8.6 x 10^9/l, C-reactive protein of 235 mg/l and a serum creatinine of 68 μmol/l. Urine analysis was positive for protein, erythrocytes and leucocytes. The chest X-ray was normal.

Figure 1. *The fourth day after the first symptoms developed, a non-blanchable maculopapular lues-like rash was noted on both palms of the left (A) and right (B) hand. Note the difference between the left and right thenar eminence. On day 7, three days after initiating doxycycline, her systemic symptoms had resolved but the palmar lesions on the right (C) and left (D) palm were slightly worse. A week later most of the skin lesions had improved with some local desquamation before complete resolution after three weeks*



WHAT IS YOUR DIAGNOSIS?

See page 233 for the answer to the photo quiz.

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PHOTO QUIZ

Nodules on the tongue and thick lips

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CASE REPORT

A 40-year-old man presented to the Emergency Department with recurrent abdominal symptoms. He often presents with complaints of abdominal pain, constipation, and lack of appetite. In earlier visits, abdominal X-rays have sometimes shown a distended intestine and fluid levels. A computed tomography (CT) scan from an earlier admission showed mild diverticulitis. His medical history reveals medullary thyroid cancer at the age of 8 years, for which he underwent a thyroidectomy. Due to bilateral pheochromocytomas, the adrenal glands were removed at 34 and 35 years of age. He has been admitted several times for severe weight loss caused by the frequently recurring abdominal pain and has psychosocial problems resulting from this burden on life.

Figure 1. *Numerous yellow-white nodules on the tongue of a patient with a history of endocrine neoplasms*

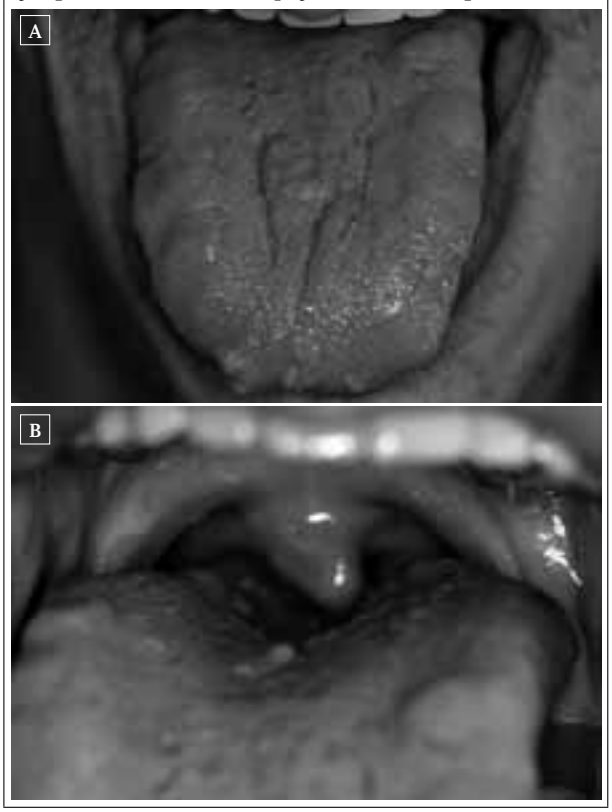
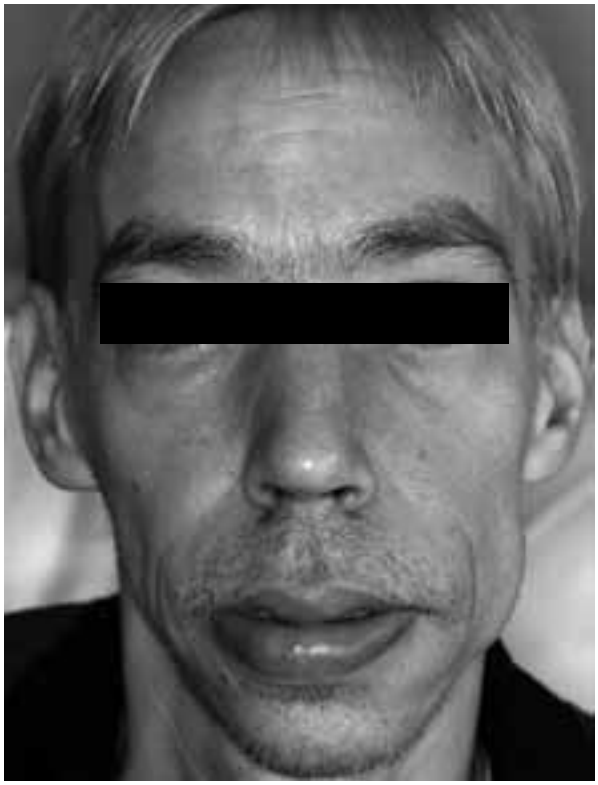


Figure 2. *A patient aged 40 years with Marfanoid facial appearance*



Apart from diffuse abdominal pain, physical examination shows nodules on the tongue, thick lips, and a Marfanoid appearance (*figures 1* and *2*). The nodules on the tongue and thick lips are pathognomonic for the underlying syndrome causing the gastrointestinal complaints.

WHAT IS YOUR DIAGNOSIS?

See page 234 for the answer to the photo quiz.

Netherlands
The Journal of Medicine

A pulmonary shadow after lobectomy: an unexpected diagnosis

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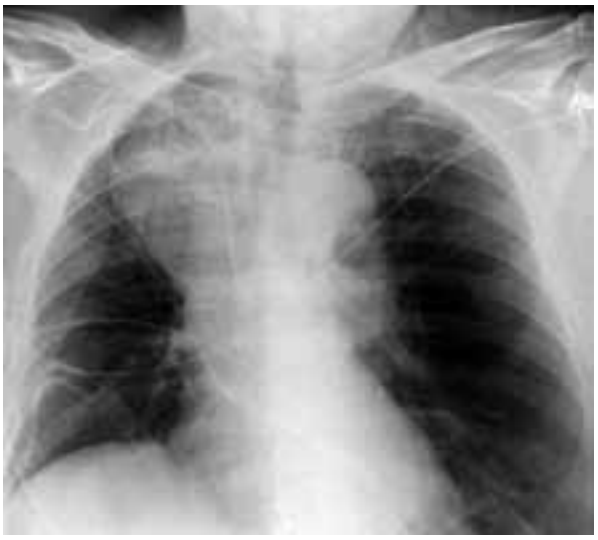
CASE REPORT

A 62-year-old man underwent a right upper lobectomy because of a recently diagnosed non-small cell lung carcinoma pT2aN0M0, stage IB. His medical history showed chronic obstructive pulmonary disease, Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification 2 and a myocardial infarction in 2009.
During the operation there were no complications. A few hours after the operation the patient could be extubated. Postoperatively, the patient had no complaints, nor were there any abnormalities on physical examination. His routine laboratory results showed slight anaemia (haemoglobin 7.0 mmol/l), a slightly decreased haematocrit level (0.32 l/l) and an increased level of C-reactive protein (88 mg/l). The chest X-ray one day after surgery showed a dense opacity in the upper zone of the right lung (*figure 1*). On the first day the pleural drain produced 1 litre of serosanguinolent fluid per 24 hours, gradually diminishing to 500 ml per 24 hours, with moderate air leak.

Figure 1. *Postoperative chest X-ray day 2*



Dense opacity in the upper zone of the right lung, to some extent radiolucent with pleural lining.

Figure 2. *CT thorax cross-section: tapered occlusion of the right middle lobe bronchus*

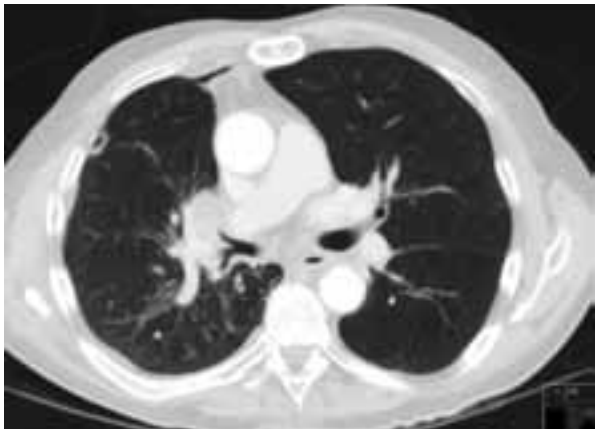
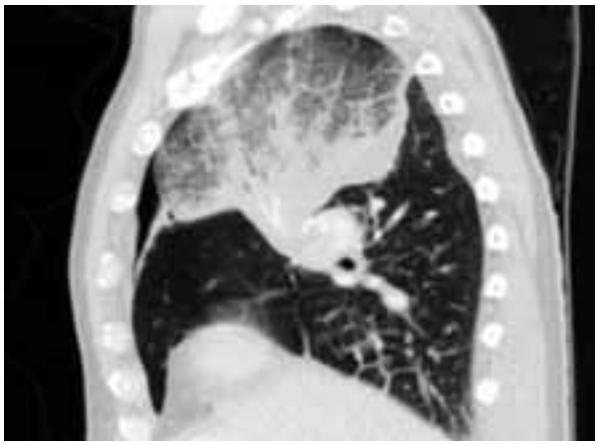


Figure 3. *CT thorax sagittal section: consolidation of pulmonary segment*



Over the following days the patient developed fever and his C-reactive protein level increased (230 mg/l). His chest X-ray remained unchanged. We additionally performed a CT scan, shown in *figures 2* and *3*.

WHAT IS YOUR DIAGNOSIS?

See page 235 for the answer to the photo quiz.

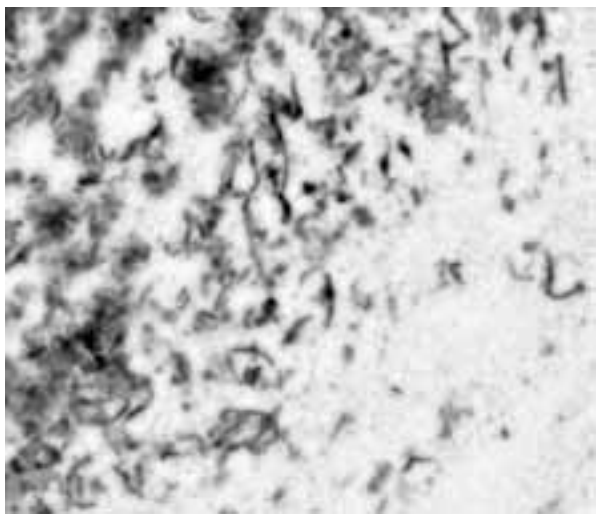
ANSWER TO PHOTO QUIZ (PAGE 230)

PYTHONS AND A PALMAR RASH

DIAGNOSIS

Many people who keep snakes also breed rats to feed their pets. After thorough questioning the patient admitted that she also bred rats and that she regularly gets bitten. She did not mention this because she did not think of it as being abnormal or helpful for finding the cause of her complaints. Her clinical presentation combined with a history of recent rat bites is very suggestive of 'rat bite fever'. We assumed that the elevated creatinine and abnormal urine findings were caused by excessive NSAID usage. Our patient was given doxycycline orally and was advised to stop taking Ibuprofen. On presentation to the outpatient clinic four days later her complaints had improved, and the swelling of the thenar eminence and the rash on her palms and soles had decreased. Her serum creatinine had normalised. The Gram stain of the pus culture showed a pleomorphic Gram-negative bacillus 0.3 to 0.5 µm wide and 1 to 5 µm long, occasionally forming up to 150 µm long filaments and beadlike chains characteristic for the *Streptobacillus moniliformis* (*figure 2*).[1] We confirmed our diagnosis using S16 rRNA sequencing.[2,3]

Figure 2. *The Gram-stain of the pus culture showed a pleomorphic Gram-negative bacillus 0.3 to 0.5 µm wide by 1 to 5 µm long occasionally forming up to 150 µm long filaments and beadlike chains characteristic for the Streptobacillus moniliformis*



As differential diagnosis we thought of Weil's disease, parvovirus B19, coxackievirus, enteroviruses and syphilis. Syphilis appeared less likely given the fact that the patient had not had any sexual intercourse for over eight years. However serology for *Treponema pallidum* was positive. We concluded that this was a false-positive result, caused by a cross reaction with the *Streptobacillus moniliformis*.[4]

Streptobacillus moniliformis is part of the normal nasopharyngeal flora of rats and other rodents.[5] Humans can be infected by bite wounds or scratches from infected rodents. Ingestion of food or beverages contaminated with infected excrements can also cause disease in humans.[4] Remarkably, wounds at the bite site heal quickly with minimal inflammation, often before the first symptoms of rat bite fever appear. Classical symptoms of rat bite fever include fever, skin rash on the peripheral extremities and migratory polyarthralgias. Complications are endocarditis, myocarditis, septic arthritis, systemic vasculitis, meningitis, hepatitis and focal abscesses. Untreated, rat bite fever has a mortality rate of approximately 10%.[4] Appearance of the described rash, especially the haemorrhagic pustules, in the setting of an otherwise nonspecific set of symptoms, should strongly suggest the diagnosis of rat bite fever.

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ANSWER TO PHOTO QUIZ (PAGE 231)

NODULES ON THE TONGUE AND THICK LIPS

DIAGNOSIS

This male patient, aged 40 years, has multiple endocrine neoplasia (MEN) syndrome type 2B.[1] MEN 2B is inherited as an autosomal dominant trait.[1] The mother and sister of this patient were also diagnosed with the syndrome. The characteristic features include medullary thyroid cancer (90% of patients), unilateral or bilateral pheochromocytomas (50% of patients), intestinal and mucosal ganglioneuromatosis (all patients), and a characteristic Marfanoid appearance. Our patient had medullary thyroid cancer and underwent a thyroidectomy at the age of 8 years. He also had bilateral pheochromocytomas, which were removed at the ages of 34 and 35 years.

Figure 1 shows the pathognomonic ganglioneuromatosis. Mucosal neuromas are the most consistent and distinctive feature of MEN 2B, appearing in all patients.[2] The presence of multiple mucosal neuromas is associated with diffuse intestinal ganglioneuromatosis, causing gastrointestinal problems (diverticulosis, persistent diarrhoea or constipation). The abdominal complaints can be a major burden on normal life. Currently, there are no treatment options for ganglioneuromatosis. This patient has been admitted repeatedly for severe weight loss and severe constipation due to gastrointestinal dysmotility, and was now admitted for severe constipation as well.

Figure 2 shows the characteristic Marfanoid facial appearance of this patient. On the left jaw line there is a lipoma present, which is not associated with the syndrome.

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ANSWER TO PHOTO QUIZ (PAGE 232)

A PULMONARY SHADOW AFTER LOBECTOMY: AN UNEXPECTED DIAGNOSIS

DISCUSSION

The chest X-ray one day after surgery showed a dense opacity in the upper zone of the right lung with pleural lining (*figure 1*). The differential diagnosis included haematoma, pneumonia, atelectasis (due to sputum retention) and torsion of the right middle lobe. The CT scan four days later showed a tapered occlusion of the right middle lobe bronchus and a consolidation of a pulmonary segment. Bronchoscopy showed an occlusion in the right middle lobe bronchus two centimetres distally to its orifice. The occlusion could not be passed with a brush. Since a lobar torsion was suspected a re-thoracotomy was performed. It appeared that the right middle lobe was distorted and as a result, already necrotic. A lobectomy of the right middle lobe was performed. The patient had an uneventful recovery and was discharged eight days after the second operation.

Lobar torsion is a very rare complication after thoracic surgery. The incidence of lobar torsion after pulmonary resection in one large study was found to be 0.089%.[1] Mostly lobar torsion involves the right middle lobe after right upper lobectomy. The differential diagnosis of the previous condition includes haematoma, lobar pneumoniae and atelectasis, and can be quite difficult to distinguish. Physical findings are not specific to reach a diagnosis. Radiography and bronchoscopy may show specific findings.

Specific radiographic findings of lobar torsion include rapid opacification or serial positional change of the affected lobe.[2] Bronchoscopy may reveal an abnormally tight and obstructed orifice of the affected lobe. Postoperative follow-up with chest X-ray is most important for the correct diagnosis of a lobar torsion.

In most case reports resection is performed due to irreversible ischaemic change of the distorted lobe. In a few patients simple detorsion was carried out; however, this may lead to serious complications. If lobar torsion is suspected, exploratory thoracotomy should be performed without delay to prevent serious morbidity and mortality.[3] In order to reduce the risk of lobar torsion the right middle lobe can be fixed to the right lower lobe, especially if the fissure is well developed.

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Netherlands
The Journal of Medicine

SPECIAL REPORT

Monoclonal B-cell lymphocytosis: Recommendations from the Dutch Working Group on CLL for daily practice

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ABSTRACT

Monoclonal B-cell lymphocytosis (MBL) is defined by the presence of small B-cell clones in asymptomatic individuals. Usually, MBL cells are characterised by a chronic lymphocytic leukaemia (CLL) phenotype ('CLL phenotype MBL'); however, an atypical phenotype ('atypical-CLL phenotype MBL') or non-Hodgkin lymphoma phenotype ('non-CLL phenotype MBL') can be found as well. The prevalence of MBL in the general population with an age over 40 years is 3 to 5%. Subjects with MBL develop CLL requiring treatment at a rate of 1 to 2% per year. At the moment official guidelines with respect to MBL are not available in the Netherlands. On the basis of the available data, we will discuss the definitions of MBL, highlight clinical consequences and offer recommendations for daily practice. Individuals with clinically suspected MBL should undergo a complete evaluation by a haematologist. In case of CLL phenotype MBL, further annual follow-up can take place by the general practitioner. If signs of progression occur patients should be referred to a haematologist.

KEYWORDS

MBL, CLL, practical guidelines

INTRODUCTION

Monoclonal B-cell lymphocytosis (MBL), a relatively new entity, is a preclinical haematological syndrome where small B-cell clones with an abnormal immunophenotype are present in the peripheral blood of asymptomatic individuals. In most cases, these clonal cells have an immunophenotype similar to chronic lymphocytic leukaemia (CLL; CLL phenotype MBL). To date, no official guidelines have been published in (inter)national medical literature. On the basis of available literature we will offer recommendations for daily practice in case of suspected MBL and in case of confirmed MBL.

DEFINITION

Recently, MBL was introduced and defined (*table 1*) in the updated iwCLL (International Workshop on CLL) classification.[1] In preceding years several groups have performed population-based studies and with the advent of more sensitive flow cytometry techniques it was found that a substantial part of the general adult population carries typical monoclonal B-cell clones in their peripheral blood, which was classified as MBL.[2-6] MBL cells are monoclonal B cells which usually express CD5. In 85% of the cases, these clones also express the other typical surface markers of CLL cells ('CLL phenotype MBL'; $CD19^{+}$, $CD20^{weak}$, $CD23^{+}$, surface Ig $(sIg)^{weak}$ and $CD79b^{weak}$).[1] Furthermore, a second category of MBL has been called 'atypical-CLL phenotype MBL'. In this category clonal B cells also express CD5, but other markers are differentially expressed as compared with CLL (e.g. CD23 negative or bright expression of CD20, CD79 or sIg). The clonal B cells of the third category of MBL, called 'non-CLL phenotype MBL' lack expression of CD5 and do express phenotypic markers resembling non-Hodgkin lymphomas, such as marginal zone lymphoma or follicular lymphoma (*table 1*). As the clonal B cells of individuals with both CLL and 'CLL phenotype MBL' share an identical immunophenotype, they need to be differentiated based on absolute B-lymphocyte count; CLL is defined by the presence of ≥5 x 10^9/l B lymphocytes and MBL is defined by the presence of <5 x 10^9/l B lymphocytes with a

Table 1. *Diagnostic criteria and nomenclature of MBL (adapted from Shanafelt et al.[2])*

Diagnostic criteria

1. Documentation of clonal B-cell population by:
   kappa:lambda ratio >3:1 of <0.3:1 or >25% of B cells lacking or expressing low-level surface immunoglobulins
2. Presence of a disease-specific immunophenotype[a]
3. Absolute B-lymphocyte count <5 x 10^9/l
4. No other features of a lymphoproliferative disorder: a) absence of B symptoms, b) normal physical exam (no lymphadenopathy or organomegaly), c.) no autoimmune/infectious disease

Subclassification

- CLL phenotype MBL
  CLL phenotype: $CD5^+CD19^+CD20^{weak}CD23^+sIg^{weak}$
- Atypical-CLL phenotype MBL
  $CD5^+CD19^+$, but CD23 weak of negative or CD20, sIg or CD79b bright
- Non-CLL phenotype MBL
  $CD5^-CD19^+CD20^+$

[a]**In the absence of a disease-specific immunophenotype, a highly skewed kappa:lambda ratio can be the result of a reactive process.**

characteristic CLL phenotype in peripheral blood.[1] Before the introduction of MBL in the recent iwCLL classification, CLL used to be classified as the presence of characteristic monoclonal B cells in the peripheral blood, with a minimum absolute lymphocyte count (ALC) of 5 x 10^9/l.[7] Since the change in the CLL diagnostic criteria from an ALC >5 x 10^9/l to a B-cell count >5 x 10^9/l, up to 40% of CLL patients who were previously classified as CLL Rai stage 0 are now diagnosed as MBL.[8,9] In literature, the terms 'low-count MBL (lcMBL) and 'clinical MBL' (cMBL) have also been introduced[2] to discriminate cases with extremely low monoclonal B-cell clones (which are only found by population screening) from cases with an asymptomatic lymphocytosis. In the literature, no clear distinction has been made between lcMBL and cMBL on the basis of the number of B lymphocytes, but most lcMBL patients do have a B-lymphocyte count below 0.5 x 10^9/l.[2,10] The risk to develop CLL requiring treatment is clearly increased in cMBL in comparison with healthy age-matched controls and not in lcMBL (see further).

PREVALENCE OF MBL

The reported prevalence of MBL in the general population varies substantially, from 0.6% to even 20% in some studies (*table 2*).[2-6] These differences are most likely due to both different sensitivity of the flow cytometry approach applied and to the age of the studied population. In an Italian and English study, in which a four-colour flow cytometry (CD5, CD19, kappa and lambda; 2 x 10^5 analysed cells)[11] was used, a prevalence of 3 to 5% was found in the general population with a mean age of 73 years (range 62 to 98 years).[3,4] A Spanish study, which applied a more sensitive approach (CD5, CD19, CD20, CD23, CD38, kappa and lambda; 5 x 10^6 analysed cells) reported a prevalence of up to 20% in the general population over 60 years of age (*table 2*).[5] There are even recent data suggesting that almost everyone older than 70 years harbours circulating CLL clones at very low numbers.[12] Currently, the consensus on the prevalence of MBL is 3 to 5% in the Western population with an age over 40 years. There is a fourfold increase of MBL in first-degree relatives of CLL patients in comparison with the general elderly population.[13,14] For young adults aged 16 to 40 years this relative risk is even 17-fold increased.[14]

There are less data on the prevalence of MBL in individuals with asymptomatic lymphocytosis. In an English study, a monoclonal B-cell population was found in 60% of the 2000 individuals referred with an asymptomatic lymphocytosis (median age 77 years): 19% with MBL and 46% with CLL.[4] A comparable study was performed in a Dutch cohort of 520 patients aged over 40 years, who presented with a relative (>60%) or absolute (>6.0 x 10^6/l) lymphocytosis. In the groups of individuals with an

Table 2. *Prevalence of CLL-like MBL in population studies (adapted from Shanafelt et al.[2])*

Study group			Flow cytometry		CLL-like MBL prevalence	
Source	**Median age**	**N**	**No. of colours**	**Events (x10^3)**	**All ages in study**	**>60 years**
US residential population[29]	53 (40-78)	1926	2	Not specified	0.6%	>0.6%[a]
US blood donors[30]	45 (18-79)	5141	2	Not specified	0.14%	0.9%
UK hospital OPs[4*]	57 (40-90)	910	4	2	3.5%	5.0%
Italy, primary care[3]	74 (65-98)	500	4	2	5.5%	5.5%[b]
UK hospital OPs[4**]	74 (60-80)	1520	4	2	5.1%	5.1%[c]
Italy, residential population[31]	55 (18-102)	1725	5	5	7.4%	8.9%
Spain, primary care[6]	62 (40-97)	608	8	50	12.0%	>20%[a]

[a]**Estimated from data;** [b]**age above 65;** [c]**age range 60-80 years; OPs = outpatients, *without lymphocytosis, ** with lymphocytosis.**

absolute lymphocyte count below 4.0 x 10^9/l, between 4.0 and 9.0 x 10^9/l, and over 9.0 x 10^9/l, monoclonal B cells were found in 2% (all MBL), 16% (87% MBL) and 66% (2.8% MBL; 90% CLL) respectively.[15]

RISK OF PROGRESSION TO SYMPTOMATIC DISEASE

For CLL-phenotype MBL, it is more relevant to define progression as the risk to develop CLL requiring treatment than the risk to develop CLL,[10] since there is an arbitrary distinction between MBL and CLL Rai stage 0. Based on the larger MBL follow-up studies the annual risk to develop CLL requiring treatment is 1 to 2%[2,4,16,17] compared with an annual risk for CLL Rai stage 0 patients of 5 to 7%. In other words, the ten-year treatment risk for MBL is 10 to 20% in contrast to 50 to 70% for CLL Rai stage 0 patients.[2] Since these studies indicate that no plateau phase is reached in the risk of progression to CLL (comparable with multiple myeloma and monoclonal gammopathy of unknown significance (MGUS)) one should question whether these patients need to be monitored in the long term. The only factor known to predict development to CLL is the actual number of B lymphocytes.[8,10,17] Roughly, MBL patients with a B-lymphocyte count below 1 to 2 x 10^9/l have a low risk to develop progressive lymphocytosis and CLL. In 90% of the cases the extent of the clone stays stable.[10] In an American study only 1.5% (1/64) of the MBL patients with a B-lymphocyte count below 1.5 x 10^9/l progressed to CLL requiring treatment.[17] In patients with more than 3.7 x 10^9/l B lymphocytes (in most cases these subjects have asymptomatic lymphocytosis) the chance to develop CLL is substantial: 72% after 2.6 years,[10,16] in contrast to 39% after 5.5 years in case of a B-lymphocyte count between 1.2 and 3.7 x 10^9/l.[16] Established risk factors for CLL, such as IGVH mutation status, cytogenetic aberrations, ZAP-70 and CD38 expression, are technically difficult to obtain in MBL subjects. So far, these factors have not shown independent prognostic power to predict progression.[2,4]

Progression to CLL of lcMBL is extremely rare in the experience of researchers in the field.[2] Since the prevalence of lcMBL can be up to 20% in the general elderly population and only a really small number of individuals develop CLL, the CLL progression risk is not expected to be increased in comparison with the risk in the general population.[17]

RISK OF CLL-RELATED MORBIDITY

CLL patients have an increased risk of infection (notably in the later stages of the disease, both due to a diminished humoral immunity and neutropenia caused by bone marrow infiltration), secondary malignancies and autoimmune diseases (especially autoimmune haemolytic anaemia and idiopathic thrombocytopenic purpura).[18,19] There is little information on CLL-related morbidity in case of MBL. In the studies described earlier with larger patient cohorts,[4,16,17] the risk of infections, autoimmune haemolysis and secondary malignancies was not investigated. However, in case of cMBL, it is known that lower numbers of circulating B lymphocytes are present in the peripheral blood in comparison with healthy individuals. In most MBL patients with more than 1.0 x 10^9/l circulating monoclonal B lymphocytes there is a complete loss of circulating normal B lymphocytes, comparable with CLL.[10] Whether decreased numbers of circulating normal B lymphocytes in cMBL patients (which does not coincide with lower immunoglobulin levels)[17] results in an increased infection risk is questionable. A very recent cohort study of 520 MBL patients from the Mayo Clinics showed a 6.5-fold increased risk of infection requiring hospital admission in these patients as age-matched healthy controls.[20] Furthermore, it is known that MBL patients have a significantly lower risk of infections compared with CLL Rai stage 0 (risk of infection WHO grade 2 to 4: 10.9 per 100 patient-years for MBL and 15.1 per 100 patient-years for CLL).[17] T-lymphocyte abnormalities have also been described in CLL, notably altered function of T lymphocytes.[21-25] Although not extensively investigated, T-lymphocyte dysfunctions do not seem to be prominent in MBL.[26] In conclusion, decreased immunity might occur in cMBL patients and awareness for infections is recommended.

RECOMMENDATIONS FOR DAILY PRACTICE

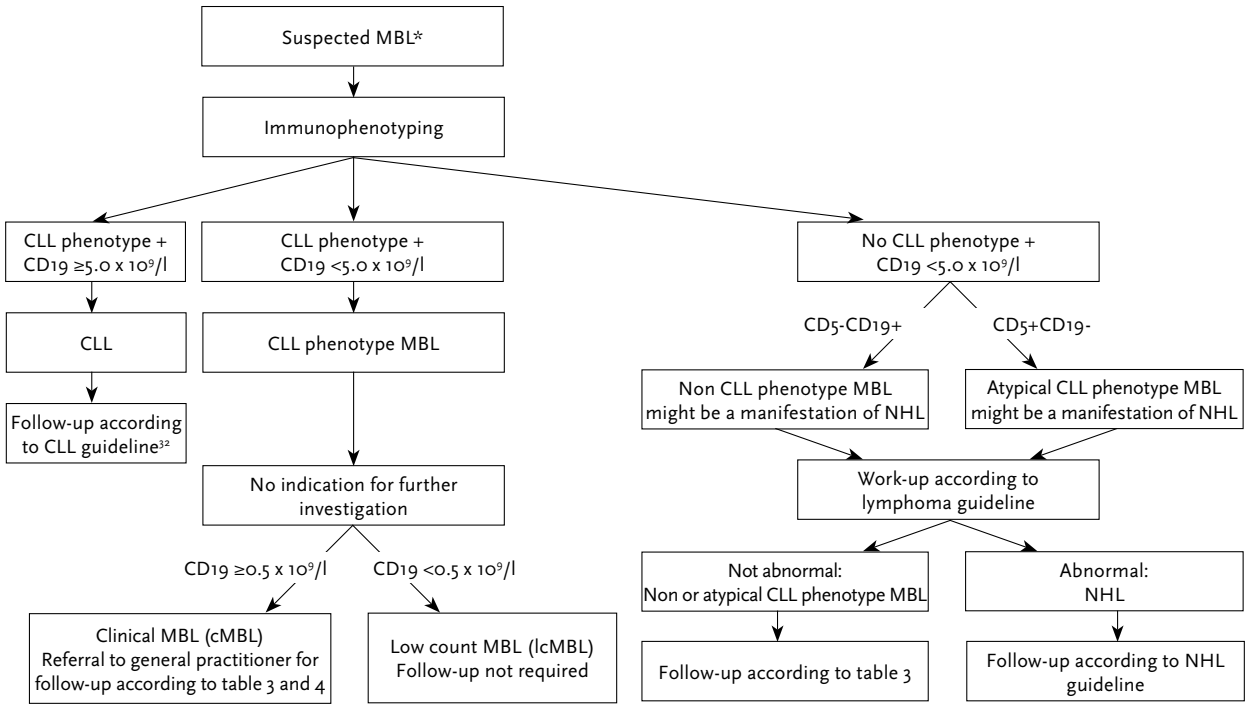
Official Dutch guidelines with respect to MBL are lacking, although recently a report in the *Nederlands Tijdschrift voor Geneeskunde* introduced the entity MBL.[27] Based on available literature and international consensus, the Dutch HOVON CLL Working Party formulated the following recommendations for daily practice (see algorithm, *figure 1*).[2,28]

How to proceed in case of:

Suspected MBL

The general advice is to avoid screening of healthy individuals outside studies for MBL. However, if a lymphoproliferative disorder is suspected, for example in case of persisting (asymptomatic) lymphocytosis, referral to a haematologist is indicated for further investigation. A thorough medical history, physical examination and complete blood count need to be performed. In case of MBL, B symptoms (fever, weight loss, night sweats

Figure 1. *Diagnostic flowchart in case of suspected MBL and follow-up of MBL*



***Patients with persistent asymptomatic lymphocytosis without lymphadenopathy at physical examination, cytopenias and B symptoms. CLL = chronic lymphocytic leukaemia; MBL = monoclonal B-cell lymphocytosis; NHL = non-Hodgkin lymphoma.**

and fatigue), palpable lymph nodes (>1 cm), hepatosplenomegaly, anaemia and thrombocytopenia need to be absent (*table 3* and *figure 1*). Additional investigation includes peripheral blood smear, absolute B-lymphocyte count and immunophenotyping with at least the following markers: CD5, CD19, CD23, CD20, CD79b, IgM, IgD, IgG, kappa and lambda (*table 1*). There is no need for a further bone marrow aspirate or imaging in case of CLL phenotype MBL. Moreover, there is no additional value for further determination of prognostic markers such as CD38, ZAP-70, IGVH mutation status or cytogenetic abnormalities.[2] Furthermore (comparable with MGUS patients) patients need to be reassured that MBL is not in itself a lymphoproliferative disorder, but a pre-leukaemic condition with an increased risk to develop CLL.

In case of atypical-CLL phenotype MBL or non-CLL phenotype MBL, a more thorough evaluation is required due to the possible presence of leukaemic non-Hodgkin lymphoma. In contrast to CLL phenotype MBL, imaging studies and bone marrow biopsy for staging are recommended. Furthermore, fluorescent in situ hybridisation (FISH) analysis for cytogenetic aberrations such as t(11;14) and t(14;18) is advised to exclude mantel cell lymphoma (in atypical-CLL phenotype MBL) and follicular lymphoma (in non-CLL phenotype MBL) respectively. In the absence of these translocations it might be a manifestation of another indolent lymphoma.[2]

Confirmed CLL phenotype MBL

Although the annual risk of progression to CLL requiring treatment is 1 to 2%, this risk turns out to be strongly dependent on the number of circulating B lymphocytes in the peripheral blood (see earlier). Based on these data it seems reasonable, depending on age and comorbidity, that cMBL patients (CD19 ≥0.5 x 10^9/l) are evaluated annually by their general practitioner. Evaluations need to consist of at least a detailed history (B symptoms), physical examination (lymphadenopathy and organomegaly) and complete blood cell count. The frequency of additional laboratory analysis should be increased to every three to six months when absolute lymphocyte counts increase by more than 5 x 10^9/l (*table 4*).[28] Patients are advised to be referred to a haematologist in case clinical CLL/lymphoma-related symptoms develop (lymphadenopathy, night sweats, infections, weight loss) or in case one of the criteria mentioned in *table 4* is met. These criteria are based on those used by a UK study which investigated the efficacy on the follow-up of CLL phenotype MBL when performed by general practitioners.[28] The benefit of Influenza vaccines has not been studied but it is reasonable to consider vaccination.

There is no need to evaluate individuals with lcMBL (CD19 <0.5 x 10^9/l), since the risk to develop CLL is not thought to be increased compared with the general population.

Table 3. *Recommendations for evaluation and follow-up of MBL in daily practice (adapted from Shanafelt et al.[2])*

Recommendations	CLL-like phenotype MBL	Atypical-CLL phenotype and non-CLL phenotype MBL
Diagnostic evaluation		
WBC count with differential	+	+
FISH with probe for t(11;14) and t(14;18)	-	+
Imaging	-	+
Bone marrow biopsy	-	+
CLL prognostic markers	-	-
Counselling and follow-up		
Patient counselling on symptoms to watch for	+	+
Risk of progression requiring therapy	1-2% per year	Undefined
History	Annual[a]	3-12 months[b]
Physical exam	Annual[a]	3-12 months[b]
CBC count with differential	Annual[a]	6-12 months[b]
CT scan chest/abdomen/ pelvis	-	Clinical judgement

+ = yes; - = no; [a]preferentially by general practitioner; [b]preferentially by haematologist.
CBC = complete blood cell; WBC = white blood cell.

Table 4. *Recommendations for change in frequency of complete blood cell count and clinical referral (adapted from Rawstron et al.[28])*

Increase frequency of complete blood cell count to 3-6 monthly if:
Absolute lymphocytes increase by more than 5.0 x 10^9/l in one year
Clinical referral is indicated if:
Presence of B symptoms
Absolute lymphocyte count >30.0 x 10^9/l
Lymphocyte doubling time less than 1 year
Anaemia (Hb <6.5 mmol/l or significantly decreasing Hb)
Absolute platelet count <100 x 10^9/l

It is recommended that the follow-up of patients with an atypical-CLL phenotype MBL or non-CLL phenotype MBL should be done by a haematologist, since there are limited data on the risk of progression (*table 3*).

RECOMMENDATIONS FOR DAILY PRACTICE

1. A substantial proportion of the general adult population carries monoclonal B-cell clones in their peripheral blood with a typical CLL immunophenotype.
2. In case of persisting asymptomatic lymphocytosis, there might be a manifestation of MBL and referral to a haematologist is indicated for a thorough evaluation consisting of medical history, physical examination, complete blood cell count and flow cytometry.
3. A distinction between 'CLL phenotype', 'atypical-CLL phenotype' and 'non-CLL phenotype' MBL needs to be made based on immunophenotyping in case of a newly diagnosed MBL.
4. Clinical MBL patients (CD19 ≥0.5 x 10^9/l) need to be evaluated at least annually with a complete blood cell count including white blood cell differentiation, since there is a reasonable chance to develop CLL requiring treatment.
5. Patients need to be reassured that MBL is a pre-leukaemic condition with an increased risk to develop CLL, but is not in itself a lymphoproliferative disorder.
6. Low-count MBL (CD19 <0.5 x 10^9/l) subjects do not need to be further evaluated, since the chance to develop CLL is not increased compared with the general population.
7. Patients with CLL phenotype MBL can be referred annually to their general practitioner for further evaluation, but follow-up of patients with atypical-CLL phenotype and non-CLL phenotype MBL should be performed by a haematologist.
8. There is no additional value for further determination of prognostic markers such as CD38, ZAP-70, IGHV mutation status and cytogenetic abnormalities in case of MBL. The only known prognostic marker in MBL is the absolute number of B lymphocytes.

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Netherlands
The Journal of Medicine

SPECIAL ARTICLE

What contributes to internists' willingness to disclose medical errors?

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ABSTRACT

Background: The release of the report 'To err is human' put medical safety and the disclosure of errors to the forefront of the health care agenda. Disclosure of medical errors by physicians is vital in this process. We studied the role of background and social psychological factors in internists' willingness to report medical errors.

Methods: Survey among a random sample of internists from five teaching hospitals in the Netherlands, all internists and internists in training at the Departments of Internal Medicine of the participating hospitals.

Results: Questionnaires were received from 115 participants (response 51%). The willingness to disclose was related to the severity of the error, with the majority of near misses not reported to the head of department or the hospital error committees. Errors were more often reported to colleagues. Positive factors in favour of disclosing were reported more often than negative ones prohibiting disclosure. Motivation, behavioural control and social barriers were related to the disclosure of errors.

Conclusion: Personal and social issues contributing to the willingness to report medical errors should be identified and addressed properly to stimulate disclosure. The creation of an atmosphere where disclosing errors is routine seems vital. In addition, it is essential to create a departmental culture where medical errors are discussed in a non-judgmental, safe environment. In order to improve reporting of medical errors, more emphasis should be placed on the individual barriers that preclude adequate reporting.

KEYWORDS

Errors, medical education, disclosure of errors

INTRODUCTION

In the past, medical errors were often hidden behind closed doors. The release of the report 'To err is human' put medical safety and the disclosure of errors to the forefront of the agenda.[1] Subsequently, studies on (handling) medical errors have been conducted. One relevant aspect is the disclosure thereof by physicians.

Adequate disclosure of medical errors is of importance for patients, physicians and society as a whole. Patients' preference for openness has often been reported.[2-5] Those having suffered from a medical error reported that openly disclosing an error afterwards can be more important than the error itself.[5,6] In addition, these studies demonstrated that acceptance of errors by patients and/or relatives is eased if they are convinced that doctors learn from them.[2]

Physicians, on the other hand, may be reluctant to openly confess a mistake. Several factors can play a role, for example guilt may be important, but also fear of consequences, from either the department, disciplinary actions or both.

In addition, systems to report errors are sometimes confusing and may differ across hospitals. Still, physicians broadly acknowledge that disclosing errors is vital to improve patient care.[7]

Despite the initiatives by hospitals, professional societies or governmental agencies, it is believed that many errors remain unreported.[7] In order to improve the disclosure of medical errors a change of attitudes and the creation of an open atmosphere within the health care setting is suggested to be vital. However, such an attitude change is not easily accomplished. It is not fully clear what factors, whether negative or positive, contribute to the willingness to report errors. Thus, to improve the disclosure of medical errors in clinical practice, it should be established what factors help or hamper doctors to report an error. By understanding these factors supportive measures can be

proposed. Such factors may be related to the clinicians' background. We wondered, for example, if older doctors would be more willing to report their errors than younger, less experienced ones. In addition, social psychological theories distinguish factors predicting whether persons are likely to display certain types of behaviour. These assert that behaviour is predicted by intention. Intention, in turn, is influenced, first, by attitudes or motivation, secondly, by self-efficacy or behavioural control, and thirdly, by social or cultural factors.[8,9] Consequently, we expect that whether or not errors are reported depends on the physicians' motivation, their perceived ability and skill to report an error ('behavioural control') and the culture they work in, i.e., their perception of the social or cultural openness to error disclosure within their department.

The aim of the current study was to investigate to what extent physicians working in internal medicine are willing to report medical errors and what factors relate to their willingness to disclose such errors.

METHODS

Participants

All internists and internists in training from the Departments of Internal Medicine at five teaching hospitals in the Netherlands were invited to participate in the study. The sample thus included doctors from different internal medicine subdisciplines such as cardiology, gastroenterology and from general internal medicine. One of the participating departments was organising a monthly meeting where an error was openly disclosed to the entire staff.

Procedures

Together with handing out the paper-based questionnaires and a pre-stamped envelope, a short introduction to the study was given at each hospital by two senior internists (GL, JH). Surveys were completed during a four-month period.

Survey questionnaire

The questionnaire covered three domains.

First, background characteristics included age, gender, clinician's position in the department, having previously made an error and having prior experience with reporting an error. For the last two variables, we distinguished between three error types: i) a near miss, having no consequence for the patient, ii) a minor error, having minor consequences for the patient, iii) a major error, having major consequences for the patient, as proposed by Blendon *et al.*[10] Dutch law requires serious errors to be reported to the responsible governmental agency (e.g. amputation of the wrong leg) and were therefore not addressed here.

Secondly, the items covering motivation, behavioural control and the departmental culture were developed for the current study based on i) qualitative interviews with senior internal medicine staff members held by one the senior authors (JdH) (n=4), ii) the questionnaire developed by Kaldjian and colleagues[11] assessing a taxonomy of Factors Affecting Physicians' Willingness to Disclose and iii) the Dutch version of the Hospital Survey on Patient Safety Culture.[12] All answers to these items were given on a five-point Likert-type scale (ranging from 'totally agree' to 'totally disagree'). Items were recoded so that higher scores indicate a higher motivation to report an error, greater behavioural control and/or perceived departmental support.

Motivation: 26 items addressed negative and positive motives to report errors (for example, negatively, "It is important to not disclose an error as it may arouse negative publicity"; or positively "It is important to disclose to prevent future errors".)

Behavioural control: 20 items related to the extent to which the clinician felt able and had the skills to report an error (for example, "If I had to report an error, I would feel stressed beforehand", or: "If I had to report an error, I would have to prepare carefully").

Departmental culture: 21 items addressed whether the clinicians perceived their department's culture as conducive or, on the contrary, creating barriers to disclosing an error (for example: "A person reporting an error is treated respectfully" or "In my department people would not treat cases confidentially").

Thirdly, we considered the clinicians' intention to report errors. As described above, we distinguished: i) near misses, ii) minor errors, and iii) major errors. Respondents were asked how probable it was that they would report such an error to four different parties: i) colleagues, ii) the head of the department, iii) the responsible hospital committee and iv) patients. They responded on five-point Likert-type scales (range 'certainly' to 'certainly not'). Higher scores indicate a greater probability to report an error.

Statistical analysis

First, descriptive statistics were used to investigate the background characteristics of respondents, to understand the patterns of intentions to report medical errors, and to investigate response patterns in the items pertaining to Motivation, Behavioural Control and Departmental Culture.

Second, based on exploratory factor analyses we created subscales to explore the relationships between the items for Motivation, Behavioural Control and Departmental Culture. Their internal reliability was assessed by calculating Cronbach's alpha (α).

Third, in relation to the willingness to report errors, sum scores for each type of error were created and a sum score for intention to report all types of error.
Finally, we ran bivariate linear regressions to investigate respondents' background characteristics, experience with previously reporting errors and scores on the motivation, behavioural control and departmental culture subscales in relation to their intentions to report different error types. Based on the results of these analyses, we ran a multivariate linear regression including all variables with a p value <0.25. Five blocks were used, with background characteristics entered first, and experience with previously reporting errors entered second. In the third block we entered Motivation subscales, in the fourth block we entered Behavioural Control subscales and in the fifth block we entered Departmental Culture. All analyses were conducted using Stata 11.1

RESULTS

Sample characteristics

A total of 226 questionnaires were distributed among internists and internists in training. Responses were received from 115 participants (response rate 50.9%). One questionnaire was omitted from analysis given the large number of missing values (>50%). Sample characteristics are given in *table 1*. Of the respondents 52% were male, 53% were staff members, and 54% came from an academic hospital. The demographics of the non-responders are unknown. However, since half of the respondents were male and half practised at an academic institution, it is suggested that the respondents are a representative study group. Under half (43%) of the respondents belonged to the department where a monthly error reporting meeting took place. With regard to experience with errors, 94% of the respondents reported having made earlier near misses of which 64% reported the error, 88% had made a minor error of which 76% had reported the error, 35% said they had made major errors of which 88% reported such error and 6% were involved in a serious accident (that all had reported on).

Table 1. *Sample characteristics (n=115)*

Background characteristics	
Age (mean ±SD)	40.57±10.67
Gender (male)	52.2%
Academic / teaching hospital	53.9%
Internists (staff) / internists in training	53.0%
Monthly meeting about errors (yes)	42.9%
Earlier experiences made / of which reported a	
Near miss	93.9% / 64.1%
Minor error	87.7 % / 76.0%
Major error	35.4% / 82.5%
Serious incident	6.2% / 100%

Intention to report

As shown in *table 2*, in most cases physicians intend to report near misses (87%) to a colleague, in one third of cases to the head of the department (35%) and/or the hospital's error and near accident committee (32%) and in about one quarter of cases to the patient (27%). Minor errors would be reported to a colleague in most cases (86%), to the head of the ward in less than half of the cases (41%), to the hospital's error and near accident committee in half (53%) and to patients in almost two-thirds of the cases (61%). Respondents indicated they would report a major error to a colleague in almost all cases (98%), to the head of ward in most cases (86%), to the hospital's error and near accident committee in most cases (90%) and to the patients in almost all cases (94%).

There is a trend for internists' willingness to report errors to increase when the error has more serious consequences.

Table 2. *Willingness to report errors (probably / certainly)*

I would report a	Near miss	Minor error	Major error
To a colleague	86.6%	85.7%	98.3%
To head of ward	34.8%	41.1%	85.7%
Hospital committee of errors and near misses	32.1%	52.6%	90.2%
Report to the patient	26.7%	60.7%	93.8%

Relevant motivational, behavioural and cultural factors

Motivation: Positive and negative motives concerning the clinicians' willingness to report errors were divergent. The most often endorsed motives to disclose an error were (see *table 3* for the three most important ones): 1) to prevent future errors (99%), 2) to enable others to learn from them (99%), 3) that it is one's responsibility (95%), 4) to improve patient safety (94%) and 5) because one would have liked this if one were a patient (91%). Important reasons prohibiting the intention to report an error were that 1) it could arouse negative publicity (21%), 2) it could harm one's reputation (20%), 3) patients' reactions might be negative (19%), 4) the risks of a complaint still exist (11%) and 5) because one did not consider themselves to be the only responsible person (8%).
Behavioural control: The most important reasons endorsed for having (lack of) behavioural control were that 1) one

Table 3. *Overview of most important motives, behavioural reasons and cultural factors to (not) report an error*

	Agree altogether/ to some extent	Mean ±SD
Motives to report an error		
To prevent future errors	99.1%	1.18±.405
So others can learn from it	99%	1.21±.429
I consider it my responsibility	94.8%	1.49±0.63
Motives not to report an error		
It could arouse negative publicity	21.1%	3.71±1.14
It could harm my reputation	20.1%	3.63±1.15
Patients' reaction could be negative	19.3%	3.67±1.14
Behavioural reasons to not report an error *If I were to report an error, I*		
Would find it difficult	67.9%	2.52±1.16
Would have to prepare carefully	65.2%	2.27±1.09
Would worry about it	64.9%	2.46±1.10
Supportive cultural factors *As regards error reporting, I find people in my department*		
To be happy to learn from errors	85.4%	1.75±.74
To respect the person reporting an error	83.7%	1.83±.76
Make it clear that errors could happen to anyone	79.1%	1.85±.82
Most important cultural barriers *As regards error reporting, I find people in my department*		
Not to treat cases confidentially	30.6%	3.23±1.14
Keep the consequences of reporting unclear	23.6%	3.41±1.11
Use openness about errors against someone later on	16.3%	3.79±1.16

would find it difficult (68%), 2) one would have to prepare carefully (65%), 3) one would worry about the reporting (65%), 4) one would be stressed beforehand (54%) and 5) one might disagree with colleagues about what had happened (43%) (see *table 3* for the most important ones).

Departmental culture: The most important supportive factors encountered within the department were 1) the department's perceived eagerness to learn from past errors (85%) and 2) the respect expected towards the person reporting an error (84%, *table 3*). In addition, over three quarters of the internists also found that 3) in their department it is clear that anyone can make an error (79%). Many emphasised the need for the person reporting an error to be treated fairly (77%), and to be provided a safe environment (77%). At the same time most perceived barriers were related to 1) the incident not being treated confidentially (31%), that 2) consequences of reporting were unclear (24%) or that 3) openness about errors could be used against someone later (16%).

Factors predicting internists' willingness to report errors

After looking at individual item descriptive statistics, scales were constructed for the intention to report near misses, minor misses, major misses and the overall intention to report errors. Reliabilities of the scales were satisfactory to good (α's were .69, .75, .68 and .82 respectively). These scales are taken as endpoints for the prediction of respondents' intention to report errors.

Background factors: Neither the respondents' gender, nor age, working in an academic hospital, being a staff member or having a regular error reporting meeting were predictive of the willingness to report errors in the univariate analysis (results not shown).

Motivation: Based on the results from the factor analysis, the items addressing motivation to report errors were subdivided into four subscales covering either positive motives that were 1) 'patient driven' i.e., being in the interest of patients (e.g., "Reporting is better for the patients' safety.") 2) 'socially driven', i.e., in the interest of others (e.g., "Reporting is better as others can learn from it.") or 3) 'personally driven', in the interest of the clinician (e.g., "If I report, I would feel less guilty.") or 4) negative motives (e.g., "Reporting might result in negative publicity."). Cronbach's α's were good (.76, .76, .72 and .81 respectively).

As shown in *table 4*, the clinicians' willingness to report near misses, major and all errors was related to socially driven motives (p=.022, p<.001 and p=.026 respectively) and to negative motives (p=.047, p=.001 and p=.005 respectively) rather than to patient driven or personally relevant motives (*table 4*).

Behavioural control: Factor analysis results suggested that the items addressing behavioural control were best described using two scales. These address either 1) emotional barriers (e.g., "I'd be afraid to get too emotional.") or 2) behavioural barriers (e.g., "I wouldn't know how to act.") Cronbach's α's were .91 and .65. The item pertaining to legal barriers did not fit either scale and was explored as a single item.

As shown in *table 4*, the clinicians' willingness to report near misses, major and all errors was related to emotional (p<.001, p=.013 and p=.003 respectively) as well as behavioural barriers (p=.006, p=.002 and p=.003 respectively). Legal barriers did not predict clinicians' intention to report errors.

Table 4. *Motivational, behaviour related and cultural factors predicting the intention to report near misses and errors (univariate analysis)*

	Near miss		Minor errors		Major errors		All	
	Stand. Beta	*P* value	Stand. Beta	*P* value	OR	*P* value	Stand. Beta	*P* value
Motivation								
Patient driven	0.10	0.299	0.15	0.126	1.14	0.037	0.16	0.104
Socially driven	0.22	0.022	0.08	0.377	1.41	<0.001	0.21	0.026
Personally driven	-0.005	0.959	-0.02	0.807	1.06	0.340	-0.05	0.626
Negative motivation	0.19	0.047	0.13	0.176	1.21	0.001	0.26	0.005
Behavioural control								
Emotional	-0.33	<0.001	-0.05	0.598	0.95	0.013	-0.28	0.003
Behavioural	-0.26	0.006	-0.08	0.386	0.81	0.002	-0.28	0.003
Legal consequences	-0.09	0.372	-0.03	0.718	0.74	0.126	-0.11	0.272
Cultural factors								
Cultural factors	-0.12	0.204	0.02	0.870	0.93	<0.001	-0.16	0.097

OR = odds ratio; Stand. = Standardized.

Departmental culture: The factor analysis results indicated that the items addressing the department's culture constituted a single construct (α=.95). The clinicians' willingness to report near misses was found to be related to the perceived supportive culture within their department (p<.001) (*table 4*).

Predicting the internists' intention to report, the multivariate approach: To further understand how the combination of the different factors was associated with clinicians' willingness to report near misses and major errors, we investigated sequential multivariate regression models. Older physicians and women were more likely to report near misses (*table 5*). In the final block the internists' gender (p=.039), socially driven motivation (p=.045) as well as the absence of emotional barriers (p=.002) explained the tendency to report near misses.
In the first block, willingness to report major errors was again stronger among older and female internists (p=.026 and p=.027 respectively). After entering the clinicians' motives, socially driven (p=.001) and negative motives (p=.012) were significantly associated with the willingness

Table 5. *Factors predicting intention to report near misses and major errors*

	Block 1		Block 2		Block 3		Block 4	
Near miss	Stand. Beta	*P* value	Stand. Beta	*P* value	Stand. Beta	*P* value	Stand. Beta	*P* value
Sex	-0.20	0.036	-0.18	0.074	-0.21	0.034	-0.20	0.039
Age	0.21	0.033	0.09	0.429	-0.01	0.948	0.01	0.926
Patient driven			-0.04	0.733	0.003	0.975	0.008	0.935
Socially driven			0.16	0.169	0.20	0.084	0.24	0.045
Negative motivation			0.10	0.327	-0.03	0.788	-0.001	0.992
Emotional					-0.34	0.003	-0.36	0.002
Behavioural					-0.03	0.778	-0.06	0.600
Cultural factors							-0.14	0.224
Adjusted R^2	0.048		0.051		0.135		0.139	
	Block 1		**Block 2**		**Block 3**		**Block 4**	
Major error	OR	*P* value	OR	*P* value	OR	*P* value	OR	*P* value
Sex	0.39	0.026	0.44	0.084	0.41	0.082	0.40	0.081
Age	1.04	0.027	0.98	0.391	0.96	0.147	0.95	0.104
Patient driven			0.95	0.482	0.97	0.706	0.96	0.626
Socially driven			1.48	0.001	1.52	<0.001	1.47	0.002
Negative motivation			1.18	0.012	1.11	0.164	1.09	0.257
Emotional					0.96	0.133	0.96	0.197
Behavioural					0.90	0.246	0.92	0.350
Cultural factors							1.03	0.218
Pseudo R^2	0.055		0.212		0.252		0.262	

OR = odds ratio; Stand. = Standardized.

to report a major error. In the final model, socially driven motives (p=.002) significantly explained the internists' willingness to report major errors.

DISCUSSION

The occurrence of errors is prominent among physicians as elsewhere. Such errors threaten patient safety and are found to be related to physician burnout and emotional problems.[13] Yet, interestingly, only recently the focus of attention has been directed to the role of the different parties involved: patients, professionals, institutions, and government. One method to reduce future medical errors is to openly discuss them. In the present study insight was gained into factors that may either promote or hinder the open disclosure of medical errors by internists and trainees in internal medicine. A survey completed by 115 internists (in training) evaluated to what extent they would be willing to report errors. We identified factors these physicians experienced as most relevant to help or hinder disclosing of errors.

The severity of the error was related to the willingness to report an error. Specifically, near misses were not reported by the majority of respondents to patients, the head of the department or the hospital safety committee. Even in the case of a severe medical error, one out of eight physicians would not be willing to disclose the error to the head of the department. In contrast, irrespective of the severity of the medical error, physicians were very likely to disclose/discuss the error with a colleague. They prefer to discuss medical errors with their peers, most likely because they feel safe among them.

As hypothesised, older and female doctors were more likely to disclose an error. Female doctors are indeed considered more patient-oriented communicators in general.[14] We speculated that older doctors would be less vulnerable than younger physicians, especially with regard to reputation. However, Kaldjian reported otherwise with younger physicians more likely to disclose an error than older physicians,[7] demonstrating that there was no consistent correlation between age and the willingness to report an error.

It is interesting to note that the respondents' attitudes towards disclosure were generally positive: they reported more reasons supporting the disclosure a medical error, and far less downsides of such disclosures. Positive motives were the prevention of future errors, the educational value of disclosing the error and, often, that it was one's responsibility to disclose. The most often reported negative motives were negative publicity, harm to reputation and an unfavourable response from the patient involved.

Two-thirds of the respondents reported that while they considered themselves eventually able to openly disclose an error, this would be perceived as difficult and more than half mentioned that it would induce personal stress. Unlike elsewhere, legal arguments were rarely perceived as an important barrier.[15] In line with other studies,[16,17] several issues related to the departmental cultures were raised. Most anticipated they would be treated fairly and respectfully and experienced a desire to let others learn from medical errors. Still, one third of respondents acknowledged that they feared that disclosure would most likely not be treated confidentially, that it would be used against them or that the consequences of the disclosure were unclear.

The positive responses suggest that many internists would be willing to report any mistake, though often severe errors and less often near misses. This is in contrast with the current conviction that most errors are not reported. It may be explained by the fact that, as our study confirmed, negative motives have a stronger impact on the willingness to report an error than personal or patient driven motives (*table 4*).

We anticipated that the participating hospital with a monthly open discussion of medical errors would result in a more favourable opinion towards open disclosure. In addition we hypothesised that those who had reported errors previously would be more willing to disclose future mistakes. Interestingly, none were found to be factors influencing the decision to report. Apparently, having a meeting where errors are discussed does not guarantee a favourable attitude towards disclosure. Indeed our study suggests that most barriers are of a more individual, personal nature.

Obviously, our study has limitations. First, although our sample size was substantial, the response rate (51%) was limited. While the non-response was comparable among staff, trainees and the various hospitals involved, it is unclear whether non-respondents were less in favour of openly disclosing medical errors than those who responded. In addition, our responses were by definition of a subjective nature, and could not be ratified with objective data. Yet, this study was specifically designed to identify personal factors that promote or hinder the disclosure of medical errors. In fact, it is the first study to base those factors on psychological theory and is therefore likely to cover all relevant aspects at stake. Also, our newly developed questionnaire turned out to yield reliable responses that were, moreover, tapping relevant domains.

In conclusion, while internists (in training) in general demonstrate a willingness to openly disclose medical errors, several factors aid in the decision to do so. Such willingness to disclose turns out to be a personal rather than an organisational issue. Personal barriers have to be overcome. Especially emotional obstacles such as being worried about the implication of disclosure and

the stress related to disclosing may be discussed with individual professionals. A socially driven motivation was found to be the most important factor in predicting the internists willingness to openly disclose errors. Organising a meeting to disclose errors is not sufficient in itself, professionals need to be convinced that disclosure is beneficial to medical care and the medical community. Therefore it should be stressed within departments that the creation of an atmosphere where disclosing errors is part of routine practice is not only vital to the patient, or the clinical care, but also serves the medical community in general. In addition, it is essential to pay attention to individual barriers along with the creation of a departmental culture where medical errors are openly discussed in a non-judgmental, respectful and safe atmosphere.[16,17] It is suggested that much could be gained by aiding the reporting physician to alleviate the perceived stress, while at the same time maintaining confidentiality. In addition, possible negative publicity surrounding the disclosure should be identified and adequately addressed, and clarity should be given regarding what the consequences are for the reporting physician.

ACKNOWLEDGEMENT

The authors would like to thank Lauris C. Kaldjian for his permission to use several items from his questionnaire. In addition, the authors thank the participants from the departments of internal medicine of the following hospitals: Academic Medical Center, Amsterdam, Onze Lieve Vrouwe Gasthuis, Amsterdam, Slotervaart Hospital, Amsterdam, Flevoziekenhuis, Almere, WestFriesGasthuis, Hoorn, all in the Netherlands.

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Taxus baccata allergy in a breast cancer patient

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Dear Editor,

We present a case report of docetaxel hypersensitivity in a breast cancer patient with known *Taxus baccata* allergy. A 42-year-old woman was diagnosed with triple-negative breast cancer pT1cN0Mx. Adjuvant chemotherapy constituted of doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2 and docetaxel 75 mg/m^2 every three weeks on day 1 for six cycles. She disclosed that while walking her dog, she experienced dyspnoea and pruritus when passing *Taxus baccata* trees. Standard dexamethasone 8 mg twice daily premedication was administered on day -1, 1 and 2. Therefore, we decided to start treatment without further adjustments. Less than five minutes after start of the first docetaxel administration of 120 mg in 250 ml saline solution, she experienced dyspnoea and pain in the chest and back. Physical examination revealed tachycardia of 102 beats/min with a normal blood pressure of 143/83 mmHg. After cessation of docetaxel and administration of clemastine 2 mg intravenously according to our local protocol, the symptoms quickly dissolved and her heart rate returned to normal. After 15 minutes, the docetaxel administration was restarted with a reduced flow of 15 ml/hour in the first 15 minutes and then slowly increasing to 100 ml/hour during the next 15 minutes, 200 ml/hour in the next 15 minutes and finally 250 ml/hour for the duration of the remainder of the infusion. The following administrations of docetaxel were given with clemastine 2 mg and dexamethasone 10 mg intravenously in addition to the standard premedication. Also, the speed of docetaxel administration was given with a stepwise acceleration, as described above. She completed treatment without any major side effects.

Docetaxel is a semi-synthetic taxane originally extracted from the needles of the European yew tree (*Taxus baccata*). Despite dexamethasone premedication, hypersensitivity was observed in up to 13.4% of all breast cancer patients treated with docetaxel-based chemotherapy.[1,2] In a study of 160 test subjects, an association between *Taxus* sp. pollen allergy and anti-paclitaxel IgG detection in sera was found, suggesting that an association between *Taxus* allergy and docetaxel-induced hypersensitivity reactions may also be present.[3] The definite aetiology of hypersensitivity reactions during docetaxel treatment remains unclear. We recommend adjustments in the docetaxel infusion rate and premedication in patients with known *Taxus baccata* allergy, in addition to standard dexamethasone premedication.[4] In this era of personalised care for cancer patients, we should invest in the early recognition of increased risk for docetaxel-induced hypersensitivity reactions in order to perform patient-tailored treatment adjustments, as suggested in our case report.

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Netherlands
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Bisphosphonate or RANK-L inhibitor for tumour-induced hypercalcaemia?

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Dear Editor,

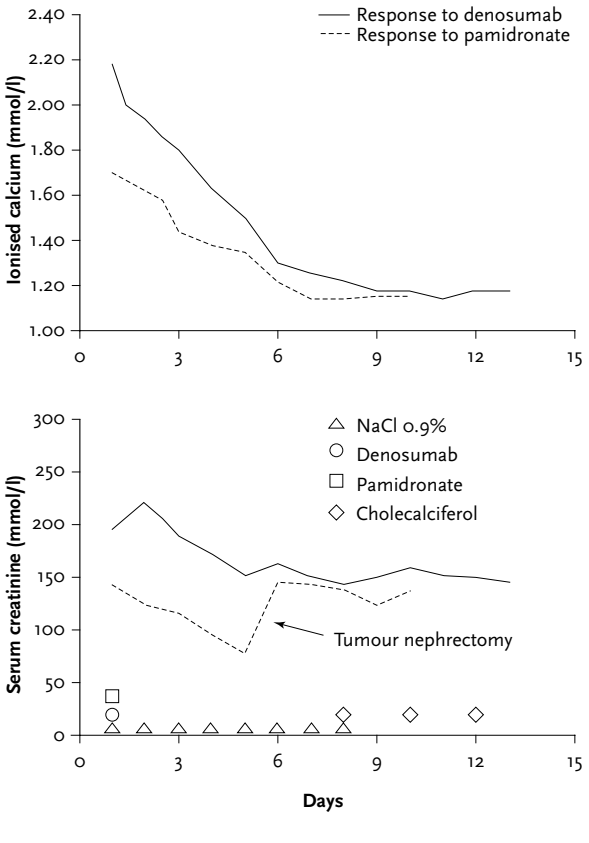
We would like to share our experience with a new treatment approach for tumour-induced hypercalcaemia complicated by renal failure in a patient with renal cell carcinoma (RCC). About 10% of RCCs produce humoral factors that may cause severe hypercalcaemia.[1] The most commonly secreted factor is parathyroid hormone-related peptide (PTH-rp), but cytokines such as IL-6, IL-1, prostaglandin E2, TNFα and TGFα and TFGβ have also been associated with RCC-related hypercalcaemia.[1-3] The underlying mechanism is enhanced osteoclast activity induced by stimulation of the receptor activator of nuclear factor-κ ligand (RANK-L), a key protein in the upregulation of osteoclast formation and activity.[1,2]

Recently, monoclonal antibodies to RANK-L have become available for the treatment of osteoporosis.[4] These antibodies are cleared by the reticulo-endothelial system. Therefore, RANK-L inhibitors such as denosumab might be of value in patients with renal failure, i.e. circumstances where bisphosphonates are relatively contraindicated.[5]

When a 48-year-old man with a recent diagnosis of RCC presented with severe hypercalcaemia and renal failure, denosumab was considered to be the agent of choice. Blood testing revealed a serum creatinine of 191 μmol/l (calculated glomerular filtration rate (GFR) 31 ml/min), ionised calcium (Ca^{2+}) 2.18 mmol/l, PO_4 1.11 mmol/l, PTH <0.3 pmol/l, PTH-rp 7.1 pmol/l (upper normal limit: 2.0 pmol/l), alkaline phosphatase 94 U/l, 25-OH vitamin D 14 nmol/l, and 1.25-OHD 59 pmol/l. A PET-CT showed an FDG-positive tumour in the right kidney, pathological uptake in mediastinal and supraclavicular lymph nodes, but no signs of bone metastases.

The patient was treated with NaCl 0.9% intravenously at a rate of 4 litres/24 hours, and a single dose of denosumab 60 mg, subcutaneously, on the day of admission. A rapid decline in serum calcium and a partial recovery of renal function was observed (*figure 1*). After one week cholecalciferol 50,000 IU was given three times to correct a concomitant vitamin D deficiency. Two weeks later the patient again presented with severe hypercalcaemia (Ca^{2+} 1.71 mmol/l, calculated GFR 45 ml/min, 25-OHD 38

Figure 1. *Course of serum ionized calcium and creatinine levels in response to forced hydration and a single dose of denosumab 60 mg, administered on the first day of admission. A second hypercalcaemic episode was treated with a similar hydration scheme plus a single dose of pamidronate, 90 mg intravenously.*



nmol/l). Upon readmission he was treated with NaCl 0.9%, 4 litres/24 hours and a single dose of pamidronate, 90 mg intravenously. The speed of decline in serum calcium was somewhat less to that induced by denosumab (*figure 1*). On the 6th day of admission tumour nephrectomy was performed. The observations in this case suggest that denosumab is a potent treatment strategy for humoral hypercalcaemia. It may become the preferred agent in case of renal failure.

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