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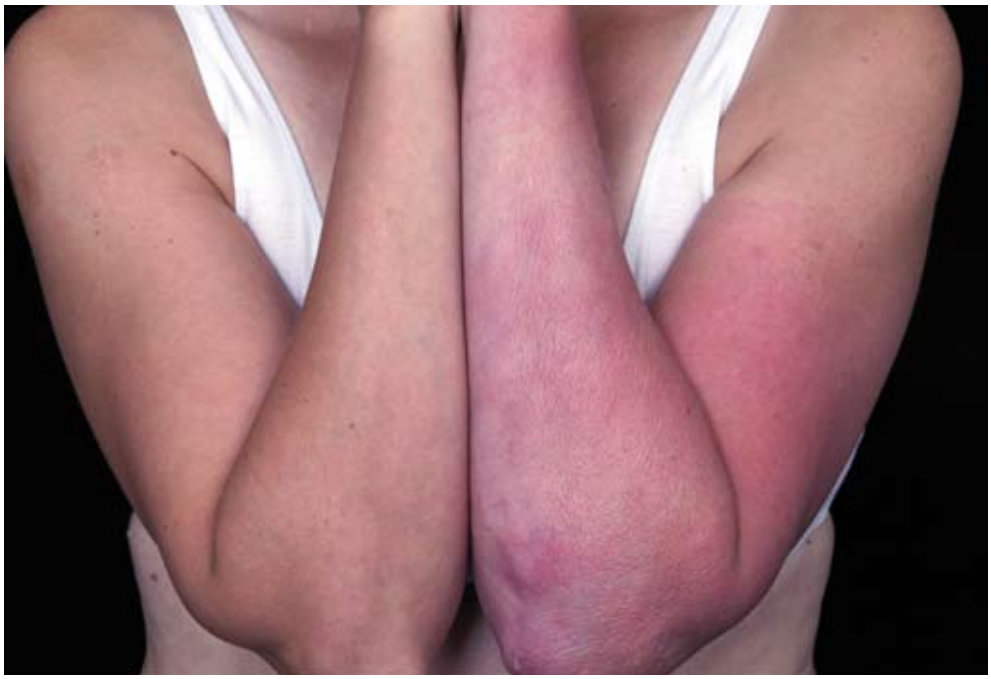

PHOTO QUIZ: Erythematous pigmentation of the arm for more than ten years, *see page 176*

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EDITORIAL

The pathophysiology of organophosphorus pesticide self-poisoning is not so simple

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The paper by Aardema and colleagues in this issue of the *Netherlands Journal of Medicine* illustrates well the problems that clinicians face with organophosphorus pesticide self-poisoning.[1] Yet the toxicological literature's image of this poisoning is beguilingly simple.[2-5] Ingestion of an organophosphorus pesticide results in inhibition of acetylcholinesterase. The resulting build up of acetylcholine causes overstimulation of cholinergic synapses in the autonomic nervous system, central nervous system and neuromuscular junction, producing the acute cholinergic crisis. Patients die from respiratory failure during this crisis, or from a delayed respiratory failure called the intermediate syndrome. Atropine and oximes treat the poisoning.

However, organophosphorus pesticide poisoning in reality is much more complicated than this. The clinical syndrome and cause of death vary according to the precise pesticide ingested.[6] The consequences of aspiration often dominate the clinical picture and treatments do not work so well.[7] As a result, the case fatality may reach 40% in even the best Western intensive care units with parathion poisoning.[8,9]

Organophosphorus pesticide poisoning is a major problem in the developing world where health care is often distant. Many patients in such regions die before they reach health care;[10,11] patient B in Aardema's paper would never have survived to hospital. Patients having a respiratory arrest at home, away from a doctor capable of intubating them, are unlikely to survive.

There seem to be two major factors that affect whether a person ingesting a substantial dose will survive to hospital admission. The first is the speed of action of the pesticide ingested. Some are active poisons and do not require any conversion to effectively inhibit acetylcholinesterase. Others are pro-poisons, or thions, requiring activation by cytochrome P450s in the gut wall and liver to become active. But this conversion may be very fast – parathion can be converted to paraoxon and cause a person to become unconscious in just 10 to 20 minutes.[9] Other thions take longer to work; for example, dimethoate is both slowly converted to its active oxon, omethoate, and a slow inhibitor of acetylcholinesterase.[12] As a consequence, severe poisoning develops over several hours, often allowing a person to survive to hospital admission.[6] Of note, thion pesticides should not all be considered as slower poisons compared with oxon pesticides as there is much variation in speed of activation between thions.

A second little mentioned factor is the solvent in which the pesticide is formulated.[6] In animal studies, we have found that a very large dose of dimethoate containing 40% cyclohexanone and 5% xylene causes apnoea after just five to ten minutes (Eddleston & Clutton, unpublished), well before clinically significant acetylcholinesterase inhibition occurs. By contrast, a similar dose of chlorpyrifos, formulated in 60% naphtha, caused no such respiratory depression. No rules seem to be available concerning the solvents used for organophosphorus pesticides. Generic manufacturers of pesticides for the Asian market tend to formulate the pesticide in 40% xylene; by contrast, branded products from the large international companies vary markedly.

The solvent used for a particular pesticide may well therefore affect the likelihood of prehospital respiratory arrest. This seems to be an area that needs careful research. We do not yet know whether solvents are responsible for early deaths; if they are, it will be valuable to identify a number of safer solvents for pesticide manufacturers.

A fall in Glasgow Coma Scale (GCS) before hospital presentation markedly increases the risk of aspiration. Multiple case series from intensive care units across Asia report that the majority of late deaths are due to aspiration

pneumonia.[13-15] However, the pathophysiological processes leading to these deaths are unclear. In particular, the effects on the lung of blood-borne organophosphorus pesticide (rather than aspirated pesticide) in human poisoning are not known; a study in dogs by Lainee and colleagues[16] reported that an intravenous dose of the organophosphorus nerve agent VX caused breakdown of the alveolar epithelial/endothelial barrier and an inflammatory/exudative infiltrate into the lungs within two hours. Such an effect may well be sufficient to initiate the acute respiratory distress syndrome (ARDS).

The incidence of ARDS in humans with pesticide poisoning after aspiration or as an effect of the absorbed pesticide is not known. Cases of ARDS have been reported after organophosphorus poisoning.[17-22] Perhaps ARDS is the common underlying pathology that explains the large number of deaths after organophosphorus aspiration? Distinguishing ARDS from aspiration pneumonia will be important since treatment is quite different.

The best way for treating poisoned patients is not yet clear.[23] The use of atropine is not contentious. A doubling dose of atropine to ensure rapid atropinisation followed by an infusion titrated to clinical features seems sensible.[24] By contrast, the administration of oximes, such as pralidoxime or obidoxime, is contentious. Their use is recommended by the WHO.[25] However, as discussed by Aardema and colleagues, the evidence for clinical benefit is weak and the subject of much debate.

What is clear is that aged acetylcholinesterase cannot be reactivated by oximes.[26] This reaction occurs quickly in poisoning with fat insoluble dimethyl compounds such as dimethoate, so that oximes are totally ineffective by 12 hours.[27,28] Getting oximes in early in such poisoning is therefore essential if any benefit is to occur. This may be why Pawar and colleagues saw a benefit from the high-dose oxime used in their study for patients presenting within two to three hours.[29,30]

Poisoning with diethyl organophosphorus pesticides such as parathion can respond to oximes for several days, as long as sufficient oxime is given to compete with the pesticide remaining in the blood and the oxime is continued for long enough.[26,31] However, fat soluble pesticides, such as fenthion (whether dimethyl or diethyl), may benefit from oximes for many weeks. After absorption, the pesticide is stored in fat. Over time, perhaps up to several weeks after ingestion, the pesticide is released into the blood and freshly inhibits acetylcholinesterase causing recurrent cholinergic crises.[32] Since this is a new reaction, ageing starts afresh and oximes should remain effective for as long as atropine is required.

The rational use of oximes is complicated,[30] especially when the pesticide ingested is not known. Some patients will not benefit. However, at present, it seems safest to follow the WHO's guideline to give oximes to all patients[25] and to continue them until atropine is no longer required. Perhaps in the future we will have more selective guidelines. However, such guidelines will always be based on knowing the ingested pesticide and this is something that is not always certain even when the pesticide bottle is brought. Where oximes are not available or where patients ingest dimethyl pesticides and present after ten hours, excellent intensive nursing care and ventilation may well be able to compensate for not using oximes.

Treating organophosphorus pesticide poisoned patients will always be messy. The early and sudden onset of symptoms will often mean that clinicians are caring for patients whose predominant pathology (aspiration pneumonia or ARDS, or anoxic brain damage) does not respond to the specific antidotes. Organophosphorus treatment is likely to remain ineffective for a significant proportion of patients as long as fast acting, highly toxic, pesticides are used in agricultural practice. Changing use from the most toxic pesticides to less toxic pesticides has had a remarkable effect in Sri Lanka where the overall suicide rate has fallen by 50% over ten years since such legislation was passed.[33] The introduction of similar legislation across Asia would have a great effect on regional and therefore global suicide rates.

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REVIEW

Organophosphorus pesticide poisoning: cases and developments

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ABSTRACT

Self-poisoning with organophosphate pesticides is a major health problem world-wide. Through the inhibition of acetylcholinesterase, organophosphorus poisoning is characterised by the clinical picture of acute cholinergic crisis. Other manifestations are the intermediate neurotoxic syndrome and delayed polyneuropathy.

In the Western world, the occurrence of organophosphorus poisoning is less prevalent due to the declining availability of organophosphate pesticides, which could render the recognition of this particular type of intoxication and its specific treatment more difficult.

In this article we discuss some recent developments and treatment dilemmas, illustrated by cases from our clinic, followed by a review of the current recommendations in the treatment of organophosphate poisoning.

KEYWORDS

Diagnosis, intoxication, oximes, parathion, treatment

INTRODUCTION

Organophosphates (OP) are used as insecticides in agricultural and domestic settings throughout the world. As nerve agents, they have also been used in warfare[1,2] and terrorist attacks.[3] The mechanism of action is through the inhibition of the enzyme acetylcholinesterase, leading to the accumulation of acetylcholine at cholinergic synapses. The excess acetylcholine causes constant acetylcholine receptor triggering, resulting in malfunction of the autonomic, somatic and central nervous systems.

Clinical manifestations of OP poisoning lead to acute cholinergic crisis (*table 1*). Although parasympathetic overstimulation tends to predominate, the overstimulation of nicotinic receptors due to excess acetylcholine can lead to sympathetic overstimulation, as well (*table 1*).[4]

A second manifestation is the intermediate neurotoxic syndrome, characterised by cranial nerve palsies, weakness of the neck and proximal limbs, and respiratory paralysis.[5,6]

OPs are highly reactive chemicals and their toxicity is not limited to acetylcholinesterase binding. Through the binding to other enzymes delayed neurological symptoms can occur as well.[4,7]

Carbamates are cholinesterase inhibitors structurally related to OP. In comparison to organophosphates they

Table 1. *Clinical manifestations of acute organophosphate poisoning*[4,13,14,16]

Muscarinic
Diarrhoea
Urinary incontinence
Miosis
Bradycardia
Bronchorrhoea
Bronchoconstriction
Salivation
Lacrimation
Emesis
Hypotension
Cardiac arrhythmias*
Nicotinic
Fasciculations
Tremors
Muscle weakness with respiratory failure
Hypertension
Tachycardia
Sweating
Mydriasis
Central nervous system
Altered level of consciousness with respiratory failure
Seizures

*Atrial fibrillation, ventricular fibrillation and heart block have been described[4,14,37]

cause a clinically indistinguishable pattern of symptoms which, however, tend to be milder and of shorter duration.[4]

Their common availability renders OP insecticide poisoning a worldwide health problem affecting millions of patients[8,9] with a high fatality rate.[10] The majority of these poisonings appear to be an act of self-harm.[9,11] Thousands die each year, especially in the Asian Pacific region, where pesticide poisoning is the most frequent cause of fatal self-poisoning.[10,12] Although exact figures on the contribution of insecticides to the number of poisonings in the Netherlands are not available, it is clear that this contribution, both in relative and absolute numbers, is very modest compared with that in many parts of the developing world.

Since 1994 we have admitted 512 patients with intoxication to our ICU, of whom eight had OP or carbamate intoxication. The relative unfamiliarity with pesticide poisoning in the Western part of the world might render it difficult for health care providers to correctly diagnose and treat OP poisoning.

In this article we will illustrate the clinical picture and treatment with three cases and discuss some recent developments and unresolved issues in the treatment of poisoning with OP insecticides.

CASE REPORTS

Patient A

A 37-year-old farmer was transferred from a community hospital to our institution on the ninth day after auto-intoxication with parathion. His medical history was nonsignificant. He had ingested an unknown quantity of parathion with suicidal intent. He had been intubated on admission. Treatment with atropine up to 4 mg/h intravenously and obidoxime 50 mg/h, after two boluses of 250 mg intravenously, was started. On the second day he was extubated. On that same day, progressive respiratory insufficiency developed, necessitating re-intubation. Antibiotics were started to treat possible aspiration. On the eighth day, while still being ventilated, his pulmonary condition worsened. He was referred to our hospital under the diagnosis of ongoing OP toxicity. On admission, he was sedated, and while being treated with dopamine 1.5 µg/kg/min and atropine 4 mg/h, he was normotensive with a heart rate of 90 beats/min and adequate diuresis. He was febrile with a temperature of 38.5°C. He was mechanically ventilated. Further medication included obidoxime 50 mg/h, potassium chloride, sufentanil, ipratropium, salbutamol, enoxaparin, cefuroxime, tobramycin, and trimethoprim-sulphamethoxazole. The chest X-ray showed bilateral infiltrates. His laboratory results showed hyperklaemia (6.7 mmol/l; range 3.6-4.8mmol/l), renal failure with a creatinine of 222 µmol/l (range 62-110), urea of 15.1 mmol/l (range 3.2-6.8) and a cholinesterase level of 140 U/l (range 3700-11,000). Arterial blood gas analysis showed a pH 7.30 (range 7.35-7.45), pCO_2 25.7 kPa (range 9.2-13.9), bicarbonate 22 mmol/l (range 21-25) and oxygen saturation 99% (range 96-100). Other laboratory results were within the normal limits. No conduction abnormalities were seen on an electrocardiogram. Trimethoprim could have played a role in both the patient's renal failure and hyperkalaemia. Other contributing factors to the latter were mild acidosis, likely linked to renal failure, and inappropriate supplementation of potassium.

Potassium suppletion and nephrotoxic drugs were stopped. Atropine infusion was decreased, and sufentanil was replaced by midazolam and morphine. Amoxicillin with clavulanic acid was started to treat suspected ventilator associated pneumonia although sputum culture did not reveal any pathogens. Obidoxime was discontinued. Optimisation of ICU care resulted in tapering of ventilatory support, improved renal function and extubation on the 12th day after initial admission. Atropine was stopped on the 13th day. On the 14th day, the patient was discharged to the medical ward with psychiatric follow-up. The prolonged course was probably due to secondary complications of ICU care such as possible ventilator-associated pneumonia and renal failure. Over-atropinisation resulting in hyperthermia can not be ruled out in retrospect; however, other signs of over-atropinisation including tachycardia and ileus were not present.

Patient B

A 61-year-old man with a history of depression, alcohol abuse and suicidal attempts was admitted to our intensive care. Shortly before admission, he had ingested an unknown quantity of parathion, whereupon he had lost consciousness. Paramedics noted asystole, and cardiopulmonary resuscitation was started. Spontaneous circulation was achieved after ten minutes. He had probably aspirated gastric contents. He was transferred to our hospital. On admission he was comatose (Glasgow-coma scale 1-1-Tube) and mechanically ventilated. He was normotensive with a heart rate of 105 beats/min. His pupils were pin-point and not responding to light. He had bronchorrhoea and diarrhoea. Fasciculations were noted. Further physical examination revealed no abnormalities. Laboratory results showed a leucocytosis of 18.6 x 10^9/l (range 4 to 10 x 10^3/mm^3), and an elevated lactate of 12.5 mmol/l (range 0.5 to 2.2 mmol/l). Further testing revealed slight liver function abnormalities: lactate dehydrogenase 610 U/l (range 114 to 235 U/l), aspartate aminotransferase 87 U/l (range 0 to 40), alanine aminotransferase 51 U/l (range 0 to 30), and γ-glutamyltransferase 64 U/l (range 0 to 65). Arterial

blood gas analysis showed profound, metabolic acidosis with pH 7.1, pCO_2 5.5 kPa, pO_2 24.1 kPa, bicarbonate of 12 mmol/l, and oxygen saturation 98%. A blood cholinesterase level was undetectable. The chest X-ray showed no abnormalities. Electrocardiogram showed no conduction abnormalities. He was treated with atropine 1 mg/h intravenously after boluses of 2 mg and 0.5 mg. Additionally, he was treated with active charcoal and diazepam 10 mg. On the second day, obidoxime was started in boluses of 250 mg. Furthermore, he received rocuronium in boluses to treat fasciculations. His course was complicated by a septic episode and persistent coma. Electroencephalography performed on day 17 showed very little activity; a somatosensory evoked potentials test performed on that same day showed no cortical activity. Based on these results treatment was stopped and the patient died on day 18.
The death of the patient was attributed to prolonged anoxia in the initial phase of intoxication. After circulation was restored, the symptoms of toxicity had been manageable.

Patient C
A 63-year-old farmer with a history of depression was admitted to our hospital after ingestion of approximately 200 ml of parathion several hours earlier. His family alerted medical services when he was found unconscious. On arrival, paramedics saw a comatose man with bradycardia (32 beats/min), bronchorrhoea and dilated pupils. He was intubated instantaneously and started on atropine and obidoxime. On arrival in our hospital, a sedated, intubated man was seen with a blood pressure of 155/85 mmHg, and a pulse of 110 beats/min. He was mechanically ventilated. Blood gas analysis showed pH 7.11, pCO_2 8.5 kPa, pO_2 57.2 kPa, bicarbonate 20 mmol/l and O_2 saturation of 99%. Physical examination showed no abnormalities. His serum parathion level was 800 µg/l (toxic above 10 µg/l) serum cholinesterase was undetectable (range 5400 to 13,200 U/l), indicating severe intoxication. He was given activated charcoal and admitted to our intensive care. Sedation with propofol was continued. Obidoxime 40 mg/h was given intravenously but stopped shortly thereafter. As bronchorrhoea worsened, atropine was started in boluses of 3 mg. On the second day, profound diarrhoea and perspiration was noted. Atropine was titrated to effect on bronchorrhoea and diarrhoea; there was no bradycardia. Boluses of 3 mg intravenously were needed about twice a day. On the seventh day a continuous infusion of atropine 3 to 6 mg/day was started. His course was complicated by pneumonia, probably due to aspiration, and bacteraemia with *Klebsiella* species. He was successfully extubated on the eighth day. Atropine was stopped on the ninth day, to be restarted on the same day due to reappearance of bronchorrhoea and diarrhoea. On the 11th day, atropine was stopped without further complications. On the 12 day, he was discharged to the medical ward. His cholinesterase level was 2000 U/l. On the 20th day, he was discharged to the psychiatric ward.

DISCUSSION

Severely intoxicated patients should receive immediate resuscitation, including circulatory support and mechanical ventilation when indicated. In all three patients immediate adequate resuscitation was indeed started. In our patients the diagnosis of OP intoxication was based on history and confirmed by the clinical picture and decreased serum cholinesterase. All three patients showed signs of acute cholinergic crisis (*table 1*).[4,13,14] However, not all signs and symptoms were present in every patient. Usually the clinical picture and history is sufficient for the diagnosis. When the diagnosis is uncertain, measurement of plasma butyrylcholinesterase (also called plasmacholinesterase or pseudocholinesterase) or erythrocyte acetylcholinesterase can be useful.[4,15] The former is an indirect biomarker of inhibition of acetylcholinesterase and has thus no direct relation to the extent of acetylcholinesterase inhibition in synapses. It can be used, however, to detect exposure to organophosphates.[15,16] Measurement of erythrocyte acetylcholinesterase does reflect acetylcholinesterase inhibition in the nervous system; although a complex interrelationship between erythrocyte and nervous system acetylcholinesterase inhibition exists,[15] levels of erythrocyte acetylcholinesterase are a good marker of severity of OP poisoning.[15,16] For more information on the difficult interpretation of cholinesterase assays, we refer to a recent review.[16]
There is much debate about the treatment of OP toxicity. This is reflected by the treatment of our patients. Important differences in treatment occurred. Most of these differences were based on interpretation of the literature available at that time.
Atropine is undisputedly the cornerstone of the treatment of acute cholinergic syndrome. It competes with acetylcholine on muscarinic acetylcholine receptors.[17] It works within minutes[18] and has a half-life of two to five hours. Uncertainty exists about the starting dose, dose escalation and duration of therapy. Some protocols use fixed boluses for every fixed time period. A protocol with a doubling of the atropine every few minutes reaches the sometimes extreme doses of hundreds of milligrammes earlier and might be more appropriate.[4,19]
Possible parameters for drug titration are miosis, excessive perspiration, hypotension, bradycardia, bronchorrhoea and bronchospasm.[18] However, later on secondary complications due to e.g. hypoxia or pneumonia or atropine overdose, which is characterised by confusion, hyperthermia, and

ileus, can complicate the interpretation of these clinical signs.[4,18] Being a selective muscarinic antagonist, atropine has no effect on the neuromuscular junction and muscle weakness.[4]

In patient C bronchorrhoea was used as a parameter for atropinisation and re-intubation. In this patient, to control diarrhoea and bronchorrhoea, a regimen of atropine 3 mg twice daily was instituted, initially resulting in sufficient control; a switch to continuous infusion was later needed to adequately control patient's symptoms. On reflection, given the half-life of atropine (two to five hours), a twice daily regimen seems illogical. The dilated pupils seen in patient C could have been caused by initial sympathetic overstimulation.[16] However, his overall clinical picture was that of parasympathetic overstimulation, including bradycardia and bronchorrhoea. It is possible that the recording of dilated pupils was made after the administration of atropine.

In patient A atropine was discontinued too early and then probably continued too long because some clinical signs were ascribed to OP instead of atropine or complications due to ICU treatment. As shown in patient C, atropine can be needed for weeks. The duration of this requirement depends on the type of OP, amount of ingested toxin and patient-related pharmacokinetic parameters. There are no clear atropine maintenance and withdrawal schedules. Daily reduction of continuous atropine dosing until clinical signs develop is one option, intermittent dosing of boluses given on indication is another. The continuous infusion of atropine as in these patients is not based on literature. Glycopyrrolate is an alternative to atropine as anticholinergic agent, although it may be less effective in counteracting central nervous system dysfunction due to organophosphorus poisoning. Its place in the therapy needs further study.[17]

Agitation and seizures are treated with benzodiazepines.[4]

The use of oximes in the treatment of OP poisoning is much debated, resulting in different and illogical oxime use in our patients. OP insecticides inhibit acetylcholinesterase by phosphorylating the serine hydroxyl group at the enzyme's active site; acetylcholinesterase is reactivated by the attack of the phosphorylated serine residue by a hydroxyl ion, thus removing the phosphate moiety from the enzyme. Before reactivation, however, the enzyme is prone to a process called ageing, whereby one alkyl side of the phosphoryl moiety is replaced by a hydroxyl group, rendering the acetylcholinesterase molecule negatively charged and therefore inaccessible for reaction with an hydroxyl ion, thus leaving the enzyme unable to be reactivated.[15,20,21] The rationale for oximes, such as obidoxime or pralidoxime, lies in their ability to catalyse the regeneration of active acetylcholinesterase by removing the phosphoryl group from inactivated acetylcholinesterase. The time frame for oximes to be effective is thus restricted to the window before ageing has occurred.[20-22] Every OP has a typical ageing time. Various systematic reviews and meta-analyses failed to find sufficient evidence for benefit from oximes or even suggested harm.[17,20,23,24] Important methodological weaknesses, including underdosing of oximes in most trials,[17,20] are major drawbacks of the trials included in these reviews. A recent randomised controlled trial including 200 patients with moderately severe OP poisoning showed reduced morbidity and mortality in patients treated with high-dose continuous pralidoxime (1 g/h for 48 h after a 2 g loading dose) compared with low-dose bolus (mortality 1% in study group *vs* 8% in control group).[25] It is the first known trial dosing oximes as recommended by the World Health Organisation (WHO) in a dose of 8 to 10 mg of pralidoxime per kg body weight per hour after a loading dose of 2 g.[26] This study, however, received criticism on methodology and ethical issues.[27-31] Some of the criticism comprised the observation that the study was biased in that only moderately severely intoxicated patients who presented very early (longest interval between presentation and randomisation 7.5 h) were included, which was acknowledged by the author.[32] Thus far, the WHO has recommended treatment with high doses of pralidoxime as mentioned above. [26]

However, in terms of evidence-based medicine the classification is level B at best. Alternatives for oximes, such as α2-adrenergic receptor antagonists or OP hydrolases, are theoretically conceivable but have either not been tested adequately or not been tested at all as yet.[8,17]

Gastric lavage and the administration of activated charcoal have no proven beneficial effect but are still frequently used.[17,18] Skin decontamination with water and soap and removal of exposed garments is advised in order to minimise the extent of intoxication.[18] Exposure of health care workers should be prevented although severe secondary intoxications have not been described. Exposure can be limited by reducing the number of caregivers involved, limiting exposure time, the usual protective clothing (eye protection, gloves and gown) and good ventilation of the room.

There are several reports of occupational exposure followed by symptoms,[33,34] although an actual secondary intoxication has thus far never been proved.[35,36] In affected health care workers, acetylcholinesterase levels were never measured;[33,34,36] most organophosphate compounds are dissolved in highly volatile foul smelling solvents which are more likely to cause complaints than the non-volatile organophosphate compounds themselves.[35] In conclusion, although a widespread problem world-wide, poisoning with insecticides is relatively rare in Western Europe. Recognition is important, as pesticide poisoning is associated with a high fatality rate. Patients are treated using standard resuscitation care with atropine to counteract muscarinic effects. Although the use of oximes is not evidence-based,

thus far it has been recommended by the WHO pending further clinical trials. Hopefully, more insight into the optimal treatment of pesticide poisoning and the regulation of availability of these highly toxic compounds will enable prevention of many deaths in the near future.

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ORIGINAL ARTICLE

Preoperative levosimendan in heart failure patients undergoing noncardiac surgery

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ABSTRACT

Background: Heart failure (HF) is a major cause of perioperative morbidity and mortality in noncardiac surgery. Preoperative optimisation of these patients is, thus, of utmost importance. Levosimendan seems promising for patients undergoing cardiac surgery; however, its safety and efficacy in HF patients undergoing noncardiac surgery have not been evaluated.

Objective: To evaluate the effects of prophylactic preoperative levosimendan administration on left ventricular function in HF patients undergoing noncardiac surgery.

Methods: HF patients with ejection fraction <30% undergoing elective noncardiac surgery in 2005 were included in this prospective study. Patients were admitted to our surgical intensive care unit one day preoperatively. Under continuous haemodynamic monitoring, the treatment protocol consisted of an initial loading dose (24 μg/kg) for ten minutes followed by a continuous 24-hour infusion (0.1 μg/kg/min) at the end of which patients underwent surgery. Echocardiography was performed before infusion (day 0) and on the 7th postinfusion day (day 7). Measurements included left ventricular ejection fraction (LVEF), velocity time integral (VTI), pre-ejection period (PEP), ejection time (ET), maximum (P_{max}) and minimum (P_{min}) transvalvular aortic pressure gradient, and maximum (V_{max}) and minimum (V_{min}) aortic velocity.

Results: Twelve consecutive patients were enrolled. Levosimendan resulted in a significant increase in LVEF, VTI, P_{max}, P_{min}, V_{max}, and V_{min} ($p<0.01$) and, moreover, a significant reduction in PEP, ET, and PEP/ET ($p=0.04$) on day 7 compared with day 0 values. No adverse reactions, complications or mortality occurred during 30-day follow-up.

Conclusion: Prophylactic preoperative levosimendan treatment may be safe and efficient for perioperative optimisation of heart failure patients undergoing noncardiac surgery.

KEYWORDS

Elective noncardiac surgery, heart failure, inotropes, left ventricular function, perioperative optimisation, prophylactic preoperative levosimendan infusion

INTRODUCTION

Heart failure (HF) is an important public health problem, with a 6 to 10% incidence in the population over 65, and a common reason for hospitalisation among elderly adults.[1] It is also a frequent and significant risk factor for perioperative morbidity and mortality[1,2] that results in a twofold higher mortality after major noncardiac surgery compared with patients with coronary artery disease or the general population.[2] The importance of HF as an independent risk factor is underlined by the fact that patients with coronary artery disease but without HF have a similar 30-day mortality rate to the general population.[1] HF patients are undergoing noncardiac surgery with an increased frequency due to their advanced age.[1] Despite advances in perioperative care, however, they still suffer substantial morbidity and mortality. Although their preoperative optimisation is of utmost importance, guidelines for their perioperative management have not been clarified. Prophylactic inotropic therapy remains controversial;[3,4] its efficacy is debatable and it has been

associated with increased myocardial oxygen consumption, arrhythmias, and even mortality.[4]

In contrast, levosimendan, a novel positive inotrope, improves cardiac performance and haemodynamics in HF patients without increasing myocardial oxygen demand or causing arrhythmias.[5-8] Its pharmacological effects last for at least seven days after discontinuation, the postoperative period in which most cardiac complications occur.[8] It has been used for perioperative optimisation in patients undergoing cardiac surgery in a few studies with promising results;[9-11] however, it has not been evaluated in noncardiac surgery before. Taking advantage of its pharmacological profile, this prospective study aimed to evaluate the safety and efficacy of prophylactic preoperative levosimendan treatment on left ventricular function in the perioperative period in HF patients undergoing elective noncardiac surgery.

MATERIALS AND METHODS

This prospective study was conducted in the surgical intensive care unit (SICU), 1st Department of Propaedeutic Surgery of the University of Athens, Hippokrateion Hospital, Athens, Greece from January to December 2005. Patients with chronic cardiac failure with a left ventricular ejection fraction <30% undergoing elective noncardiac surgery were included in the study. Exclusion criteria were heart failure due to restrictive or obstructive cardiomyopathy or to nontreated severe valvular disease, history of ventricular tachycardia or fibrillation, second- or third-degree atrioventricular block, systolic arterial blood pressure <85 mmHg, heart rate >120 beats/min at rest, severe renal failure (defined as creatinine clearance <30 ml/min), and severe hepatic cirrhosis (defined as class C according to the Child-Pugh scoring system).[12] Institutional Review Board approval was obtained prior to study initiation and written, informed consent was signed in all cases.

Preoperative risk stratification for each patient was performed according to the Goldman Cardiac Risk Index,[13] New York Heart Association (NYHA),[14] and American Society of Anaesthesiologists (ASA) classification.[15] All patients were admitted to the SICU the day before surgery for levosimendan treatment and close haemodynamic monitoring, including continuous arterial blood pressure monitoring via a radial artery catheter (systolic: SAP, mean: MAP, and diastolic arterial pressure: DAP), heart rate (HR) via electrocardiogram, urine output through a bladder catheter, pulmonary artery catheter data, and pulse oximetry. In addition, blood gas analysis was performed every three hours and blood tests every 12 hours. Blood tests included white blood cells, platelets, haematocrit, haemoglobulin, coagulation, glucose, urea, creatinine, electrolytes, amylase, lactic dehydrogenase, creatinine phosphokinase and creatinine phosphokinase-MB, troponin, and liver function tests.

Transthoracic echocardiographic evaluation was performed on admission to the SICU, prior to levosimendan administration (day 0), and on the 7th postinfusion day (day 7). Measurements included left ventricular ejection fraction (LVEF), velocity time integral (VTI), pre-ejection period (PEP), ejection time (ET), maximum (P_{max}) and minimum transvalvular aortic pressure gradient (P_{min}), maximum (V_{max}) and minimum aortic velocity (V_{min}). The VTI x HR product and PEP/ET fraction were also estimated.

After right cardiac catheterisation, echocardiography, and initiation of haemodynamic monitoring, levosimendan was administered. The levosimendan treatment protocol consisted of an initial loading dose (24 μg/kg) for ten minutes which was followed by a continuous 24-hour infusion (0.1 μg/kg/min). Criteria for dose reduction were hypotension (systolic arterial pressure <80 mmHg), heart rate >140 beats/min or increased by >25 beats/min for at least ten minutes and arrhythmias. If these continued after dose reduction or anaphylactic or other adverse reactions occurred, levosimendan treatment protocol was immediately terminated.

All patients remained under continuous haemodynamic monitoring in the SICU during the whole administration period and underwent surgery immediately after the end of infusion under the same intraoperative haemodynamic monitoring. Monitoring was continued postoperatively in the SICU until 24 hours postinfusion. Patients were then discharged from the SICU to the ward. Noninvasive monitoring in the ward included arterial pressure, heart rate, electrocardiogram, pulse oximetry, and urine output every three hours, clinical evaluation by the same surgical team every three hours, blood gas analysis every 12 hours, and blood tests once daily. After discharge from the hospital, patients were seen on the 7th, 14th, and 30th postoperative day.

Statistical analysis was performed with the SPSS 12.0 software statistical package. Data are expressed as median ± SD (standard deviation) and ranges. Comparisons between recorded data on day 0 and day 7 were performed using the nonparametric Wilcoxon signed-rank test. Haemodynamic variables at 0 min, 10 min, and 24 hours were compared using paired-samples t-test. A p value <0.05 was regarded as statistically significant.

RESULTS

During the one-year study period, 12 consecutive patients were included in our study. Patients' demographics, surgical procedures, and preoperative Goldman Cardiac

Risk Index, NYHA functional class, and ASA physical status are shown in *table 1*. Median age was 75 ± 3 years (range: 64-83 years); 8 (66.7%) of them were men. Median hospital stay was 5 ± 2.2 days.

The cause of HF was coronary artery disease in ten (83.3%) and hypertension in two (16.7%) patients. Four patients (33.3%) had previously had a myocardial infarction, all of whom more than six months prior to surgery, four (33.3%) had diabetes mellitus, seven (58.3%) hypertension, four (33.3%) peripheral arterial occlusive disease, three (25%) hypercholesterolaemia, and one patient (8.3%) had undergone coronary artery bypass surgery. Regarding concomitant medication of the study patients, eight (66.7%) were receiving angiotensin-converting enzyme inhibitors, five (41.6%) digoxin, five (41.6%) loop diuretics (furosemide), four (33.3%) nitrates, three (25%) β-blockers, three (25%) statins, two (16.7%) spironolactone and one patient (8.3%) diltiazem.

Levosimendan was well tolerated in all patients. No hypotension, heart rate >140 beats/min or increase in heart rate by >25 beats/min, or arrhythmias were identified during the observation period. Discontinuation or dose reduction was not necessary in any of the patients. No adverse reactions, complications or mortality occurred during 30-day follow-up.

Haemodynamic data of the patients during levosimendan infusion are presented in *table 2*. Levosimendan showed no significant effect on SAP, MAP, DAP, PAP or PWP, whereas a significant increase in CO (p=0.01) and a reduction of SVR (p=0.01) were observed. Heart rate increased from 75 ± 9.2 beats/min to 89 ± 7.6 beats/min and 90 ± 5.4 beats/min at 24 hours and on day 7 (p=0.05), respectively.

Echocardiographic measurements before levosimendan administration (day 0) and on the 7th postinfusion day (day 7) are presented in *table 3*. Levosimendan resulted in a significant increase of 11% in LVEF (from 21 ± 4.2 to 32 ± 7.8, p<0.01). Effects of levosimendan on ejection fraction in each patient are depicted in *figure 1*; all patients experienced a significant improvement in LVEF on day 7. In addition, compared with day 0 values, VTI and VTI x HR product were significantly increased (from 21.2 ± 3.6 cm to 23.5 ± 3.2 cm, p<0.01 and from 1396.7 ± 418.3 cm/min to 2168.9 ± 235.1 cm/min, p<0.01, respectively). Moreover, PEP, ET and PEP/ET were significantly decreased on the 7th postinfusion day when compared with preinfusion values (70 ± 22.2 msec *vs* 90 ± 24.5 msec, p=0.04, 260 ± 34.4 msec *vs* 270 ± 30.4

Table 1. *Demographics, surgical procedures and preoperative risk stratification of the patients*

Patient	Sex	Age	Operation	Goldman Cardiac Risk Index	NYHA	ASA
1	Female	64	Open cholecystectomy	I	2	3
2	Male	72	Abdominal hernia repair	I	2	4
3	Male	78	Abdominal hernia repair	I	2	3
4	Female	77	Abdominal hernia repair	I	2	3
5	Male	83	Abdominal hernia repair	I	3	4
6	Male	77	Hartmann's procedure	III	3	4
7	Male	78	Adhesiolysis	III	3	4
8	Male	75	Choledochojejunostomy	II	2	4
9	Male	83	Open cholecystectomy	III	3	4
10	Female	67	Abdominal hernia repair	II	2	4
11	Female	77	Abdominal hernia repair	II	3	4
12	Male	70	Abdominal hernia repair	II	2	4

NYHA = New York Heart Association functional class; ASA = American Society of Anaesthesiologists physical status.[15]

Table 2. *Haemodynamic data during levosimendan infusion*

Variable	Value 0 min	Value 10 min	Value 24 hrs	p value (0 *vs* 10 min)	p value (0 min *vs* 24 hrs)
Heart rate (beats/min)	75 ± 9.2	85 ± 8.4	89 ± 7.6	NS	0.05
Systolic arterial pressure (mmHg)	154 ± 17.5	150.5 ± 22.9	149 ± 15.6	NS	NS
Diastolic arterial pressure (mmHg)	73 ± 6.2	72 ± 9.4	71 ± 10.9	NS	NS
Mean arterial pressure (mmHg)	99 ± 9.3	97.5 ± 13.4	96 ± 11	NS	NS
Pulmonary artery pressure (mmHg)	19.5 ± 7.8	19 ± 7.2	20 ± 5.2	NS	NS
Pulmonary wedge pressure (mmHg)	10 ± 5.9	10 ± 6.3	11 ± 4.1	NS	NS
Cardiac output (l/min)	4.2 ± 0.5	5.1 ± 0.7	6.7 ± 0.8	0.01	0.01
Systemic vascular resistance (dyn. sec/cm^5)	1710.5 ± 223.2	1342 ± 264.6	970.5 ± 212.3	0.01	0.01

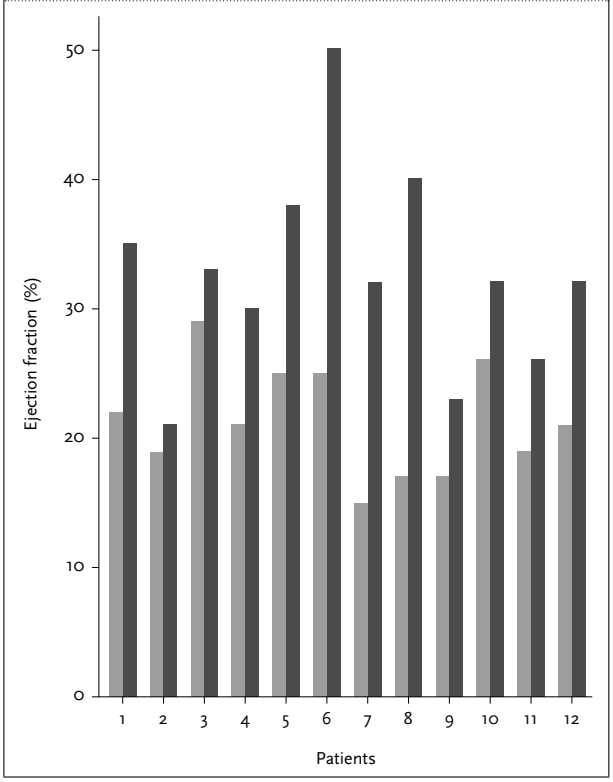
NS = not statistically significant.

Table 3. *Comparison between echocardiographic measurements before levosimendan administration (day 0) and on the 7th postinfusion day (day 7)*[1]

Variable	Day 0	Day 7	p value
Left ventricular ejection fraction (%)	21 ± 4.2	32 ± 7.8	<0.01
Velocity time integral (cm)	21.2 ± 3.6	23.5 ± 3.2	<0.01
Velocity time integral x heart rate (cm/min)	1396.7 ± 418.3	2168.9 ± 235.1	<0.01
Pre-ejection period (msec)	90 ± 24.5	70 ± 22.2	0.04
Ejection time (msec)	270 ± 30.4	260 ± 34.4	0.04
Pre-ejection period/ejection time	0.3 ± 0.1	0.2 ± 0.1	0.04
V_{max} (m/sec)	1.2 ± 0.1	1.4 ± 0.1	<0.01
V_{min} (m/sec)	0.8 ± 0.1	0.9 ± 0.1	<0.01
P_{max} (mmHg)	6.1 ± 1.6	8 ± 1.1	<0.01
P_{min} (mmHg)	3 ± 0.5	4.3 ± 0.8	<0.01

[1]**Values are expressed as median ± SD (standard deviation). V_{max} = maximum aortic velocity; V_{min} = minimum aortic velocity; P_{max} = maximum transvalvular aortic pressure gradient; P_{min} = minimum transvalvular aortic pressure gradient.**

Figure 1. *Ejection fraction before levosimendan infusion (■) and on the 7th postinfusion day (■)*



msec, p=0.04, and 0.2 ± 0.1 *vs* 0.3 ± 0.1, p=0.04, respectively). Levosimendan treatment also exerted a significant effect on P_{max} (from 6.1 ± 1.6 mmHg on day 0 to 8 ± 1.1 mmHg on day 7, p<0.01), P_{min} (from 3 ± 0.5 mmHg to 4.3 ± 0.8 mmHg, p<0.01), V_{max} (1.2 ± 0.1 m/sec *vs* 1.4 ± 0.1 m/sec, p<0.01), and V_{min} (0.8 ± 0.1 m/sec *vs* 0.9 ± 0.1 m/sec, p<0.01).

DISCUSSION

Heart failure is a major cause of perioperative morbidity and mortality in patients undergoing noncardiac surgery, making strategies to reduce cardiac events in such high-risk patients of utmost importance.[1,2,16] Perioperative cardiac evaluation and therapeutic interventions for prevention of cardiac complications, however, are mostly focused on the management of myocardial ischaemia. In contrast, there is still very little known about the perioperative cardiac optimisation of HF patients scheduled for elective noncardiac surgery. The lack of strict guidelines for the management of these patients underlines the complexity of the problem.

Prophylactic use of inotropic support remains controversial. Flancbaum *et al.* suggested that preoperative correction of abnormal haemodynamic parameters with inotropes, crystalloids, packed red blood cells, and/or afterload reduction may reduce postoperative cardiovascular complications in a retrospective study of patients undergoing major elective noncardiac, nonthoracic surgery[3] while, in a prospective randomised trial, Hayes *et al.* reported that dobutamine failed to improve outcome and was associated with increased mortality.[4]

Levosimendan is a calcium sensitiser with inotropic and vasodilatory properties, the safety and effectiveness of which have been shown in several studies of HF patients.[5-8,17-21] Levosimendan in patients with left ventricular systolic dysfunction results in beneficial haemodynamic effects with decreases in left and right filling pressures and systemic vascular resistance and increases in stroke volume and cardiac index. Moreover, the current literature, although limited, suggests that prophylactic levosimendan in cardiac surgery is safe and efficient in terms of cardiac performance, haemodynamics, duration of intubation, and survival.[9-11] However, it has not been evaluated in HF patients undergoing noncardiac surgery. Given its long-lasting effects on cardiac performance, the objective of this study was to evaluate the safety and efficacy of prophylactic preoperative levosimendan administration in these patients and, particularly, its effects on left ventricular function.

A significant increase in LVEF, VTI, VTI x HR, P_{max}, P_{min}, V_{max}, V_{min}, and CO along with a reduction in PEP, ET, PEP/ET, and SVR were identified seven days after levosimendan treatment. These effects were observed in each study patient. Levosimendan had no significant effect on arterial blood pressure while heart rate was marginally increased. Levosimendan infusion was well tolerated in all patients and no additional inotropic support, dose reduction or withdrawal were necessary and no arrhythmias, adverse reactions, complications or mortality occurred during 30-day follow-up.

Levosimendan has been shown to improve left ventricular function without having an effect on arterial pressure or proarrhythmic properties.[5,8-10,18,20] Such effects may be significant since perioperative left ventricular dysfunction is a predictor of postoperative cardiovascular complications and mortality, while left ventricular ejection fraction is one of the most important predictors of prognosis in HF patients.[22,23] It has also been reported to increase survival compared with dobutamine or placebo, a result that was maintained for 180 days.[5,6,20] Regarding heart rate, some studies suggest that it may be increased particularly with high doses of levosimendan[11,21] while others found no significant effect.[9,20] Since a higher heart rate may be detrimental in such patients, the effect of levosimendan on heart rate and its relation to the administered dose merit further study.

Calcium sensitisers are a new class of inotropic agents that enhance myocardial contractility through augmenting the sensitivity of the myofilaments to calcium by binding to troponin C. Levosimendan has unique characteristics as it stabilises the interaction between calcium and troponin C by binding to troponin C in a calcium-dependent manner.[7,24] Increased sensitivity to calcium is probably its main mechanism of action while phosphodiesterase enzyme inhibition is a less important mechanism.[7,25] In contrast to other agents, levosimendan has the advantage that the increased contractility is achieved without energy expenditure, thus improving cardiac performance and haemodynamics without increasing myocardial oxygen consumption.[5-7,25] Furthermore, it exerts vasodilatory properties through activation of ATP-dependent potassium channels in smooth muscle of peripheral, pulmonary, and coronary vessels. It thus results in coronary vasodilatation improving heart oxygenation and showing protective effects to the myocardium.[7,25] Interestingly, it also has beneficial anti-inflammatory, antioxidant, and antiapoptotic effects.[17-19] These immunomodulatory properties may contribute to improvement of cardiac performance.

The active metabolite of levosimendan, OR-1896, has a long half-life of approximately 80 hours and can be detected in the circulation up to two weeks after discontinuation of a 24-hour infusion.[25] Beneficial effects on cardiac performance are, therefore, sustained for at least seven days after termination of a single 24-hour infusion.[8] In agreement with this observation, improvement in left ventricular function was identified on the 7th postinfusion day in our patients. This characteristic of levosimendan seems very important since optimisation of cardiac performance is maintained throughout the immediate postoperative period when perioperative stress is higher and cardiovascular complications are, therefore, more likely to occur.

Our results indicate that levosimendan may have promising effects for perioperative cardiac optimisation of HF patients undergoing elective noncardiac surgery in terms of safety and efficacy. The present study, however, is limited due to the small number of patients and the lack of a control group in order to exclude any potential effects of other factors than the infusion of levosimendan. Our study shows, however, that levosimendan can be safely administered in chronic heart failure patients undergoing noncardiac surgery. These data would support a prospective, randomised, controlled trial. Further studies are, therefore, needed to evaluate the cardioprotective benefit and safety of levosimendan in these patients. Sound clinical judgment, close perioperative monitoring, and individualised therapeutic approach are essential for reduction of postoperative cardiac morbidity and mortality in this fragile group of patients.

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CASE REPORT

Visceral involvement in an immunocompetent male: a rare presentation of cat scratch disease

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ABSTRACT

We report a case of an adult, immunocompetent male with lymphadenopathy of both groins, para-aortal lymph nodes and multiple lesions in the spleen. A neoplasm was excluded by histology of the largest lymph node from the left groin. The diagnosis of cat-scratch disease (CSD) became apparent when serological testing for *Bartonella henselae* showed to be positive. A review of literature shows that disseminated (visceral) infection is a rare presentation of CSD.

KEYWORDS

Bartonella henselae, cat-scratch disease, spleen, visceral

INTRODUCTION

Cat-scratch disease (CSD) is an infectious disease generally seen among children and young adults and is caused by *Bartonella henselae*. It presents with a primary dermal lesion and regional lymphadenopathy after a scratch from an infected cat. Disseminated infection with extended lymphadenopathy, visceral involvement, and neurological and ocular manifestations is rare in adults and immunocompetent persons.

CASE REPORT

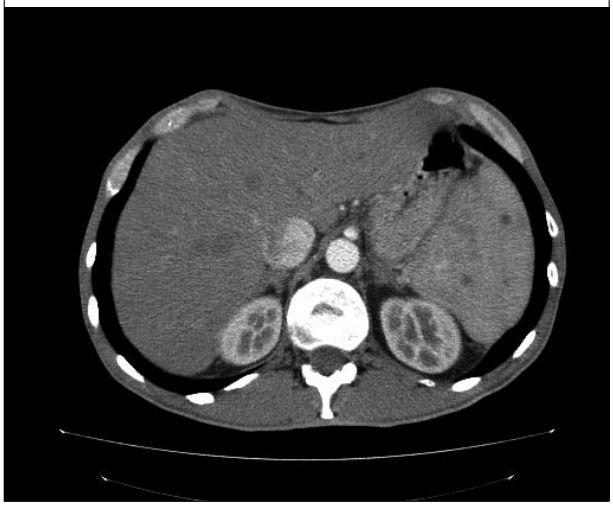
Two weeks before admission to our hospital, a 49-year-old man noticed a painful swelling in the left groin. For a few days this was accompanied by fever and transpiration during the night. After his divorce, about a year ago, he suffered an unknown amount of weight loss. He had not had any unsafe sexual intercourse during the previous year.

At physical examination he was in a clinical good condition with a temperature of 38.6°C. In the left groin, a painful enlarged lymph node of 3.5 cm was palpable. There was also a slightly enlarged lymph node in the right groin. No enlarged lymph nodes were detectable in the cervical and axillary regions. Physical examination of the heart, lungs and abdomen was normal.

Laboratory testing showed a raised C-reactive protein (145 mg/l) and a peripheral white blood cell count of 12.0 x 10^9/l with 15% monocytes. Serological studies for various infectious diseases were taken at that time. Needle biopsy of the largest lymph node in the left groin had no purulent aspect and was aseptic. The lymphocyte populations were normal (CD4/CD8 ratio 2.4 and kappa/lambda ratio 1.8).

Abdominal computed tomography (CT) showed enlarged lymph nodes in both groins and a pathological enlargement of lymph nodes in the para-aortal region. Multiple hypodense round lesions were found in an enlarged spleen (*figure 1*). Because we could not exclude a neoplasm at this time, we decided to extirpate the largest lymph node from

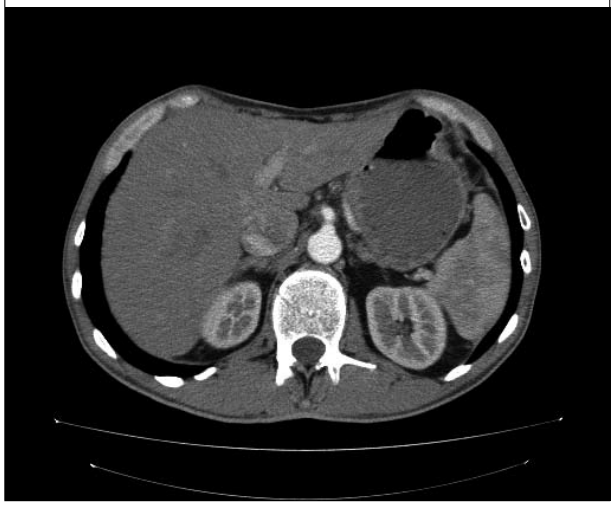
Figure 1. *Multiple hypodense round lesions are visible in the enlarged spleen on admission*



the left groin. Histology of this lymph node revealed a sclerosed aspect, without signs of malignancy or acute inflammation.

After two weeks the ELISA for *B. henselae* IgM proved to be positive and the IgG specific for *B. henselae* was 3.53 g/l. Afterwards he remembered that he had been scratched by a cat. Serological tests were negative for other pathogens, such as HIV and chlamydia trachomatis. We had no suspicion of immunodeficiency in this patient, because of the lack of infections in his medical history, the negative HIV serology and a normal serum electrophoresis. Afterwards we asked the pathologist to stain the lymph node for *Bartonella*. A Giemsa staining showed intracellular micro-organisms. We decided not to treat him with antibiotics because of his good clinical condition and the fact that CSD is a self-limiting disease. Three months later the CT scan of the abdomen showed that the lesions in the spleen had completely disappeared (*figure 2*). Seven months after presentation the ELISA for *B. henselae* IgM had become negative and serological tests showed a raise in specific IgG levels (5.5 g/l).

Figure 2. *After three months, the spleen regained its normal size and the lesions resolved*



DISCUSSION

CSD is a world-wide infectious disease caused by *B. henselae*, a Gram stain negative, intracellular rod. In the Netherlands the incidence of CSD is approximately two cases per 100,000 and about 300 to 1000 cases per year.[1] Studies show that about 14 to 53% of the cats and kittens have positive serology testing for *B. henselae*. There are indications that cats are not permanently infected, but are periodically virulent.[2]

CSD typically presents with a localised papule after a cat scratch. Lymphadenopathy affects the proximal lymph region and arises within one to two weeks of inoculation and can persist over 12 months. One-third of the patients have systemic symptoms such as fever, headache and lethargy. The diagnosis of CSD can be made on the typical history of a recent scratch combined with typical clinical findings. Laboratory diagnosis is based on a positive IgM serology. The tiny *B. henselae* can not be seen in sections stained by tissue Gram methods, but can be found in Giemsa-stained sections.[3] A positive polymerase chain reaction (PCR) for *B. henselae* on tissue is the ultimate evidence for CSD. This test is not available in many laboratories. The clinical findings with a positive IgM for *Bartonella* and seroconversion give enough evidence for the diagnosis of CSD. We did not perform PCR on the lymph node. CSD is a self-limiting disease and does not need antimicrobacterial treatment, although there are reported cases of disseminated CSD treated with antibiotics.[4] Antibiotics with proved clinical efficacy are macrolides,[5,6] gentamicin, rifampicin, tetracycline and ciprofloxacin. Bass *et al.* report a significant decrease in lymph node volume in the first month after treatment with five days of azithromycin.[5] In our hospital only immunoincompetent patients with CSD are treated with antibiotics.

Lymphadenopathy and visceral involvement is rare in CSD. A small number of the patients present with lymphadenopathy and granulomas in the liver, bones, lungs and spleen. Less common manifestations of CSD include the oculoglandular syndrome, meningitis and pneumonia. In the last two decades, several reports about visceral involvement in CSD have been published. Two articles report a patient with granulomas in the liver and spleen without lymphadenopathy.[7,8] Daybell *et al.* report a splenic rupture due to a disseminated CSD, which is a very rare complication. What is remarkable is the large numbers of immunoincompetent patients who suffer from disseminated CSD. Persons infected with HIV can present with bacillary angiomatosis and hepatic peilosis due to CSD.[9]

Our case shows the possibility of lymphadenopathy and lesions in the spleen due to CSD. The combination of lymphadenopathy and lesions in the liver and spleen can be seen in infectious diseases such as *Entamoeba histolytica*, mycobacterium tuberculosis or pyogenic bacteria such as *Salmonella* and *B. henselae*. On the other hand, neoplasms such as Hodgkin's and non-Hodgkin's lymphoma and acute leukaemia should always be included in the differential diagnosis.[10] In this case, histology of the largest lymph node excluded malignancy. Our patient recovered spontaneously within a few months.

CONCLUSION

This case demonstrates the possibility of lymphadopathy and involvement of the spleen due to CSD in an immunocompetent adult person. That is why we emphasise

the importance of considering CSD when lymphadenopathy and lesions in visceral organs are present, even though the patient is immunocompetent.

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CASE REPORT

Paraganglioma of the urinary bladder

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ABSTRACT

Since paragangliomas of the urinary bladder are rare and not easily recognised, histological examination is often the only leading key to diagnosis. We report on a patient with a paraganglioma of the urinary bladder. Although the patient presented with classical signs and symptoms, these were only appreciated after histological examination of a transurethral resection specimen had elucidated the correct diagnosis.

KEYWORDS

Micturition-induced palpitations, paraganglioma, urinary bladder

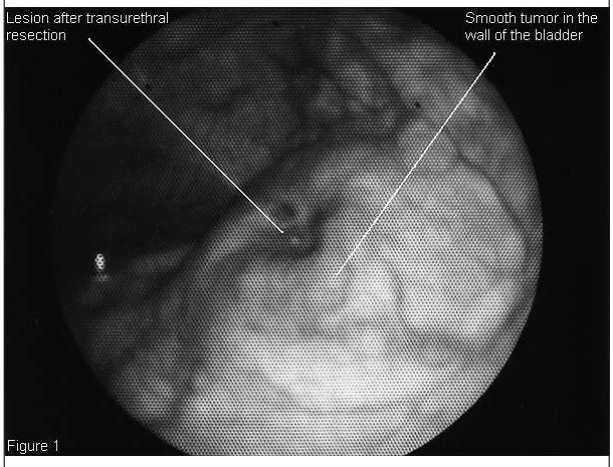
INTRODUCTION

Pheochromocytomas are catecholamine-producing tumours usually localised in the adrenal medulla. However, 9 to 23% may arise extra-adrenally and are referred to as paragangliomas.[1] Since paragangliomas of the urinary bladder are rare and not easily recognised, histological examination is often the only key leading to diagnosis. We report on a patient with a paraganglioma of the urinary bladder. Although the patient presented with classical signs and symptoms these were only appreciated after histological examination of a transurethral resection specimen had elucidated the correct diagnosis. In presenting this case and a supplementary review of previously published cases and literature, we bring attention to the specific signs and symptoms and management of paraganglioma of the urinary bladder.

CASE REPORT

A 47-year-old man presented to the urologist with headache, palpitations, sweating and pallor immediately following micturition. Ultrasonography revealed an abnormal mass in the urinary bladder wall. This was confirmed by cystoscopy demonstrating a smooth tumour in the wall of the bladder with normal mucosa (*figure 1*). Additional computed tomography of the abdomen showed a solitary tumour limited to the bladder wall (*figure 2*). Subsequently, transurethral resection was performed to obtain tissue material for histological examination. During this procedure, a transient elevation of blood pressure with a concomitant decrease in heart rate occurred (*figure 3*). Histological examination revealed positive immunostaining for anti-S100, anti-CD 56, antichromogranin and antisynaptophysin, compatible with a paraganglioma. After referral to the department of internal medicine, additional testing showed that the plasma concentration of norepinephrine was already substantially elevated before micturition with a threefold increase directly following micturition (*table 1*). Urinary excretion of

Figure 1. *Cystoscopy showing a smooth tumour located in the urinary bladder wall with normal mucosa*



The impression in the middle of the tumour is due to the transurethral resection performed during a previous cystoscopy.

Figure 2. *Computer tomography scan of the abdomen showing a tumour with a diameter of 35 mm in the urinary bladder wall*

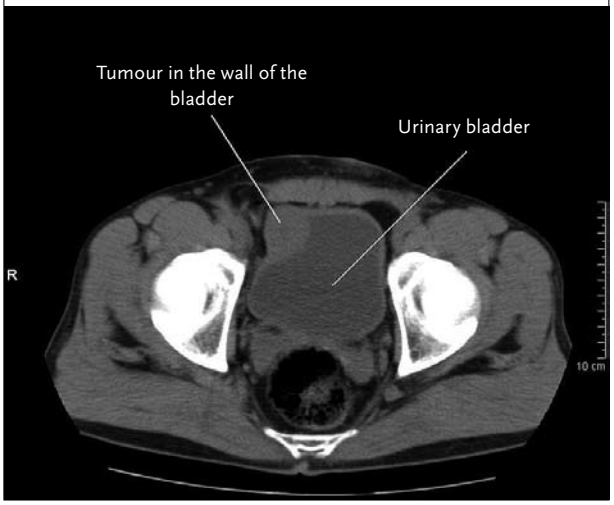


Figure 3. *Haemodynamic parameters during transurethral resection in a patient with a paraganglioma of the urinary bladder*

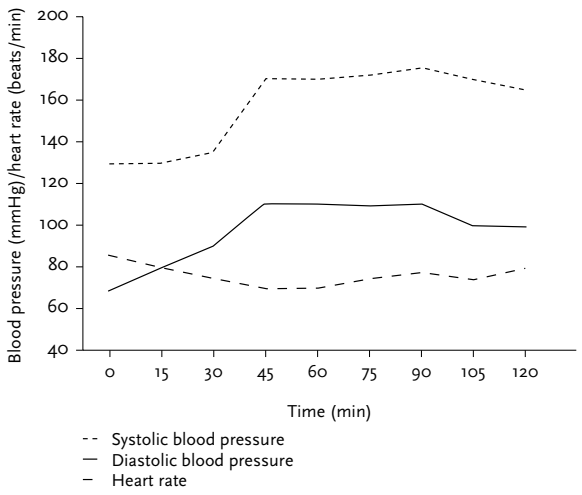


Table 1. *Norepinephrine, epinephrine and dopamine plasma concentrations in a patient with a paraganglioma of the urinary bladder*

	Supine position		
	Before micturition (preoperative)	**Post-micturition (preoperative)**	**Post-micturition (postoperative)**
Norepinephrine (100-600 pg/ml)*	2130	6116	173
Epinephrine (20-100 pg/ml)*	16	7	22
Dopamine (0-60 pg/ml)*	10	86	6

* **Normal, reference values are given in parenthesis.**

metanephrine in 24-hour urine samples remained within the normal range. However, urinary concentrations of normetanephrine were elevated up to 8.70 µmol/24 h (reference value: <5.1 µmol/24 h). Metaiodobenzylguanidine scintigraphy (iodine-131-MIBG) showed no uptake. Following treatment with α- and β-adrenergic blocking agents, a partial cystectomy was performed without complications. In the postoperative phase, the plasma norepinephrine level returned to normal and the patient's symptoms disappeared. Because of the extra-adrenal localisation of the pheochromocytoma occurring at an age of 47 years, genetic testing was performed to identify the risk of inheritance. We searched for germ-line mutations of genes encoding for succinate dehydrogenase (SDH) subunits B and D. However, no such mutations were found. Up until now, there are no signs of recurrence.

DISCUSSION

In 1953 Zimmerman *et al.* reported the first case of bladder paraganglioma.[2] Paragangliomas of the urinary bladder are rare and represent 6% of all paragangliomas and constitute less than 1% of all bladder tumours.[3,4] They occur more frequently in women than in men, primarily during the second and third decades.[3,5] The embryonal origin of these tumours is uncertain. Small nests of paraganglionic tissue may persist along the aortic axis and in the pelvic regions and migrate into the urinary bladder wall during development.[5] Most paragangliomas of the urinary bladder are solitary and localised submucosally on the dome or the trigone of the bladder.[4,5] Histopathological examination shows a typical Zellballen pattern of growth and positive staining with S-100, chromogranin, NSE and synaptophysin. Between 5 to 15% of the paragangliomas of the urinary bladder are said to be malignant; however, no reliable histological criteria exist to distinguish malignant from benign neoplasms. Malignancy is suspected in case of local invasion or distant metastases.[4,5]

Contraction of the bladder musculature and changes in bladder pressure during micturition lead to systemic release of catecholamines and eventually to intermittent hypertension during or directly after micturition;[3] 55 to 60% of patients have haematuria. Furthermore, headache, palpitations, diaphoresis, dysuria, anxiety and recurrent cystitis may occur.[3-5] Hypertensive crises may be triggered by micturition, defecation, sexual activity, ejaculation or bladder instrumentation.[3]

The diagnosis of pheochromocytomas in general is established by measurement of catecholamines and catecholamine metabolites (metanephrine and normetanephrine) in plasma and 24-hour urine samples. The majority (83%) of paragangliomas of the urinary bladder are hormonally active. However, preoperative

diagnosis of paraganglioma of the urinary bladder may be difficult since levels of catecholamines and their metabolites in plasma and urine can be normal.[5] A rise in plasma catecholamines is to be expected directly following micturition and attempts should be made to obtain plasma samples at that moment.[3] After biochemical confirmation, additional radiological imaging should be performed to locate the tumour. The most useful imaging techniques to localise primary and metastatic paragangliomas of the urinary bladder are cystoscopy and computed tomography or magnetic resonance imaging. Although all functional imaging methods are hampered by the excretion of radioisotopes in the urine, thus lowering their ability to localise a paraganglioma close to the kidneys or urinary bladder, iodin-131-MIBG scanning is essential to search for multifocal tumours or metastases. If the MIBG scan is negative, positron emission tomography (PET) imaging should be performed with specific ligands, preferably 6-[18F]-fluorodopamine ([18F]-DA) or [18F]-dihydroxyphenylalanine ([18F]-DOPA) whenever available.[1] About 80% of the paragangliomas can be seen on cystoscopy, revealing a submucous tumour with intact or superficially ulcerated overlying mucosa.[4,5]

Pheochromocytomas generally occur sporadically, but may also be inherited as part of several distinct syndromes such as multiple endocrine neoplasia type 2A and type 2B, von Hippel-Lindau's syndrome and von Recklinghausen's neurofibromatosis type 1 or paraganglioma syndromes associated with germ-line mutations of genes encoding for SDH subunits B, C and D (SDHB, SDHC, SDHD).[6,7] Carriers of SDHB mutations are at increased risk of extra-adrenal or metastatic pheochromocytomas as well as recurrence.[8-10] Therefore, it has been suggested that all patients younger than 50 years of age, patients with either bilateral pheochromocytoma, extra-adrenal or multifocal pheochromocytoma or with a family history of pheochromocytoma or paraganglioma should undergo genetic testing.[6,7,9,11]

Surgical resection is the treatment of choice after preoperative treatment with α- and β-blocking agents. Due to the multilayer involvement of the bladder wall, open surgery to perform a partial cystectomy is recommended.[12,13] Transurethral resection is believed to be feasible in tumours <2 to 3 cm without deep parietal infiltration.[3] In the presence of proven metastasis, radical cystectomy with pelvic lymphadenectomy is recommended.[4] Radiotherapy and chemotherapy have limited effectiveness. Since MIBG is specifically taken up by chromaffin tumours, treatment with MIBG radiotherapy has also been reported. Long-term annual follow-up is recommended in all paragangliomas.[4,5]

CONCLUSION

Paragangliomas of the urinary bladder are rare. Although, as in our case, patients might present with typical signs and symptoms, they are not easily recognised and diagnosis is sometimes achieved only after excision and histological examination of the tumour.

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CASE REPORT

Acute renal failure in *Plasmodium malariae* infection

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ABSTRACT

We report an unusual case of transfusion-transmitted malaria which remained undiagnosed for several months in an Italian woman splenectomised and polytransfused for thalassaemia major. The infecting species was *Plasmodium malariae*, and the patient developed acute renal failure, severe thrombocytopenia, and hepatic failure. Treatment with chlorochine was followed by a slow, but complete recovery of renal function.

KEYWORDS

Acute renal failure, chlorochine, malaria

INTRODUCTION

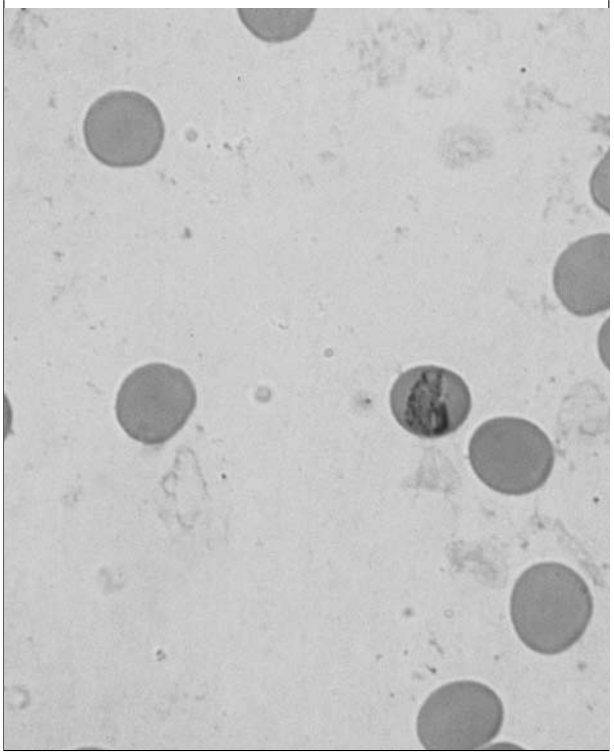
Malaria is one of the world's most important infections and, although it has been eradicated from temperate zones, the growing popularity of travel to the tropics is placing an increasing number of travellers at risk for acquiring the disease.

In this paper we report a case of a woman whose clinical history was unusual in both epidemiological and clinical characteristics.

CASE REPORT

A 35-year-old Italian woman with thalassaemia major, splenectomised and maintained on monthly blood transfusions since she was 10 years old, was admitted to our hospital because of recurrent fever with multiorgan involvement. The patient had been in a stable condition until four months prior to admission, when she become febrile with a 72 to 96 hour cyclical fever reaching 40°C, lasting 12 to 24 hours, and associated with chills and shivering. After unidentified therapies at home were unsuccessful, she was admitted to another hospital in our city. She was discharged with a presumptive diagnosis of polyserositis of unknown origin, and treated with steroids. Nevertheless the patient continued to have recurrent episodes of high fever alternating with apyrexia. On admission to our hospital she was febrile and reported having severe asthenia, mild dyspnoea, arthralgia, myalgia, diarrhoea and oliguria. On examination she appeared ill; her blood pressure was 110/70 mmHg with a heart rate of 105 beats/min. She had marked oedema in the lower extremities, and a haemorrhagic rush extended from her arms to her neck. A chest radiograph disclosed small, bilateral pleural effusions and an enlarged cardiac silhouette. An echocardiogram showed a small pericardial effusion. Blood and urine testing revealed a red blood cell count of 2.7 x 10^{12}/l, haemoglobin 4.6 mmol/l and platelets 56 x 10^{9}/l; mixed bilirubin 62 µmol/l; aspartate aminotransferase 113 U/l; alanine aminotranferase (ALAT) 51 U/l; international normalised ratio (INR) 1.6; creatinine 262 µmol/l, urea 21.5 mmol/l, Na^{+} 130 mmol/l and K^{+} 5.1 mmol/l; serum proteins were 430 mg/l, albumin 240mg/l and urinary protein excretion (24 h) was 0.63 g/d; serological tests for infectious diseases and three haemocultures were negative. On the third hospital day the patient's temperature rose to 38°C and she became anuric, with an increase in creatinine (468.5 µmol/l) and urea (25.3 mmol/l). Extracorporeal dialysis treatment was started, and microscopy of stained thin and thick blood films, at a magnification of 1000 x, was performed. Surprisingly, microscopic examination revealed the presence of erythrocyte inclusions compatible with *Plasmodium malaria* infection (*figure 1*). Our laboratories confirmed the diagnosis of *P. malaria* infection. Therapy with chloroquine (1 g/day) was started and continued for

Figure 1. *Erythrocyte inclusions compatible with Plasmodium malaria infection*



five days. The fever disappeared after three days; hepatic enzyme tests improved and platelets rose to a normal value. The patient was discharged after two weeks and continued ambulatory haemodialysis treatment. Three months later, dialysis was discontinued and, at eight-month follow-up, the creatinine had decreased to 106.08 µmol/l while urinary protein excretion (24 h) was 350 mg/d and blood pressure was normal. A specific investigation performed by the Ministry of Health revealed that the infection was transmitted by an occasional blood donor, a missionary of Philippine origin, who was a chronic and asymptomatic carrier of *P. malaria* infection.

DISCUSSION

Malaria is an acute and sometimes chronic infection caused by protozoan parasites of the genus *Plasmodium*. Malarial parasites undergo a sexual phase in *Anopheles* mosquitoes and an asexual stage in humans. In the vertebrate host, release of merozoites from ruptured hepatic mature schizonts initiates the blood stream infection and eventually the clinical symptoms of malaria. The attack is initiated by the synchronous rupture of erythrocytes with the release of new merozoites; therefore the recurrence of fever at 48-hourly intervals (*P. vivax* and *P. ovale*, sometimes *P. falciparum*) and at 72-hourly intervals (*P. malariae*) depends on the lifecycle of the parasite. Diagnosis is usually established by demonstrating parasites in thick and thin blood films. Species-specific serological tests are useful for detection of infected blood donors, and molecular biology is especially promising. In a prospective study, malaria parasitaemia was present in 38.7% of Nigerian children with nephrotic syndrome.[1] Malaria infections have repeatedly been reported to induce nephritic syndrome and acute renal failure. People who are not immune because they live in a nonendemic area had a higher risk of developing acute renal failure when compared with semi-immune subjects living in endemic areas such as Uganda and Nigeria.[2] It is still not known why the nephritic syndrome seen with *P. malariae* infection is associated with proliferative glomerular lesions in Ugandan patients, whereas Nigerian patients have more membranous lesions. Acute renal failure is a life-threatening complication of malaria infection. In the majority of cases *P. falciparum* is the causative agent of malarial acute renal failure (MARF), although MARF due to *P. vivax* has been occasionally reported.[3] Prevalence of MARF in endemic areas seems to be increasing[4] and the reported mortality of MARF is still very high, ranging from 15 to 45%. The histological picture of MARF consists of a variable mixture of acute tubular necrosis, interstitial nephritis and glomerulonephritis; proteinuria is less than 100 mg/24 h in 60% of cases.[4,5] In *P. falciparum* infection MARF often occurs in association with signs of multiorgan involvement, and jaundice, anaemia and thrombocytopenia are present in more than 70% of cases.[6-8] *P. malariae* is the established cause of chronic malarial nephropathy, although a few cases have been associated with *P. vivax* in children.[5-8] This complication affects children and shows the characteristic histopatological lesion of mesangiocapillary glomerulonephritis with subendotelial immune complex deposits containing IgG, C 3 and malarial antigens.[8] The clinical presentation includes proteinuria and nephritic syndrome. In our report we describe an unusual case of MARF with nephrotic range proteinuria and manifestations of multisystem involvements due to *P. malariae*. The development of MARF as a complication of a *P. malariae* infection is very rare and as far as we know, it has not been previously reported in Western countries. The patient's clinical condition did not allow us to perform a kidney biopsy so that the exact nature of the acute renal failure could not be established. The clinical course of the disease was characterised by a progressive increase in proteinuria which had risen to more than 600 mg/24 h at the time of admission to our hospital. This finding is consistent with the glomerular involvement which is reported in *P. malariae* infection. Both the long duration of the disease before the correct diagnosis, and the unstable haemodynamic conditions of the patient might have significantly worsened the clinical course of the renal disease. In fact, it is noteworthy that in *P. falciparum* infections, MARF is usually associated

with volume depletion, intravascular haemolysis, massive parasitaemia, colestatic jaundice and hypotension. Apart from jaundice, signs of hepatic dysfunction are unusual. In recent years, there have been an increasing number of reports favouring the existence of malarial hepatopathy from Asian countries, especially from India.[9] The liver plays a key role in the lifecycle of the plasmodium and in some cases it is seriously involved; in *Falciparum* malaria, there are reports[10-11] of a spectrum of hepatocellular dysfunction ranging from mild derangement of liver function tests with conjugated hyperbilirubinaemia, elevated ALAT and INR, thrombocytopenia and coagulopathy to liver failure and fulminant hepatic failure; liver damage is said to be related to cyto-adherence of parasitised red blood cells in the portal venous flow with ischaemia, intrahepatic cholestasis, and increased apoptosis and oxidative stress.[12] Most of these features were present in our patient at the onset of MARF. Furthermore, the treatment with steroids before the correct diagnosis was made did not ameliorate the clinical course of the disease, confirming the current concept that there is no definitive evidence for a dominating role of corticosteroids in the treatment of acute malaria complications.[8,13]

The unusual sequence of events which influenced the course of the infection made us consider the many problems associated with managing infective risk:

- the use of occasional blood donors can cause many diagnostic problems in the case of transmitted infectious disease, especially with regard to some nonendemic diseases;
- a single reading of the film by the optic microscope can lead to the correct diagnosis.

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SPECIAL REPORT

Clinical practice guideline for cardiovascular risk management in the Netherlands

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INTRODUCTION

Preamble

In most developed countries, including the Netherlands, cardiovascular disease (CVD) is a leading cause of morbidity, mortality, and health care costs. Guidelines for CVD prevention should contain a comprehensive, evidence-based strategy towards both primary and secondary prevention. In addition, guidelines should be aimed at a broad spectrum of health care providers, both in primary care as well as in more specialised hospital settings.

Until recently, different national guidelines existed for the management of hypercholesterolaemia and hypertension in the Netherlands, whereas the emphasis has nowadays shifted to management of global CVD risk. In addition, separate guidelines existed for primary care and hospital care settings.

In 2001, the Medical Council of the Dutch Institute for Healthcare Improvement CBO took the initiative to develop a national multidisciplinary guideline for global cardiovascular risk management. This paper provides a summary and short commentary on this guideline.

Aims and scope

The aim was to establish a guideline for optimal and cost-effective primary and secondary CVD prevention. The guideline is based on assessment of absolute CVD risk and replaces previous separate guidelines for hypertension and hypercholesterolaemia. In addition, the guideline integrates separate guidelines for general and hospital-based practice, and is intended for use by general practitioners, medical specialists and allied health professionals, such as dieticians, physiotherapists, nurse practitioners, and physician assistants.

The guideline addresses the most common forms of CVD: coronary artery disease, cerebrovascular disease, and peripheral arterial disease. It does not address screening for CVD in the general population, genetic disorders of lipid metabolism or excessive forms of dyslipidaemia, and management of hyperglycaemia in diabetes mellitus.

Finally, the Working Group emphasises that the recommendations reflect 'best practice' for the average patient, not statutory regulations for all individual patients. In general, the guideline advocates individualised care and shared decision making. Non-adherence to the recommendations is not a basis for formal complaints or financial sanctions (such as non-reimbursement by health insurance companies). Health care workers are advised, however, to document their motivation for not adhering to the guideline recommendations.

Methods

A guideline development group was formed, involving all the relevant professional disciplines. All group members as well as the associations they represented are listed at the end of this paper. The guideline development group comprised general practitioners (5), internists (3), cardiologists (3), a vascular surgeon, a neurologist, epidemiologists (5), a health economist, and two methodologists from the CBO.

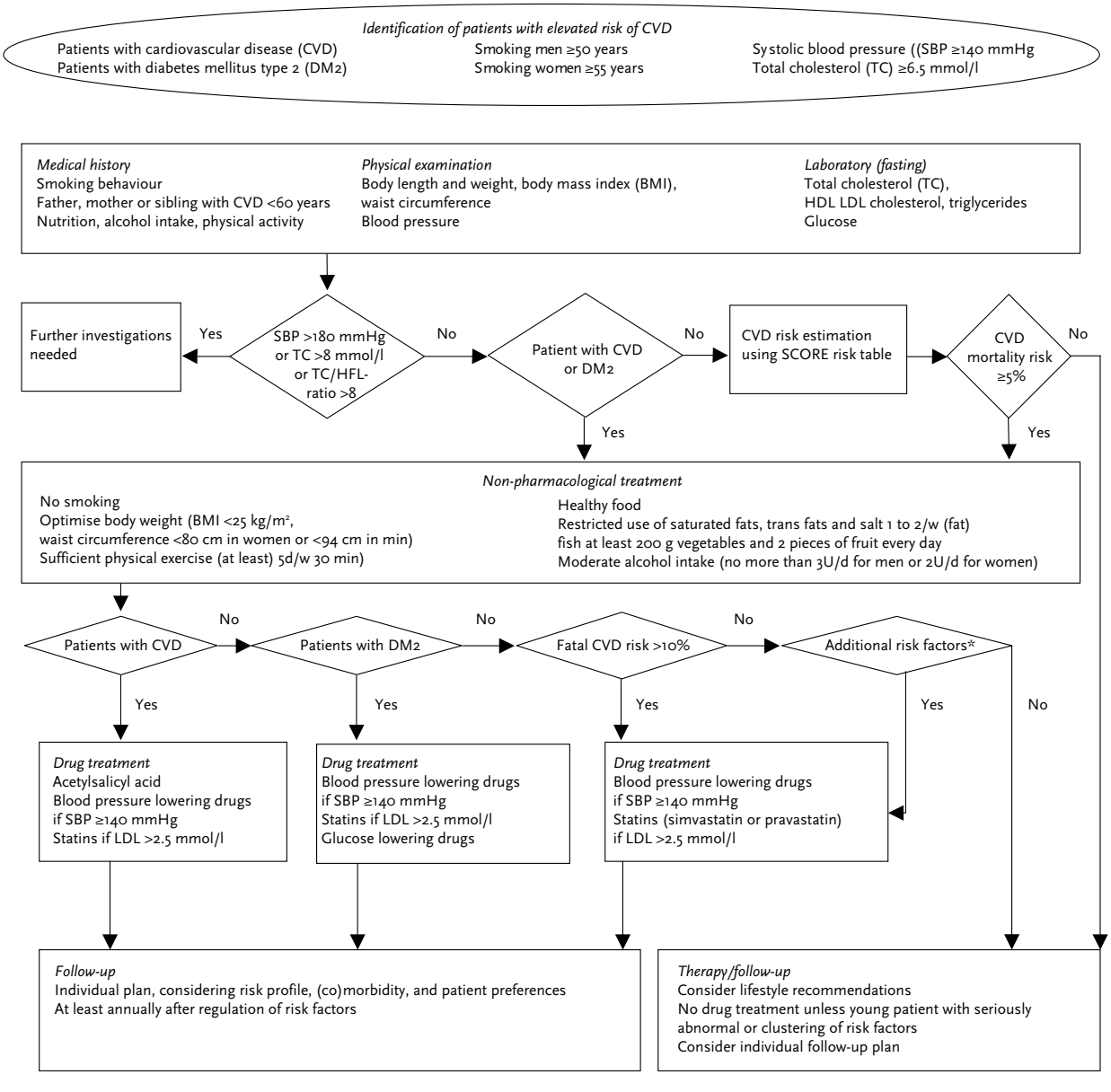
The group started by discussing the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (Third Joint Task Force),[1] as well as the existing national

guidelines for hypertension and for hypercholesterolaemia. Additional literature searches were conducted for updating the literature. The recommendations in the European guideline were used for adaptation to the Dutch context. Data on absolute CVD risk were derived from original Dutch epidemiological studies. The guideline working group formulated recommendations based on informal consensus within the group. The first draft of the guideline was finished in June 2005. This draft was sent for external review to all relevant stakeholders. The final guideline was endorsed by all scientific associations represented in the guideline development group in June 2006

GUIDELINE SUMMARY

The guideline is summarised in *figure 1*. This figure as well as the full text version of the guideline can be downloaded at www.cbo.nl/product/richtlijnen/folder20021023121843/rl_overzicht. The full text version includes an extensive

Figure 1. *Flowchart Dutch guideline cardiovascular risk management 2006*



***Additional risk factors: father, mother, brother or sister with CVD <60 years; obesitas (BMI >30 kg/m2, waist circumference >88 cm in women or >102 cm in men); end organ damage, such as (micro)albuminuria, impaired renal function or left ventricular hypertrophy.**

technical background document containing the supporting evidence as well as a budget impact analysis.
The subsequent steps of the guideline are outlined below.

Identification of high-risk patients

All patients with a previous CVD diagnosis are considered as high-risk patients. The risk of most patients with type 2 diabetes mellitus (DM2) is also elevated. In both patient categories, a full risk profile should be obtained. In individuals without previous CVD or DM2, signs or symptoms, a family history of premature CVD, visible overweight or a specific request from the patient may prompt inquiry into smoking behaviour or measurement of blood pressure or serum cholesterol levels. It is recommended to obtain a complete CVD risk profile if one of the following is present:

- systolic blood pressure ≥140 mmHg
- total cholesterol ≥6.5 mmol/l
- smoking in men ≥50 years or women ≥55 years of age.

Diagnostic procedures

A complete risk profile should be obtained by collecting information on the risk factors listed in *figure 1*. Blood pressure should be measured twice on at least two separate days, adhering to specific instructions outlined in the guideline. In addition to the recommended blood tests in *figure 1*, patients with hypertension require measurement of serum creatinine and potassium level. Testing for microalbuminuria and obtaining a 12-lead electrocardiogram can be considered in individual cases.
Additional investigation for secondary hypertension is warranted in case of:

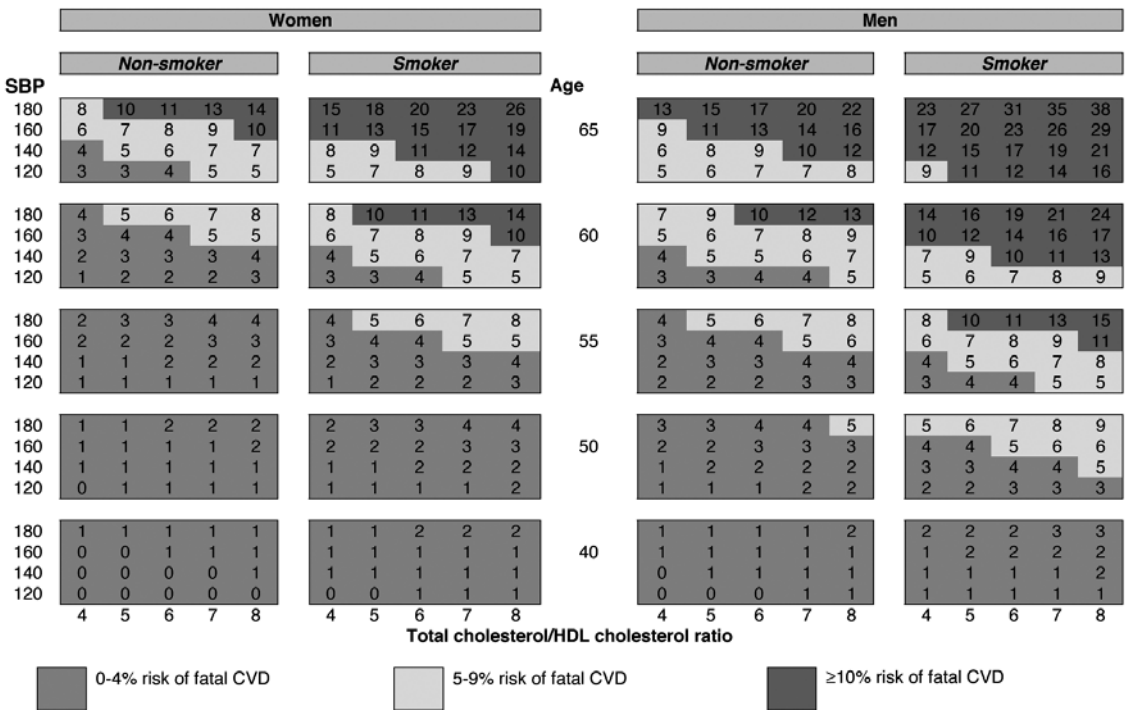
- specific clinical signs (e.g. Cushing habitus);
- strongly elevated systolic blood pressure (>180 mmHg);
- hypokalaemia (serum potassium <3.5 mmol/l);
- renal insufficiency;
- unresponsiveness to treatment.

In addition, further testing is recommended for excessive hyperlipidaemia (e.g. total cholesterol >8 mmol/l or total cholesterol/HDL cholesterol ratio >8).

Assessment of absolute CVD risk

For individuals without previous CVD and DM2, the ten-year risk of developing fatal CVD is assessed using the SCORE risk table, calibrated for Dutch CVD mortality data (*table 1*).[2] The values for blood pressure and lipid levels in the table are applicable regardless of whether patients are treated with antihypertensive or lipid-lowering drugs.

Table 1. *Risk of fatal cardiovascular disease (CVD) for patients without CVD and without diabetes mellitus type 2*



Estimate of the level of the ten-year risk (%) of death from CVD in the Netherlands for non-smoking and smoking women and men aged 65, 60, 55, 50 and 40 years with the aid of the SCORE risk function.

The presence of additional risk factors, including family history of premature CVD, (central) obesity, and physical inactivity, may lead to a higher risk than suggested in the SCORE risk table.

Nonpharmacological treatment

Recommendations for lifestyle modifications are given to all individuals with previous CVD, DM2 or an estimated ten-year risk of fatal CVD of ≥5%. Specific recommendations are outlined in *figure 1*, and are discussed in detail in the technical background document. Patients should be offered contact details of patient organisations that provide information and support for lifestyle interventions.

Pharmacological treatment

As illustrated in *figure 1*, three categories of individuals are distinguished for the purpose of tailoring pharmacological treatment. All recommendations are accompanied by footnotes in the technical background document.

Patients with CVD

- Aspirin is recommended, unless there is a concomitant condition requiring oral anticoagulation. In case of intolerance to aspirin, clopidogrel is a suitable alternative.
- Antihypertensive therapy is recommended if systolic blood pressure is ≥140 mmHg or if a history of cerebrovascular disease (TIA or stroke) is present. The choice of drugs depends on comorbidity
- Beta-receptor blockers are recommended for patients with a history of coronary artery disease or heart failure due to coronary artery disease.
- Angiotensin-converting-enzyme (ACE) inhibitors are recommended for patients with a history of coronary revascularisation, myocardial infarction or heart failure due to coronary artery disease, even if systolic blood pressure is <140 mmHg.
- Statin therapy is recommended if the plasma LDL-cholesterol level is >2.5 mmol/l or, if LDL cholesterol is ≤2.5 mmol/l in very-high-risk patients characterised by the presence of multiple other risk factors (e.g. recurrent myocardial infarction, clustering of uncontrolled risk factors).

Patients with DM2

- Antihypertensive therapy is recommended if systolic blood pressure is ≥140 mmHg.
- Statin therapy is recommended if the plasma LDL-cholesterol level is >2.5 mmol/l, except in young patients with a low risk profile and good glycaemic control (i.e. HbA1c <7%). Conversely, a highly unfavourable risk profile (e.g. poor metabolic control, renal complications, clustering of risk factors) justifies statin treatment even if LDL cholesterol is ≤2.5 mmol/l.

Individuals free of CVD or DM2

- Treatment recommendations for this group are based on the estimated ten-year risk of fatal CVD. In general, smoking cessation is recommended prior to initiation of drug treatment.
- Antihypertensive therapy is recommended if systolic blood pressure is ≥140 mmHg and estimated ten-year risk of fatal CVD is ≥10%. Patients with a systolic blood pressure of ≥180 mmHg should receive antihypertensive treatment, regardless of their risk profile.
- Statin therapy is recommended if the plasma LDL-cholesterol level is >2.5 mmol/l and estimated ten-year risk of fatal CVD is ≥10%.
- Individuals at intermediate CVD risk (5-10%) and systolic blood pressure ≥140 mmHg or LDL cholesterol >2.5 mmol/l are amendable to antihypertensive or lipid lowering treatment, respectively, if at least one of the following is present:
  - family history of premature CVD, i.e. <60 years in a parent or sibling;
  - obesity, i.e. body mass index >30 kg/m^2, or waist circumference >88 cm (in women) or 102 cm (in men);
  - target organ damage, such as (micro)albuminuria, renal insufficiency, or left ventricular hypertrophy.
- Young individuals (<50 years) almost universally have a ten-year risk of fatal CVD of <5%. Such individuals are nonetheless candidates for pharmacological treatment if there is clustering of multiple risk factors or a strongly positive family history of premature CVD.
- Elderly individuals (>70-75 years) often have a high (>10%) ten-year risk of fatal CVD based on their age alone. In principle, these individuals are candidates for preventive pharmacological treatment, but mass-scale polypharmacy and medicalisation should be avoided. Thus, treatment decisions must be individualised. As a rule, pharmacological primary CVD prevention requires that life expectancy is not limited due to comorbidity.

Drug classes

- Antiplatelet drugs are prescribed to all patients with documented CVD. The standard recommended dose is 80 mg of acetylsalicylic acid. Combination therapy with oral anticoagulants is not recommended. Aspirin is not recommended for primary prevention.
- Antihypertensive drugs of different classes have, on average, equally strong antihypertensive effects. Compelling indications for specific classes of antihypertensive drugs are listed in the full-text version of the guideline. If none are present, low-dose hydrochlorothiazide is recommended as initial drug. In the elderly, β-receptor blocker monotherapy is discouraged. Combination therapy is preferred over high-dose single-drug therapy. Blood pressure should be

checked at two to four weekly intervals until the treatment goal is reached. The target level for systolic blood pressure is <140 mmHg. In patients with DM2, further lowering of systolic blood pressure is recommended.

- Cholesterol-lowering drugs include statins as the only standard recommended drugs. Simvastatin (40 mg) or pravastatin (40 mg) are drugs of first choice. The effect on LDL cholesterol should be assessed within three months of treatment. Target values are different for the following categories:
  - patients with CVD or DM2 should reach a target LDL-cholesterol level of <2.5 mmol/l. If not, switching to atorvastatin or rosuvastatin could be considered. Addition of other lipid-lowering drugs lacks evidence base;
  - individuals without CVD or DM2 who are prescribed a cholesterol-lowering drug for primary prevention should reach a target LDL-cholesterol level of <2.5 mmol/l, or a decrease in LDL cholesterol after statin treatment of at least 1 mmol/l.

Follow-up

An individualised follow-up schedule is recommended for all patients. The aims of regular visits are to discuss compliance to lifestyle measures and drug treatment, and to evaluate treatment effects. A follow-up interval exceeding 12 months is not recommended. Laboratory investigations depend on comorbidity and drug use. As most high-risk patients are at increased risk of developing DM2, fasting glucose measurement is recommended every three to five years. Interruption of pharmacological treatment is not recommended.

DISCUSSION

In the full-text version of the guideline, many aspects of the guideline are discussed in more detail. However, a few areas of discussion deserve specific attention in this article.

Morbidity versus mortality risk

The guideline development group adopted the SCORE risk chart for estimating absolute cardiovascular risk, in contrast to previous Dutch guidelines, in which the Framingham risk score was used.[3] The choice for SCORE was based on the higher number of included subjects in the source population and the fact that the risk model is based on a European population.[2] The major drawback of SCORE is that only the risk of fatal CVD is estimated. Including nonfatal CVD risk, however, is paramount to quality-of-life aspects and to cost-effectiveness analyses of guidelines. Moreover, patients themselves are commonly interested in risk of morbidity rather than in risk of death alone. In annex 2 of the guideline, a method for converting fatal to fatal plus nonfatal CVD risk is presented.

Risk threshold for treatment

In the previous Dutch guideline for treatment of hypercholesterolaemia, a 20% ten-year risk of fatal plus nonfatal CVD was recommended as a treatment threshold. This risk corresponds to the currently recommended risk threshold of 10% for fatal CVD. When the previous guidelines were being designed, arguments for determining the risk threshold included a cost-effectiveness analysis based on a cost estimate of € 20,000 per quality-adjusted life year (QALY) for statin treatment. In the past decade, however, the cost of simvastatin, which is now available generically, has dropped from € 700 to approximately € 180 per year. Likewise, the cost of several antihypertensive drugs with established effectiveness and safety has decreased. The guideline development group decided that this decrease in costs should not lead to a lower risk threshold for preventive treatment. Lowering the risk threshold for fatal CVD from 10 to 8%, for example, would have a major impact. Firstly, it would increase the ten-year number-needed-to-treat for simvastatin from 33 to 42 per fatal CVD event prevented. On a population scale, the impact would be substantial, as the number of currently untreated individuals in the Netherlands amendable to treatment with either a statin and/or an antihypertensive drug would increase by almost one million (from 3,270,500 to 4,125,800). As a consequence, the impact this would have on the national health care budget would be substantial (1.1 billion euro after five years, assuming 100% prescription of the cheaper, generic drugs). Moreover, the guideline development group concluded that such large-scale medicalisation of the population would be undesirable.

Risk assessment in DM

The SCORE risk chart does not calculate risk in patients with DM2. Although some studies have suggested that CVD risk in these patients equals risk in patients with a previous CVD diagnosis,[4] the results of later studies were not conclusive.[5,6] Obviously, there is substantial heterogeneity between patients with DM2 in terms of their CVD risk. The guideline development group decided to recommend low risk factor threshold levels for initiation of antihypertensive therapy (systolic blood pressure >140 mmHg) and lipid-lowering therapy (LDL cholesterol >2.5 mmol/l). Entering these thresholds in the United Kingdom Prospective Diabetes Study (UKPDS) risk engine (www.dtu.ox.ac.uk/index.php?maindoc=/outcomesmodel) revealed that these values were usually related to absolute CVD risk levels above the 10% threshold used for preventive drug therapy in nondiabetics.[7] Only if the remaining variables of the risk profile (e.g. age, glycaemic control, family history, ethnicity) are favourable do these blood pressure and LDL-cholesterol levels translate into risks lower than the treatment threshold. Therefore, the guideline included a statement on considering no statin treatment in young DM2 patients with a favourable risk profile.

Risk estimation in young and elderly individuals

A major area of controversy is the use of absolute CVD risk estimates to guide preventive treatment in young and in elderly people. As is evident from *figure 2*, absolute ten-year CVD mortality risks rarely reach the 10% threshold in individuals below the age of 50 years. The guideline development group discussed the option of recommending extrapolation of absolute risk to the age of 60 years, as is suggested in the 2003 ESH/ESC hypertension guidelines.[8] However, such extrapolation would result in an enormous increase in relatively young people who would be considered for drug therapy.[9] Moreover, no strong evidence is available on the efficacy and safety of pharmacological CVD prevention beyond a period of more than ten years. Based on these arguments, the guideline development group decided to recommend drug treatment for primary CVD prevention in young individuals only if a risk factor is markedly increased or if clustering of multiple risk factors is present. It was also felt that no strict criteria should be defined for this purpose, and treatment decisions should always be individualised.

The reverse problem is encountered in elderly individuals, who almost universally reach the treatment threshold for preventive drug treatment as age progresses. This can be appreciated from *table 1*, although it requires extrapolation of the calculated risks, as the SCORE model does not calculate risks for individuals older than 65 years.[2] The guideline development group acknowledged that antihypertensive and cholesterol-lowering drugs are also effective in the elderly. However, a standard recommendation to initiate these drugs in all elderly patients with a >10% ten-year risk of fatal CVD was considered undesirable, as it would lead to massive prescription, and thus medicalisation, in elderly people. Hence, as in younger people, a more liberal recommendation was made to consider preventive treatment in elderly, and to decide on drug treatment based on risk profile, general health and life-expectancy and patient preferences.

Implementation of the guideline

The guideline was made publicly accessible via the internet (www.cbo.nl/product/richtlijnen/folder20021023121843/rl_overzicht). The printed version of the guideline was freely distributed to all general practitioners, as well as to all physicians registered in Internal Medicine, Cardiology, and Neurology. In addition, a patient brochure and risk calculator were produced and distributed. Based on the guidelines, an internet-based 'decision aid' was made publicly available to help patients to make informed treatment decisions.

Following endorsement of the guideline, a nationwide platform was established consisting of representatives from patient organisations and health professional associations. The mission of this platform is to facilitate and optimise implementation of the guideline.

Updating of the guideline

The Dutch Institute for Health Care Improvement CBO aims to update the literature and modify the recommendations, if needed, at least every two years.

NOTE

Members of the guideline development group Dutch guideline cardiovascular risk management: W.A.B. Stalman (chair), T. Scheltens, J.S. Burgers, C.W.P.M. Hukkelhoven, S.M. Smorenburg, J.D. Banga, D.W.J. Dippel, S.J. van Dis, D.E. Grobbee, A.W. Hoes, B.A. van Hout, J.W. Jukema, P.J.E.H.M. Kitslaar, D. Kromhout, R.J. Peters, M.L. Simoons, Y.M. Smulders, C.D.A. Stehouwer, S. Thomas, E.P. Walma, Tj. Wiersma.

Participating associations: Dutch Institute for Health Care Improvement CBO, Dutch Association for Internal Medicine NIV, Netherlands Heart Foundation, Netherlands Association for Cardiology NVVC, Netherlands Association for Surgery NVVH, Netherlands Association for Neurology NVVN, Dutch College of General Practitioners NHG, Dutch Epidemiology Association.

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PHOTO QUIZ

Unusual cause of chronic ascites

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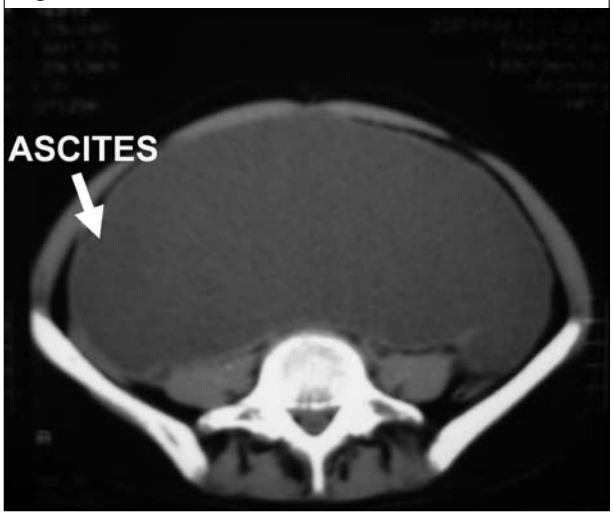
CASE REPORT

A 28-year-old lady had a laparoscopic right ovarian cyst puncture for primary infertility. On the fourth postoperative day she developed progressive abdominal distension, becoming massive by the 12th day and necessitating large volume therapeutic paracentesis. Her bowel movements and urine output were normal. Haemogram and biochemical renal and liver parameters were normal. Chest X-ray, ECG and echocardiogram were normal. Sonography of the abdomen and computed tomography revealed massive ascites. Ascitic fluid colour was straw coloured, with 10 to 15 polymorphs, protein 120 g/l and amylase 0.3 µgl.

The present admission was for rapid reaccumulation of ascites and repeated therapeutic paracentesis. On examination, she was afebrile with mild pallor. Vital signs were stable. Abdominal examination revealed tense ascites. Other systems were normal. Haemogram and liver function tests were normal. Serum creatinine was 130 µmol/l. Ultrasonography of the abdomen and computed tomography (*figure 1*) were performed. Ascitic fluid was transudate with a creatinine level of 590 µmol/l.

Figure 1. *CT abdomen shows ascites*



WHAT IS YOUR DIAGNOSIS?

See page 180 for the answer to this photo quiz.

Netherlands
The Journal of Medicine

PHOTO QUIZ

Erythematous pigmentation of the arm for more than ten years

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CASE REPORT

A 43-year-old female visited the outpatient department because of an erythematous pigmentation of the left arm for more than ten years. The fading started on the forearm and extended to the upper arm. She developed cutaneous swelling and nodules on the elbow. She did not complain of any joint pain. Physical examination revealed a red-purple pigmentation on a thin atrophic skin (*figure 1*) and four firm nodules on the left elbow (*figure 2*).

Figure 1. *Red-purple pigmentation on a thin atrophic skin*

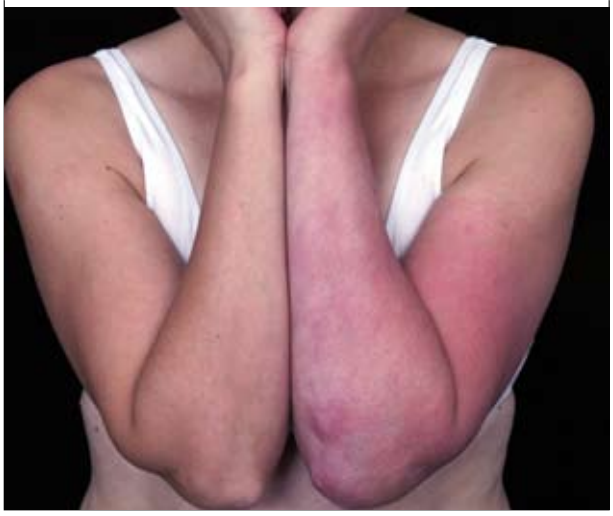
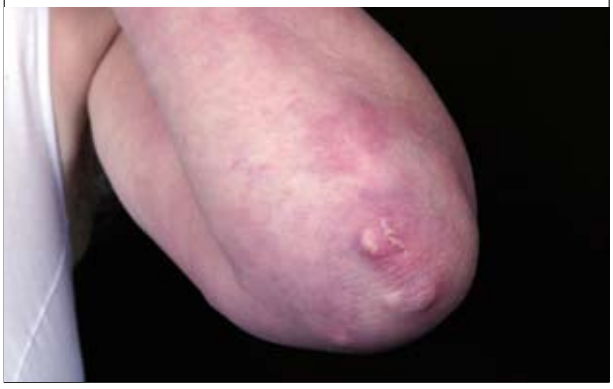


Figure 2. *Four firm nodules on the left elbow*



WHAT IS YOUR DIAGNOSIS?

See page 179 for the answer to this photo quiz.

Netherlands
The Journal of Medicine

Comments on the review article: Ascites in cirrhosis: a review of management and complications

Dear Sir,

We read with great interest the comprehensive and up-to-date review article by Kuiper *et al.* entitled Ascites in cirrhosis: a review of management and complications.[1]

We feel that a few points need further clarification. The serum-ascites albumin gradient (SAAG) threshold level of 11 g/l is an indicator of portal hypertension (with an approximate accuracy of 97%) and not a 'hepatic cause of ascites'.[2] Certainly cirrhosis and alcoholic hepatitis are 'hepatic causes' but we are not sure that we can classify cardiac failure, myxoedema or portal vein thrombosis (all associated with SAAG >11g/l) as such. SAAG in other words is not a pathogenesis identifier test. It simply provides the clinician with an accurate, indirect estimate of the portal pressure.[3]

The authors classify as 'useful' tests of the ascitic fluid the cell count, amylase, triglyceride concentration, chylomicrons and in 'selected cases cytological and immunological examination'. It is, we believe, unfair to group together tests that come into different stages of the ascites investigation algorithm, if at all.

The cell count is the single most useful test for ascitic fluid. Runyon suggests that the practice of ordering every available fluid test on every paracentesis can be counterproductive and if only drops of fluid can be obtained, they should be sent for cell count.[3] Furthermore, he suggests that on the basis of cost analysis the ascitic fluid tests can be classified as routine (cell count, albumin and total protein), optional (culture in blood culture bottles, glucose, LDH and amylase) and unusual (cytology, triglyceride, bilirubin and TB smear).[3] Kuiper *et al.* have not mentioned the use of leucocyte esterase reagent strips (dipsticks) in the bedside screen for SBP. Several studies suggest that they can be used to shorten the tap-to-antibiotic time, especially in out-of-hours paracenteses.[4]

The Ricart *et al.* study to which the authors refer (reference 48 in the original article) used amoxicillin/clavulanic acid every eight hours and not four times daily.[5] Most authorities suggest an initial dose of spironolactone at 100 mg (50 mg is probably inadequate for moderate ascites),[3] and a recently reported study suggests beneficial effect of albumin in the group of patients with SBP and bilirubin >64.8 µmol/l, and creatinine >88.4 µmol/l.[6]

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4. Koulaouzidis A, Bhat S, Karagiannidis A, et al. Spontaneous bacterial peritonitis. Postgrad Med J 2007;83:379-83.
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We would like to thank Koulaouzidis *et al.* for their interesting comments.

We agree that the serum-ascites-albumin gradient (SAAG) >11 g/l is an indicator of portal hypertension. Since the article is focused on ascites in cirrhosis we took the liberty of stating that an SAAG ≥11 is *indicative* for a hepatic cause, not diagnostic. As can be seen in our *table 1*, extrahepatic causes for ascites were recognised.[1]

It was not our intention to suggest that all diagnostic tests should always be done in all patients with ascites. We agree that these diagnostic tests come into different stages of the ascites investigation algorithm. The leucocyte cell count is indeed the most important diagnostic test in ascites. It is the golden standard in diagnosing spontaneous bacterial peritonitis (SBP). However, as stated in our article, when the aetiology of ascites is not certain, additional testing such as amylase and triglyceride concentration is often necessary. Electronic coulter counting of cells in ascites may define cells as leucocytes which in fact may be malignant cells, so in selected cases we think there is still a place for cytology and immunology of ascitic fluid.

Table 1. *Aetiology according to the serum ascites albumin gradient*

<11 g/l	Infection
	Nephrotic syndrome
	Malignancy
	Pancreatitis
≥11 g/l	Cirrhosis
	Budd-Chiari syndrome
	Veno-occlusive disease
	Alcoholic hepatitis
	Congestive heart failure

Leucocyte esterase reagent strips have been examined in several studies as a bedside diagnostic tool for SBP. The studies differ in methodology and the results of these studies are contradictory.[2,3]

The final comment on our article made by Koulaouzidis *et al.* concerns the subgroup of patients with SBP eligible for albumin infusion. This is in line with our assumption that those patients with Child Pugh score C, i.e. those with severe liver dysfunction, benefit most from the addition of albumin to the treatment regimen.

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3. Comments on the publication by Nousbaum. Hepatology 2007;46(5)1666-9.

ANSWER TO PHOTO QUIZ (ON PAGE 176)

ERYTHEMATOUS PIGMENTATION OF THE ARM FOR MORE THAN TEN YEARS

DIAGNOSIS

A biopsy of the skin showed a small epidermis and a lymphohistiocytic infiltration of the dermis. Biopsy of a nodule showed collagenous connective tissue with histiocytic elements. Laboratory investigations showed a positive test for *Borrelia burgdorferi* (IgG).

On the basis of the clinical, histopathological and serological findings, the diagnosis acrodermatitis chronica atrophicans (ACA) with juxta-articular fibrotic nodules was established. ACA is a late stage of Lyme borreliosis. It is usually distributed on the lower legs and feet. In 10 to 20% of patients with ACA, localised increase of dermal collagen leads to juxta-articular fibrotic nodules.[1,2] As in most cases, our patient did not remember a tick bite or erythema chronicum migrans at the site of the ACA.

Treatment is important to prevent progression and the development of extracutaneous complications such as neuropathy, tendinitis and arthritis.[3] Our patient was treated with doxycycline 100 mg twice daily for one month. Seven months later the noduli had disappeared (*figure 3*) and there was a clear decrease in the pigmentation (*figure 4*).

Figure 3. *Seven months later the noduli had disappeared*

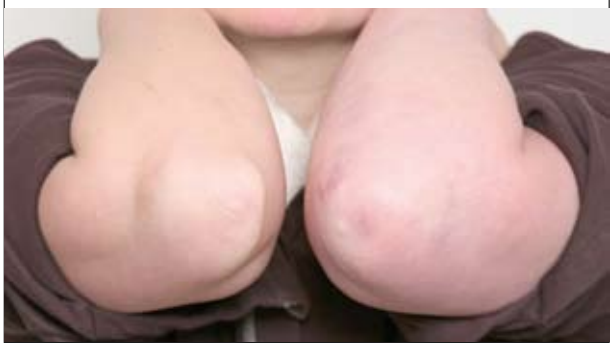
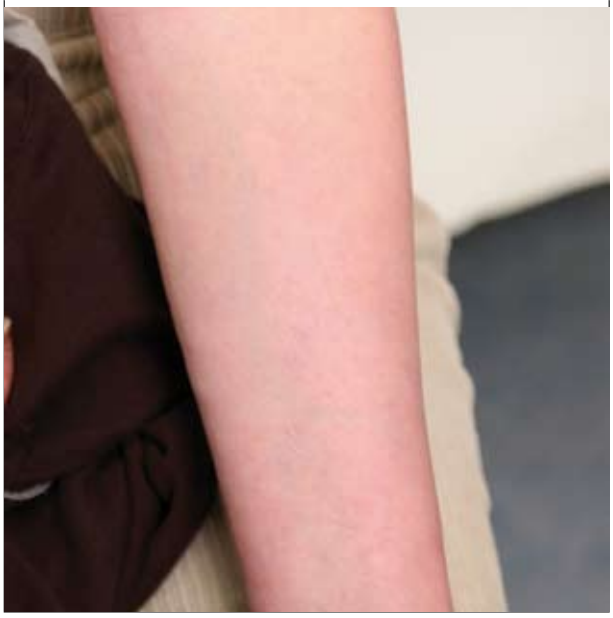


Figure 4. *Pigmentation had clearly decreased*



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ANSWER TO PHOTO QUIZ (ON PAGE 175)

UNUSUAL CAUSE OF CHRONIC ASCITES

The computed tomography (CT) (*figure 1*) shows massive ascites with hydronephrosis of the right kidney and intravenous urogram (*figure 2*) shows the spillage of urine into the peritoneal cavity. The patient has urinary ascites (post-traumatic), confirmed by an elevated level of creatinine in the ascitic fluid.

Figure 1. *CT abdomen shows ascites*

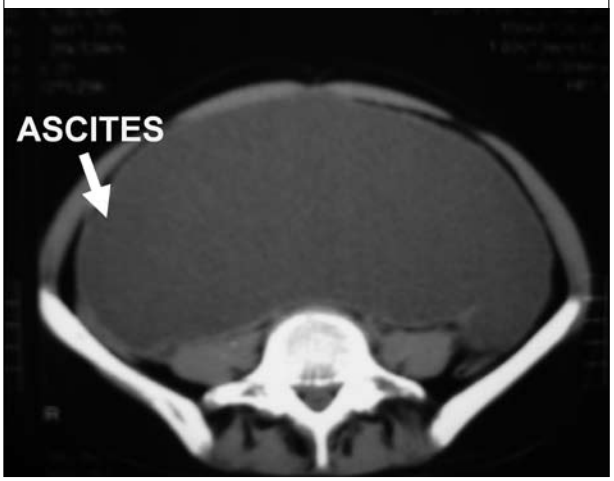
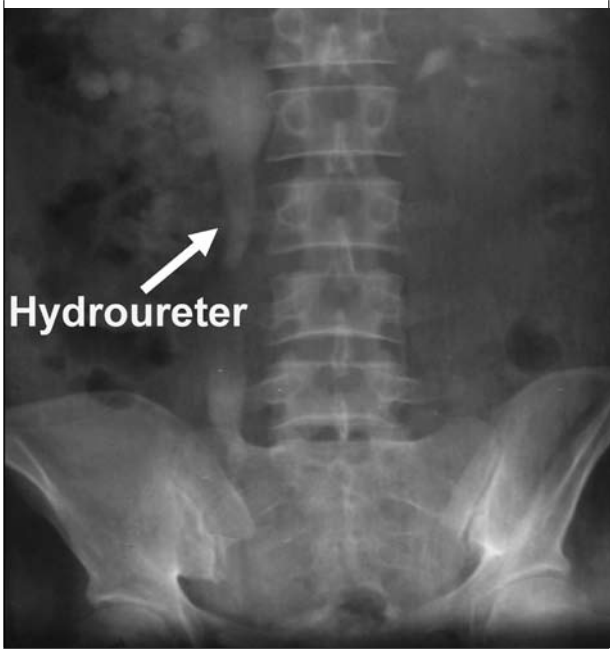


Figure 2. *IVU shows rightsided hydrouretronephrosis with extravasation of contrast into the peritoneal cavity*



Urine leaks and urinomas result from disruption of the urinary collecting system at any level from the calyx to the urethra and can accumulate within or outside the peritoneal cavity respectively. The former is referred to as urinary ascites. The leakage is often post-traumatic, either iatrogenic or after a blunt or a penetrating injury to the lower abdomen.[1,2] Iatrogenic injury to the urinary collecting system can occur during laparoscopic colectomy and gynaecological practice.[3] Urinary ascites manifests as peritonitis within two to three days or is at times delayed in the absence of peritonitis. Contrast-enhanced helical CT is diagnostic for suspected leaks from the kidney and ureter. Retrograde CT cystography confirms an intraperitoneal rupture of bladder. Ultrasound may not be informative. A diagnostic intraperitoneal fluid aspiration and elevated creatinine levels is a complementary diagnostic tool. Intravenous pyelogram and renal scintigraphy have a limited role in the diagnosis of urinary ascites. Surgical repair is treatment of choice.

In the present case, intravenous urogram (*figure 2*) confirmed the spillage of urine into the peritoneal cavity. Percutaneous nephrostomy and ureteric stenting had failed. Through a modified Gibbson's incision, a thin-walled cavity 3 x 3 cm in size was seen near the right lower ureter, which was communicating with the peritoneal cavity. The ureter was transected at this level and a Boari's flap taken from urinary bladder was used for reconstruction. Postoperatively there was no reaccumulation of ascites.

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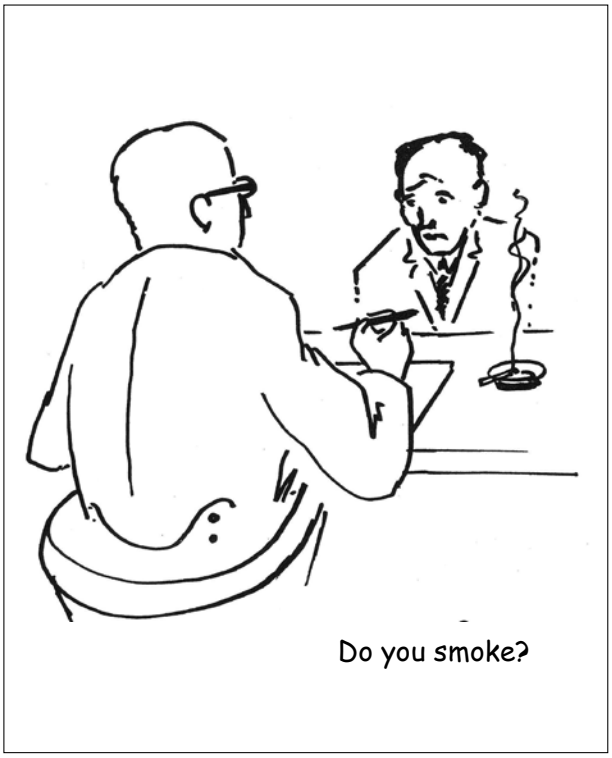
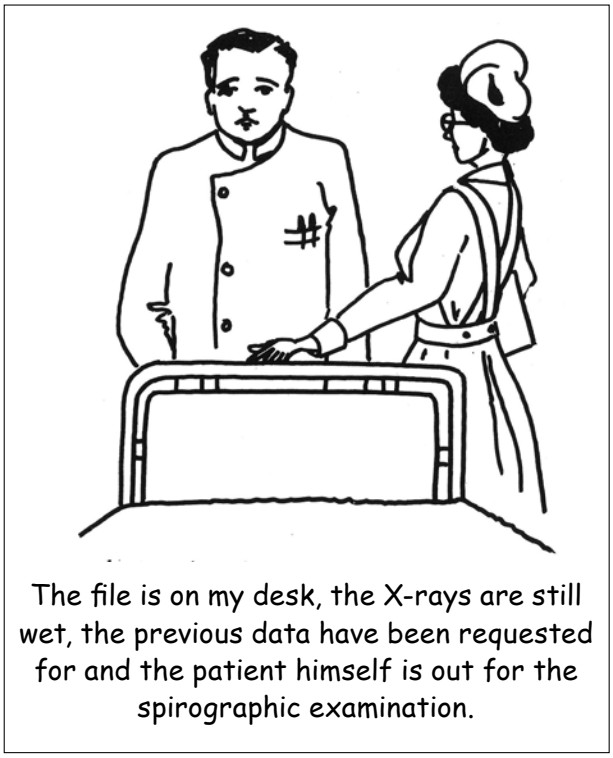
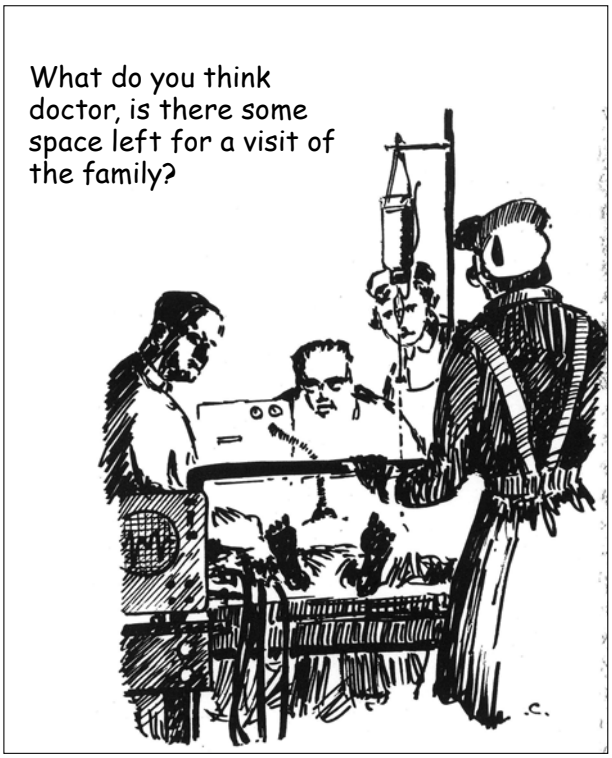
SPECIAL REPORT

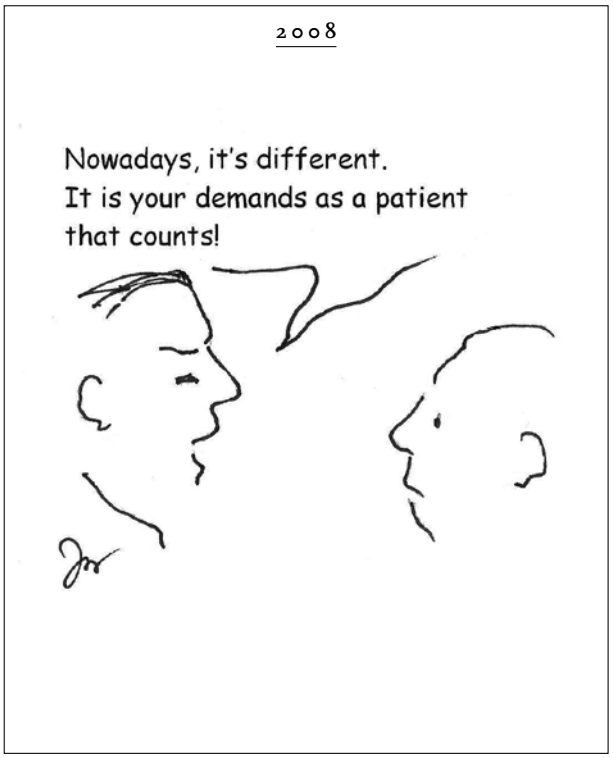
50 years *Netherlands Journal of Medicine*

The first three cartoons, published in 1966 in a series of modern delevopments in medicine, is still of current interest.









MONTHLY NJM ONLINE HITLIST

The table lists online hits for all articles published in the January issue of *the Netherlands Journal of Medicine* 2008 (available online on PubMed since 21 January 2008).

Article	Hits
EDITORIAL	
The hepatitis C virus burden: a Dutch point of view	97
REVIEW	
Review on diagnosis and treatment of focal segmental glomerulosclerosis	231
ORIGINAL ARTICLES	
Prevalence of hepatitis C in the general population in the Netherlands	123
Gastrointestinal symptoms are still common in a general Western population	76
CASE REPORTS	
Hairy cell leukaemia presenting with ascites, pleural effusion and increased CA 125 serum level	57
Rituximab for the treatment of glomerulonephritis in hepatitis C associated cryoglobulinaemia	142
Extrapulmonary lymphangioleiomyomatosis: an unusual cause of biliary tract obstruction	60
SPECIAL REPORT	
50 years *Netherlands Journal of Medicine* – Reminiscences of three successive editors	46
PHOTO QUIZZES	
A patient with a neck mass	85
A patient with abdominal pain and a rash	93
LETTERS TO THE EDITOR	
Transmission of hepatitis C genotypes in the Netherlands amongst recently genotyped patients	59
Referral of hepatitis C virus seropositive patients in primary care in the Netherlands	50
Rationale and design of the virological response and ribavirin dosage (virid) study in hepatitis	64
MONTHLY NJM ONLINE HITLIST	
For all articles published in October 2007	38
Total	**1221**

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The Netherlands Journal of Medicine publishes papers in all relevant fields of internal medicine. In addition to reports of original clinical and experimental studies, reviews on topics of interest or importance, case reports, book reviews and letters to the editor are welcomed.

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A *Covering letter* should accompany the manuscript, identifying the corresponding person (with the address, telephone number, fax number and e-mail address). Conflicts of interest, commercial affiliations, consultations, stock or equity interests should be specified. In the letter one to three sentences should be dedicated to what this study adds. The letter should make it clear that the final manuscript has been seen and approved by all authors. All authors should sign the letter. The letter should either be submitted through http://mc.manuscriptcentral.com/nethjmed or faxed to the editorial office (+31 (0)24-354 17 34).

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The *Title page* should include authors' names, degrees, academic addresses, correspondence address, including telephone number, fax number, e-mail address and grant support. Also the contribution of each author should be specified.
The title should be informative and not exceed 90 characters, including spaces. Avoid use of extraneous words such as 'study', 'investigation' as well as priority claims (new, novel, first). Give a running title of less than 50 characters. If data from the manuscript have been presented at a meeting, list the name, date and location of the meeting and reference and previously published abstracts in the bibliography. Give a word count (including references, excluding tables and legends) at the bottom of this page.

The *Abstract*, not exceeding 250 words, should be written in a structured manner and with particular care. In original articles, the Abstract should consist of the following paragraphs: Background, Methods, Results and Conclusion. They should briefly describe the problem being addressed in the study, how the study was performed and which measurements were carried out, the most relevant results, and what the authors conclude from the results.

Keywords: Include three to five keywords.

The *Introduction* should be brief and set out the purposes for which the study has been performed.

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References should be numbered consecutively as they appear in the text (after the punctuation and in square brackets). Type the reference list with double spacing on a separate page. References should be in the language they are published in, conform the 'Vancouver' style for biomedical journals (N Engl J Med 1991;324:424-8).

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

1. Smilde TJ, van Wissen S, Wollersheim H, Kastelein JJP, Stalenhoef AFH. Genetic and metabolic factors predicting risk of cardiovascular disease in familial hypercholesterolemia. Neth J Med 2001;59:184-95.
2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

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Case reports containing concise reports on original work will be considered for publication. Case reports which are relevant for understanding the pathophysiology or clinical presentation of disease may also be accepted under this heading. Selection of case reports will be based on criteria as outlined in a special report by the editors (Drenth et al. The case for case reports in the Netherlands Journal of Medicine. Neth J Med 2006;64(7):262-4). We advise potential authors to take notice of the instructions in this report. Articles published in this section should be no longer than 1000 words, and supplied with a summary of about 60 words, preferably no more than two figures and/or tables, and no more than 15 references.

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