Netherlands
The Journal of Medicine

PUBLISHED IN COLLABORATION WITH THE NETHERLANDS ASSOCIATION OF INTERNAL MEDICINE

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Biosis database; embase/excerpta medica; index medicus (medline) science citation index, science citation index expanded, isi alerting services, medical documentation services, current contents/clinical medicine, PubMed.

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Contents

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EDITORIAL

Preparing for the next influenza pandemic

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ABSTRACT

The Dutch Ministry of Health, Welfare and Sport is determined to be as well prepared as possible for an influenza pandemic, if one should occur. Various measures based on the use of vaccines, antiviral agents and guidelines are being implemented or prepared. The aim is to maintain social and economic infrastructure as much as possible during a pandemic outbreak of influenza. In this context, the ministry is drawing on advice provided by the Health Council in two separate reports.[1,2]

KEYWORDS

Antiviral medicines, avian influenza, flu vaccines, influenza pandemic

INTRODUCTION

An influenza pandemic is a global epidemic caused by a new strain of the influenza virus, against which people have yet to acquire resistance. Such pandemics are very unpredictable, but they do occur with a degree of regularity. On the basis of expert advice, the ministry is working on the assumption that there is a real possibility of another influenza pandemic at some time in the not-too-distance future. In order to be as well prepared as possible, the ministry is currently working on a number of preparatory initiatives, in line with the Health Council's advice.

VACCINES

As the Health Council rightly points out, vaccination affords the best protection against influenza. One can assume that there will not yet be a vaccine against the virus strain involved.[3] Generally speaking, it takes at least six months to develop a vaccine and manufacture it on a large scale. The Dutch government is currently negotiating with a manufacturer to ensure that a vaccine against any future pandemic influenza strain is available in the Netherlands as soon as possible following its development. The government sees it as its responsibility to provide the highest possible protection at the onset of a pandemic. At this point, the availability of antiviral agents becomes vital.

ANTIVIRAL AGENTS

Treatment with antiviral agents such as oseltamivir and zanamivir reduces the duration of the illness in otherwise healthy patients by one to two days. Such treatment is also associated with a lower risk of pneumonia and reduced reliance on antibiotics. Antiviral agents can additionally be used on a prophylactic basis.

Where the use of antiviral agents for pandemic response is concerned, it is important to distinguish between the treatment of the first cases detected when a pandemic reaches the country and wider use in the context of a manifest pandemic. At the start of a pandemic, one may expect to have a small number of isolated patients who are quickly tracked down by the municipal health services. Under such circumstances, the Council advises the

preventive treatment of family members, people living in the same household and other close contacts of the patient. By adopting this strategy, it is hoped that the pandemic can be prevented from spreading so quickly or even nipped in the bud. If in practice it proves possible to identify the first cases in the Netherlands caused by a pandemic virus strain, perhaps because they involve people who have just returned from a region where the pandemic is already established, we will implement the Council's advice and make antiviral agents available to people who may have been infected but have not (yet) developed symptoms of the illness.

If efforts to contain the pandemic are unsuccessful, or if the arrival of the pandemic from abroad involves a large number of simultaneous cases, the government's guidelines on responding to a manifest pandemic will come into operation. Under such circumstances, preventive treatment will be abandoned and, as recommended by the Health Council, the emphasis will switch to making antiviral agents available to anyone in the country showing symptoms of the illness. Implementation of this policy will depend on us having a much larger stock of antiviral agents at our disposal than at present. The modest current stock (sufficient for 225,000 courses of treatment) therefore needs to be built up to the point where roughly five million people can be treated.

TREATING INFLUENZA

The accepted wisdom in the Netherlands is that influenza is something one does not treat; it is better to simply wait for the body to deal with it. Many people will therefore find it difficult to understand the logic of holding a large stock of antiviral agents for treatment of the illness. Nevertheless, there are sound reasons for adopting such a policy from the Ministry of Health's point of view. Namely, the treatment of influenza during a pandemic is intended not so much to benefit the individual patient, as to be advantageous to the health of the wider community. As indicated above, the plan is to administer antiviral agents on a preventive basis when a pandemic first reaches the country, with a view to stopping the pandemic from spreading so quickly, or even nipping it in the bud. However, it also makes good sense to use antiviral agents to treat patients during a manifest pandemic. Such treatment has a beneficial impact on the subsequent course of the illness, as the patient builds up immunity against the new virus strain. If a patient who has acquired immunity is subsequently reinfected by the virus, he or she will not become ill or will become less seriously ill. Treatment with antiviral drugs also makes patients less contagious which will probably lead to a lower morbidity. Another reason for treatment is that influenza victims who are given antiviral agents recover one to two days sooner than they would otherwise have done. This may not sound like a great benefit, but if one assumes that a substantial part of the population is ill at any one time, the overall impact is huge.

CONCLUSION

The object of using antiviral agents when an influenza pandemic first reaches the country or when the arrival of a pandemic is regarded as imminent is to contain the spread of the illness.[4] The success of such a policy will to a large extent depend on the implementation and logistics. Accordingly, the ministry intends to draw up a distribution plan in consultation with the interested parties. The aim is to incorporate this plan into the guidelines before the end of 2005.

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REVIEW

Use of antiviral agents and other measures in an influenza pandemic

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ABSTRACT

The Dutch Ministry of Health asked the Health Council for advice on how to prepare for a possible influenza pandemic. In two advisory reports the Committee responsible indicated the measures that it believes would need to be taken if such a pandemic were to reach the Netherlands. During a pandemic, the Committee recommends that every resident of the Netherlands with influenza-like illness should be treated with neuraminidase inhibitors such as antiviral agents. This approach serves to mitigate the course of the disease, to reduce infectivity and to allow patients to build up immunity to the virus. Since up to 30% of the population could become ill, the Committee anticipates that a stock of five million courses of the neuraminidase inhibitor oseltamivir is sufficient. If a pandemic were to occur at a time that the stock does not exceed the present 225,000 courses, the committee advises restricting treatment to three specified groups of patients. If the first few patients are traced shortly after they fall ill, the Committee recommends treatment of the patient and postexposure prophylaxis for his/her close contacts. The Committee does not advocate prophylaxis in general, but it can envisage prophylaxis for particular groups of patients or under particular circumstances. The Committee believes that in order to reduce rapid spread of the virus, schools should be closed and events where large numbers of people gather in a confined space should be cancelled. Because this recommendation would have major social and economic consequences, the Committee understands that its implication will depend on the anticipated severity and extent of the pandemic. The Committee regards vaccination against influenza as the best means of protecting the population. The development of a vaccine should be the absolute priority.

KEYWORDS

Antiviral agents, influenza, pandemic, risk groups, ring prophylaxis, treatment

INTRODUCTION

In the Netherlands, influenza viruses give rise to epidemics virtually every year. Epidemics recur because of what is known as antigen drift in the influenza A and B viruses, brought about by mutations in the genes for the virus proteins haemagglutinin (H) and neuraminidase (N).[1] In patients, the antibodies formed in response to the infection protect against reinfection by the same virus strain and – by a process known as cross-protection – against a strain with a similar antigen composition. The more this antigen drift has occurred, and therefore the more different a strain is from anything an individual has previously encountered, the less benefit is afforded by cross-protection and the greater the risk that the mutated strain will cause influenza in the individual in question. Among risk groups, such as older people, vaccination is used to reduce the chances of influenza infection. The composition of the vaccine is adjusted annually in line with the virus strains in circulation. Vaccination provides adequate protection as long as the antigen composition of the strain with which a person comes into contact is reasonably similar to that of the strains used for preparation of the vaccine.

Influenza viruses occasionally also lead to pandemics (i.e. epidemics on a global scale). Pandemics occur because of antigen shift, brought about by the transfer of genetic material from one virus strain to another (particularly

the genes for the H and N proteins).[1] Antigen shift leads to the development of a virus strain whose antigen composition is very different from its predecessors, with the result that the population has insufficient (cross-)protection against such a virus and existing vaccines are ineffective. Three such pandemics have occurred during the twentieth century.[2] The 'Spanish influenza' pandemic of 1918 claimed tens of millions of lives, making it one of the most serious outbreaks of an infectious disease on record.[3] Unlike the epidemics, influenza pandemics are, to a great extent, unpredictable. Thus, although it is generally expected that another influenza pandemic will occur, we cannot predict when this will be.[2] Furthermore, if a pandemic arises abroad it is difficult to predict how long it will take before it reaches our country. And once it has arrived here, we can only make a partial estimate of how many people will fall ill, which population groups are at greater risk and which individuals, after becoming ill, run a greater risk of complications. In contrast to the situation during an influenza epidemic, when fatalities are confined mainly to older people, during a pandemic higher levels of mortality can also occur amongst people who do not belong to the classic risk groups.[4] During the 'Spanish influenza' pandemic such a pandemic-specific risk group was formed by 20 to 40 year olds.[4,5]

The massive incidence of avian influenza in South-East Asia in the last few years appears to have increased the risk that a virus strain may emerge that is capable of triggering an influenza pandemic.[6,7]

The Dutch Ministry of Health asked the Health Council for advice on how to prepare for a possible pandemic. The Health Council published two advisory reports in which the Committee responsible indicated the measures that it believes would need to be taken if such a pandemic were to reach the Netherlands.[8,9] The objectives underlying the Committee's recommendations are: to level the pandemic over time by reducing the number of subclinical and clinical cases and to contain the impact of infection by means of antiviral therapy with neuraminidase inhibitors.

The Committee's recommendations are based on the current, limited, state of knowledge. This is due to both the unpredictability of a pandemic and the relative lack of scientific information on neuraminidase inhibitors.[10,11] The Committee is therefore at present only able to indicate what it believes would, in theory, be the best course of action. The Committee's advice is therefore that its recommendations should be kept in line with advances in knowledge and that the opinion of experts should be sought when making decisions on what action is to be taken (for example, the recently established Centre for Infectious Diseases). The chances of gaining some insight into the pandemic will improve if it begins abroad and only reaches the Netherlands after some time has elapsed. Use can then be made of data from the countries that have already been affected.

NEURAMINIDASE INHIBITORS AS ANTIVIRAL AGENTS

In the preceding years, the Dutch government has stockpiled approximately 225,000 courses of the neuraminidase inhibitor oseltamivir (a second-generation antiviral agent). The Committee endorses the Dutch government's choice for neuraminidase inhibitors, since first-generation antiviral agents have relatively severe side effects on the central nervous system in particular and because of the relatively rapid emergence of strains resistant to the first-generation agents.[10] Research into new neuraminidase inhibitors is in progress,[12] but it is unlikely that such agents will be available in ample quantities for several years, mainly because development work on a number of them has been halted.[13] In the event of there being a shortage of oseltamivir, the Committee considers that the neuraminidase inhibitor zanamivir could be purchased, but only for those patients who are unlikely to experience problems with the inhalations that are required with this remedy.

The committee has applied the following definitions.

Prophylaxis

The use of oseltamivir (a single daily dose of 75 mg for a period of up to six weeks) by a person who shows no symptoms of illness, with a view to preventing infection.

Postexposure prophylaxis

The use of oseltamivir (a single daily dose of 75 mg for seven days) by a patient's family, housemates and other contacts after possible exposure but before the manifestation of symptoms. Postexposure prophylaxis for this period reduces the incidence of influenza in treated households and diminishes excretion of the virus by people who become ill in spite of such prophylaxis.[14]

Treatment

Oseltamivir (two daily doses of 75 mg for five days) or zanamivir (two inhalations of 5 mg twice a day for five days) should be used in patients showing symptoms of illness consistent with infection by the influenza virus, such as fever, a suddenly acquired cough and, for example, headache or aching muscles.[15] When an influenza virus is in circulation, it is very likely that a patient displaying such symptoms has been infected with the virus.[16] The Committee emphasises the importance of starting treatment as soon as possible after the appearance of the first symptoms, and certainly within 48 hours. If treatment is started later, it may not be effective.[3,10]

THE FIRST CLINICAL CASES

When the first clinical cases are recorded, it is likely that outbreaks will be isolated and affect a small number of patients only. If this is the case, and if these patients are traced shortly after they fall ill, the Committee recommends treatment of the patient and postexposure prophylaxis for his/her family or household and other close contacts.[17] In a recent publication, the phrase 'ring prophylaxis' was coined to describe this type of strategy.[18] Mathematical analyses indicate that the recommended strategy could mitigate or even stop a pandemic.[19-21] The Committee's advice is that these measures should even be adopted when stocks of neuraminidase inhibitors are limited to the 225,000 courses mentioned earlier.

TREATMENT

During a manifest pandemic, the Committee recommends that any resident of the Netherlands displaying a clinical picture that resembles influenza should be treated with neuraminidase inhibitors – preferably as soon possible, but no later than 48 hours after the onset of the first clinical symptoms. This approach serves to mitigate the course of the disease and helps patients to build up immunity to the virus, meaning that they will not fall ill (or at least that they will be far less affected) in the event of a second infection. The Committee's advice implies that stocks of neuraminidase inhibitors need to be expanded to such an extent that there is enough to treat all residents of the Netherlands with influenza. Since it is estimated that up to 30% of the population could become ill during a pandemic,[22-25] the Committee anticipates that a total stock of five million courses of oseltamivir is sufficient.
If a pandemic were to occur at a time that the stock of neuraminidase inhibitors does not exceed the present 225,000 courses, the Committee recommends restricting treatment of the first clinical symptoms to patients from the following three groups:

- People from the risk group that was accorded the highest level of priority in the Health Council's advisory report on *Vaccination policies in case of an influenza pandemic*,[26] except for the patients with furunculosis. This risk group comprises patients with serious abnormalities or functional disorders affecting the airways, lungs or heart who, despite receiving medication, would be at great risk of lung or heart function decompensation if they were to be infected by the pandemic influenza virus. Patients with an insulin-dependent form of diabetes mellitus also belong in the category with the highest level of priority;
- People in the pandemic-specific risk group (if such a risk group exists);
- Professionals, that is to say all those responsible for the diagnosis, treatment and care of influenza patients and all those with logistical responsibility for the requisite medication.

During scarcity of neuraminidase inhibitors, otherwise healthy people should receive treatment only in the event of hospitalisation due to complications following influenza.

PROPHYLAXIS

The Committee does not advocate prophylaxis with neuraminidase inhibitors, even if there are adequate stocks, because then protection would only be conferred for as long as the compound is used. After the therapy is stopped, the person would still be vulnerable to the virus owing to a lack of immunity. Moreover, research findings from the United Kingdom suggest that the provision of prophylaxis to all the residents of a nursing home or care home as soon as one resident shows symptoms consistent with influenza would require large quantities of neuraminidase inhibitors.[27]
During a manifest pandemic, however, the Committee can envisage that the neuraminidase inhibitors might be used prophylactically in particular groups or under particular circumstances. What it has in mind here are patients whose immune system is compromised (e.g. as a result of bone marrow transplantation) or the occurrence of influenza in a department of a care home or nursing home that can easily be isolated. The Committee recommends that the decision on whether to administer prophylaxis should be left to the individual patient's attending physician.
Following influenza vaccination, one may not be fully resistant to infection for several weeks, since it takes some time to build up immunity. If sufficient stocks of neuraminidase inhibitors are available while the virus is circulating, the Committee advises giving neuraminidase inhibitors on a prophylactic basis to the predefined (pandemic-specific) risk groups and professionals during the period that they are building up immunity following vaccination.
The Committee's recommendations regarding the use of neuraminidase inhibitors in an influenza pandemic are summarised in *table 1*.

GENERAL MEASURES

The Committee believes that, in order to reduce rapid spread of the virus, schools should be closed down and events where large numbers of people gather in a confined space should be cancelled for the duration of the pandemic. The Committee realises that this measure would have

Table 1 *Use of neuraminidase inhibitors in an influenza pandemic*

	Treatment	**Prophylaxis**
When the pandemic first reaches the Netherlands	Index patients[a]	Families, housemates and other contacts of index patients: post-exposure prophylaxis
In a manifest pandemic or in the event of large-scale virus introduction from abroad		
If neuraminidase inhibitors are in short supply	Risk groups[b], professionals[c] and (where relevant) people in pandemic-specific risk group[a]; otherwise healthy people: in the event of hospitalisation due to complications	
If neuraminidase inhibitors are not in short supply	Patients displaying symptoms consistent with influenza	Individual patients[d] and risk groups, professionals and (where relevant) people in pandemic-specific risk group[e]

[a]As soon as possible following the appearance of the first symptoms; if treatment is not started within 48 hours, it may not be effective. [b]Patients with serious respiratory, pulmonary or cardiovascular abnormalities or dysfunction, who if infected with the pandemic influenza virus would be at serious risk of pulmonary or cardiovascular function decompensation, patients with an insulin-dependent form of diabetes. [c]All persons responsible for the diagnosis, treatment and care of influenza patients, or for logistic management of the necessary resources. [d]Where considered appropriate by the doctor in charge of the individual patient. [e]Following vaccination and while the virus is circulating.

major social and economic consequences. It therefore understands that the decision to close schools will depend on the anticipated severity and extent of the pandemic, which would largely be determined by the characteristics of the virus (for example its pathogenicity and the speed at which it spreads).

The Committee regards vaccination against influenza as the best means of protecting the population against an influenza pandemic. The development of a vaccine should be the absolute priority. However, it is likely to be six to twelve months before a vaccine against the relevant pandemic strain can be developed and produced in sufficient quantities. Should vaccine stocks prove inadequate, the Committee recommends that priority should be given to the particular groups defined earlier for preferential treatment during scarcity of neuraminidase inhibitors.

CONCLUSIONS

The Committee's recommendations are based on the current, limited, state of knowledge. In view of the paucity of the scientific data available, the Committee recommends that, during any future pandemic, proper arrangements should be made to document the use of neuraminidase inhibitors and the results of such use, in order to provide data for subsequent analysis. This recommendation especially concerns the monitoring for emergence of viral resistance to neuraminidase inhibitors. Until recently, influenza strains resistant to neuraminidase inhibitors were very rarely encountered. In a recently published study, however, virus strains resistant to oseltamivir were isolated in nine of 50 treated children.[28] It is not (yet) clear whether the resistant strains are transferable to other people, or how infectious the new strains are. Further research in this field is strongly recommended.[29]

The Committee has not been in the position to quantify the cost-effectiveness of its recommendations (e.g. in terms of the cost per quality-adjusted life-year). It believes that there are too many uncertainties – not only of a factual nature (e.g. the timing of the pandemic and the characteristics of a future pandemic virus) but also uncertainties that can only be eliminated through (possibly arbitrary) policy choices.

The Committee regards the procurement of a sufficiently large stock of neuraminidase inhibitors as just one of the elements required in order to prepare for the use of these compounds during a pandemic. The Committee does not believe that its remit includes a detailed elaboration of the logistical implications of its recommendations. It therefore confines itself to noting that the success of the use of neuraminidase inhibitors will depend to a great extent on the way in which this strategy is implemented.

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REVIEW

Helicobacter pylori, obesity and gastro-oesophageal reflux disease

Is there a relation? A personal view

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ABSTRACT

The incidence and prevalence of gastro-oesophageal reflux disease is rising. Changing dietary habits and increasing body weight can be held responsible. In several studies a close relation was found between body weight and the occurrence of reflux disease. It may be concluded that there is a definite relation between body mass index and the occurrence of reflux disease. *H. pylori* probably also plays a role. *H. pylori* causes changes in fundic leptin levels and plasma levels of ghrelin. Eradication of *H. pylori* infection can increase appetite leading to a rise in body mass index due to a higher caloric intake. *H. pylori* can be a 'protective' factor against the development of overweight. Since only a minority of overweight or obese patients with gastro-oesophageal reflux disease will lose weight successfully, medical treatment with effective acid suppression will be the mainstay of the treatment of reflux disease in patients with a high body mass index.

KEYWORDS

Gastro-oesophageal reflux disease, ghrelin, *H. pylori*, leptin, obesity

INTRODUCTION

Gastro-oesophageal reflux disease is caused by reflux of stomach and duodenal contents into the oesophagus. Reflux can be the result of failure of the natural antireflux barrier between the gastric cardia and the oesophagus. The most important pathophysiological mechanism causing reflux is long-lasting spontaneous relaxation of the lower oesophageal sphincter (LOS) or low pressure in the LOS. A hiatus hernia is an additional risk factor. The incidence and prevalence of gastro-oesophageal reflux disease is rising, at least in the Western world. This will be accompanied by an increasing incidence of the complications of gastro-oesophageal reflux.[1,2]

The incidence of overweight and obesity has also been reported to be rising. It can be expected that complications due to overweight will also rise. Changing dietary habits and the increasing body weight may possibly induce reflux disease.

And finally, the incidence of *H. pylori* infection in the Western world has been decreasing for almost forty years. It has been reported that following eradication of *H. pylori*, reflux disease and/or an increase in body weight can develop. In the present paper the possible relations between *H. pylori*, obesity and reflux disease are discussed.

REFLUX DISEASE

Gastro-oesophageal reflux disease can present clinically in several ways. In most studies, patients are included who have reflux oesophagitis with or without symptoms, patients with an abnormal pH recording in the distal part of the oesophagus, or patients with symptoms without ever undergoing endoscopy. In addition, *H. pylori*-positive as well as *H. pylori*-negative patients, and patients who have had undergone successful anti-*H. pylori* therapy are included. Studies including only patients who have never had *H. pylori* are sparse.[3] Not every patient with the typical reflux symptoms actually suffers from reflux oesophagitis nor does every patient with reflux oesophagitis have reflux. In daily practice, the majority of patients with

more severe forms of reflux oesophagitis do not have reflux symptoms but merely complain of dysphagia.[4]

GASTRO-OESOPHAGEAL REFLUX DISEASE AND OBESITY

Increased intra-abdominal pressure plays an important role in the mechanism of reflux.[5] In several studies no relation was found between body weight and the occurrence of gastro-oesophageal reflux disease.[6,7] However, in recent years several studies have been published which show different results. Overweight and obesity go along with an important increase in the occurrence of gastro-oesophageal reflux.[8-10] Patients with overweight or obesity suffered more often from gastro-oesophageal reflux than controls with a normal body weight. The pressure in the LOS also appeared to be lower in patients with a higher body mass index.[11] Wilson and co-workers studied the relation of body mass index and the presence of a hiatus hernia and reflux oesophagitis.[12] A total of 1389 consecutive patients were studied. Oesophagitis was seen in 189 patients; the remainder were used as control group. Patients were divided in three groups according to body mass index: normal weight (BMI 20 to 25), overweight (BMI 25 to 30), and obesity (BMI >30). Reflux oesophagitis was more often present with a hiatus hernia and/or a higher body mass index. There was no difference between men and women or race. Body mass index was also an independent risk factor for development of a hiatus hernia.[12] A dose-effect relation was detected.[13] Murray and co-workers studied the relation of body weight and reflux symptoms in the Bristol *Helicobacter pylori* Project. Overweight was a risk factor for developing reflux, but obesity was an even higher risk. The severity of reflux symptoms correlated significantly with body weight.[14] The relation of body mass index and reflux was stronger in women, especially in premenopausal women.[13-15] Population-based studies showed that a higher body mass index is not only a risk factor for gastro-oesophageal reflux disease, but also for development of an adenocarcinoma in the oesophagus.[16,17] This relation is also present with carcinomas of the gastric cardia but not with squamous cell carcinoma of the oesophagus. El-Seraq and co-workers carried out logistic regression analysis in order to identify risk factors.[3] Overweight and obesity were independent risk factors for the more severe forms of reflux oesophagitis according to the Los Angeles classification.[3] The pressure in the LOS can be lower in patients with a higher body mass index, but there is no difference in manometric findings in the body of the oesophagus compared with patients with a normal body weight. Oesophageal peristalsis is normal.[18] Patients with gastro-oesophageal reflux disease often have intolerance for certain kinds of food. They tend to avoid these foods. Ingestion of food with excess in fat, especially animal fat and cholesterol, increase the risk for gastro-oesophageal reflux disease.[16] Food low in fat and high in fibre appears to have a protective effect. Obviously, a high body mass index is the result of a feeding pattern in which the intake of calories exceeds the daily needs. Despite this observation, fat and a high body mass index are independent risk factors for development of gastro-oesophageal reflux disease.[16]

H. PYLORI AND REFLUX DISEASE

Despite the fact that there is an ongoing discussion in the literature as to whether or not *H. pylori* protects against development of reflux disease and eradication causes reflux disease,[19-22] it is clear that *H. pylori* has definite effects on gastric acid production.[23,24] The effect depends on the distribution of the *H. pylori*-associated gastritis. Patients with an antral predominant gastritis have an elevated maximal stimulated acid production. Patients with a corpus predominant gastritis or a pangastritis have a lower acid production. With effective acid suppressive therapy a shift occurs from antral predominant gastritis to corpus predominant gastritis or pangastritis.[25,26] Patients included in clinical trials are not allowed to take acid suppressive drugs prior to inclusion. But the majority had already been treated with acid suppressive drugs in the past; naive patients are seldom included in trials. One can assume that the effects of acid suppressive therapy on the *H. pylori*-associated gastritis will not subside in a short period of time. Hence presence or absence of *H. pylori* can have a major effect on the results of studies evaluating gastro-oesophageal reflux disease. In duodenal ulcer disease, if *H. pylori* has been successfully eradicated, reflux oesophagitis has been reported to occur.[27] The patients who actually developed reflux oesophagitis also had a significant increase in body weight. The dietary habits must have changed, otherwise this weight gain would not have occurred!

H. PYLORI AND OBESITY

Recent research can explain the effect of *H. pylori* eradication on body weight.

Identification of ghrelin has revealed complex interactions in regulation of food intake.[28] Ghrelin is an important factor in appetite and satiety. Plasma ghrelin concentrations, gastric ghrelin mRNA, and ghrelin positive cell numbers in gastric mucosa are significantly lower in *H. pylori*-positive subjects.[29,30] However, this finding has not been invariably confirmed.[31] After successful eradication of *H. pylori* the number of ghrelin positive cells increases significantly irrespective of the presence of gastric atrophy.[30] This could lead to increased appetite and weight gain. Also, in an experimental study in which *H. pylori*

infection was induced, significant decrease in ghrelin mRNA levels and plasma ghrelin levels occurred.[32] Not only ghrelin levels increase after eradication, intra gastric acidity also increased by 14%.[33] This possible mechanism links *H. pylori*, obesity and reflux disease.

Leptin is another important hormone. Fasting and starvation decrease gastric leptin mRNA and protein level, and this fall produces a signal to eat. Hence, increased leptin signalling leads to decreased food intake and, in addition, to increased energy expenditure and increased thermogenesis.[34] Leptin is produced in the fundus of the stomach. Stretching of the fundus due to food intake probably leads to a decrease in fundic leptin, an increase in plasma level of leptin, and to a feeling of satiety. *H. pylori* infection significantly increases gastric leptin expression.[35] Eradication of *H. pylori* decreases gastric leptin expression. The plasma leptin levels do not change, but there is a significant decrease in immunoreactivity of leptin in mucosa of the fundus.[35] This decrease was accompanied by an increase in body mass index in the studied patients. Because the serum levels of leptin did not change, this weight gain must be due to a local effect in the fundus. The effects of *H. pylori* on ghrelin and leptin strongly suggest that the bacterium 'protects' against obesity. The decreasing incidence of this infection may be contributing to an increase in appetite and food intake.

CONCLUSION

From the presented data it can be appreciated that there is a certain relation between body mass index and reflux disease, *H. pylori* and reflux disease, and *H. pylori* and obesity. The exact relation and the consequences are not yet entirely clear. The primary cause of the rising body weight is the changes in lifestyle, at least in the Western world. The intake of fat and carbohydrates increases, while physical activity clearly decreases. It can be postulated that body weight can increase after eradication of the bacterium, and that reflux disease can develop in patients who had a *H. pylori*-associated pangastritis due to acid suppressive therapy. It can be postulated that *H. pylori* infection due to effects on leptin and ghrelin protects against intake of large amount of calories in these patients.

The prevalence of *H. pylori* infection is decreasing, possibly leading to a loss of this 'protective' factor. Young people in the Netherlands no longer acquire *H. pylori*. Is obesity in the youngsters in part caused by the lack of this 'protective' factor? Should *H. pylori* not be eradicated? Should the stomach be colonised by *H. pylori*? The bacterium is absolutely the cause of major morbidity. Weight gain, due to normalisation of ghrelin and leptin, after successful eradication can be controlled by dietary measures. Even if reflux disease does develop, than treatment with acid suppressive therapy is generally available.

The increasing body weight can be held responsible for at least a major part of the rising incidence of gastro-oesophageal reflux disease. Whether all these assumptions are true should be the goal of future studies.

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Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Evaluation of Endocrine Tests B: screening for hypercortisolism

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ABSTRACT

Background: While reference values for 24-hour free urinary cortisol excretion and the overnight 1 mg dexamethasone-suppression test in the healthy population are available, cut-off values in patients clinically suspected of Cushing's syndrome have to be established.
Methods: This was a prospective follow-up study in one academic centre of 144 patients with clinical suspicion of Cushing's syndrome (group A) and 50 patients with adrenal incidentaloma (group B) who were referred for putative hypercortisolism between 1 January 1993 and 1 January 2003. The 24-hour urinary free cortisol and post-dexamethasone plasma cortisol were measured. Accurate diagnosis of (absence of) Cushing's syndrome was confirmed by histopathological data and long-term follow-up. Based on the data obtained in group A, sensitivity, specificity and receiver operating characteristic (ROC) curves were calculated.
Results: Complete follow-up was obtained in 86%, and partial follow-up was obtained in 8% of patients. Median follow-up was 36 (1 to 122) months. In group A, 17 patients were found to have Cushing's syndrome. In this group median 24-hour urinary free cortisol was 77 (<5 to 51458) nmol/24 hours and median post-dexamethasone plasma cortisol was <50 (<50 to 4900) nmol/l. Area under the ROC curve was 0.958 for 24-hour urinary free cortisol and 0.985 for post-dexamethasone plasma cortisol. Optimal cut-off values were 180 nmol/24 hours (sensitivity 94%, specificity 93%) and 95 nmol/l (sensitivity 100%, specificity 94%) respectively.
Conclusion: We established cut-off values for 24-hour free urinary cortisol excretion (180 nmol/24 hours) and for post-dexamethasone plasma cortisol (95 nmol/l) in the evaluation of patients referred for hypercortisolism.

KEYWORDS

Adrenal incidentaloma, cortisoluria, Cushing, dexamethasone-suppression test, screening

INTRODUCTION

The laboratory investigation of patients clinically suspected of having Cushing's syndrome is usually divided into two distinct phases. The first diagnostic phase tries to establish the presence of hypercortisolism, which is the hallmark of Cushing's syndrome. In the second phase, the cause of the hypercortisolism is established.
The 24-hour excretion of urinary free cortisol and the overnight 1 mg dexamethasone-suppression test are widely accepted as screening tests.[1-3] We previously established reference values for 24-hour excretion of urinary free cortisol and the 1 mg dexamethasone-suppression test.[4]
It should be realised that the reference values established in healthy controls are not necessarily of discriminative value in the patients referred for evaluation. For instance, obese subjects are more likely to be screened for Cushing's syndrome than lean patients, and obesity is associated with disturbances in cortisol metabolism mimicking Cushing's syndrome.[5] Thus, it is also necessary to estab-

lish cut-off values within the patient group that is referred because of clinical suspicion of Cushing's syndrome.
We prospectively studied the data of all patients referred to our hospital with suspected Cushing's syndrome over a ten-year period. Referral was based either on clinical characteristics or on incidental findings of imaging studies.

MATERIALS AND METHODS

Patients

In this study, data from all patients who underwent endocrine evaluation for Cushing's syndrome at the Department of Endocrinology of the Academic Medical Centre, Amsterdam between 1 January 1993 and 1 January 2003 were analysed. If a patient had repeated tests during the study period, only the first set of tests was used to evaluate the diagnostic accuracy.
A definite diagnosis of Cushing's syndrome was made on the basis of clinical data and histopathological data obtained by surgery. Patients referred because of an adrenal incidentaloma were analysed separately and were excluded from the formal analyses with regard to test characteristics.
Patients who had a clear, final diagnosis and patients who were still being seen in our hospital in 2003 were considered to have adequate follow-up. To obtain follow-up data for those patients who were no longer visiting our hospital, we contacted their general practitioners by telephone, asking specifically about a diagnosis of Cushing's syndrome, pituitary or adrenal surgery and chronic systemic steroid use before considering follow-up as negative. Patients who had moved some years after being tested but in whom Cushing's syndrome had not been diagnosed at their last GP visit were considered to have a partial follow-up.

The 24-hour excretion of urinary free cortisol

Patients were asked to collect two separate consecutive 24-hour urine samples. During this collection, the urine was to be kept refrigerated. Total urine volumes as well as concentrations of free cortisol and creatinine were measured. The mean urinary excretion of these two samples was used for analysis. If total creatinine excretion in the sample with the highest creatinine excretion was more than 150% of the creatinine excretion of the other sample, both samples were excluded, but if only one 24-hour sample was obtained this was used for analysis.

Overnight 1 mg dexamethasone-suppression test

This test was performed one day after the second 24-hour urine collection. On day 1, a blood sample was taken at 08.30 hours by venipuncture. At 23.00, 1 mg of dexamethasone was given orally. On day 2, a second blood sample was taken at 08.30 by venipuncture. Both samples were taken in the postabsorptive phase, in seated position and after 30 minutes rest. In both samples concentrations of ACTH and cortisol were measured.

Analytical methods

Measurement of adrenocorticotrophic hormone (ACTH) and (urinary) cortisol was carried out in duplicate.
Initially, plasma cortisol was measured by fluorescence polarisation assay on a TDX analyser (Abbott Laboratories, Chicago, IL, USA). After five years we switched to a luminescence immunoassay on an Immulite I analyser (DPC, Los Angeles, CA, USA). Long-term reproducibility was monitored by comparing with the laboratory results in the Dutch National External Quality Assessment Scheme (NEQAS) for Ligand Assay of Hormones (LWBA). The Abbott cortisol assay consistently measured 15% higher than the all trimmed mean, while the DPC assay equalled this value during the study period. Hence, the Abbott cortisol concentrations were divided by 1.15 to convert to the DPC cortisol values. Both assays had an interassay variation coefficient of 9% at the level of 200 nmol/l and 5% at the level of 850 nmol/l. Detection limit for both assays was 50 nmol/l.
Urinary cortisol was measured by an in-house high performance liquid chromatography (HPLC) method. Long-term reproducibility was monitored by comparing with the laboratory results in the United Kingdom NEQAS. A consistent negative difference of 30 to 40% was seen compared with the (immunoassay) all trimmed mean. Internal quality control samples, used during periods of two years, showed an interassay variation of 10.5% at levels of 49 and 126 nmol/l. Detection limit was 5 nmol/l.
In 1993 and 1994 ACTH was measured by immunoradiometric (IRMA) assay and after this period by immunoluminometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Because ACTH is not covered by the LWBA, long-term reproducibility was monitored by internal quality control samples. New kit lot numbers were compared with quality control samples that were used in the old kit lot numbers. No significant changes were seen during the study period. The interassay variation was 7.5% at levels of 30 and 320 ng/l. Detection limit was 1 ng/l.

Statistical analysis

Values below the detection limits of the assays were included in the analyses as having a value of 50% of the detection limit. Variables were tested for normality using P-P plots. For normally distributed variables, means, standard deviation and T tests were used. For other variables medians and nonparametric tests were used. ROC curves were created to establish the optimal cut-off values for urinary free cortisol levels and post-dexamethasone cortisol levels. Statistical analysis was performed using SPSS for Windows version 11.5.0.

RESULTS

A total of 194 patients was evaluated, 49 men and 145 women. Of these patients, 144 were referred because of clinical suspicion of Cushing's syndrome (group A), whereas the other 50 were tested because of an incidental adrenal mass (group B). Follow-up was complete for 86% of all these patients. Partial follow-up was obtained for 8% of patients, whereas in 6% no follow-up was obtained. None of the 100 patients who were followed-up by a contact with the general practitioner developed Cushing's syndrome. Median duration of follow-up was 36 (1 to 122) months.

The patient characteristics are presented in *table 1*. Patients in group A were significantly younger and had a higher body mass index than those in group B. The proportion of women was higher in group A than in group B, as was the proportion of women on oral contraceptives. Cushing's syndrome was diagnosed in 17 patients (12%) in group A. Of these, eight patients had an ACTH-producing pituitary adenoma, five an adrenal adenoma/adenocarcinoma and four an ectopic ACTH-producing tumour. Within group A, patients with Cushing's syndrome had a significantly higher diastolic blood pressure than those without.

On the basis of our historical cut-off values we classified five patients in group B as Cushing's syndrome. Three patients in group B had an increased plasma cortisol (>140 nmol/l) after dexamethasone and in two of these an adenoma was removed surgically; in the other the diagnosis of bilateral adrenal hyperplasia was made and the patient is still being followed up. Two patients had a urinary free cortisol of over 145 nmol/24 hours; in one of these the diagnosis of an adenoma was made and in the other an adenocarcinoma.

In 14 patients another final diagnosis (e.g. phaeochromocytoma or adrenal metastasis) was made.

Urinary free cortisol

The 24-hour urinary free cortisol was measured in 142 patients in group A, and in 46 patients in group B. Data for urinary free cortisol (mean of both samples) are presented in *figure 1*. Median urinary free cortisol was 77 (range <5 to 51458) nmol/24 hours in group A and 73 (range <5 to 304) nmol/24 hours in group B. In group A (but not in group B) the difference in urinary free cortisol between those without and those with Cushing's disease was significant (median 68 and 609 nmol/24 hours, respectively, p<0.001 Mann-Whitney U test).

Within group A, there was a nonsignificant difference in urinary free cortisol between women using and those not using oral contraceptives (median 92 and 69 nmol/24 hours, respectively, p=0.10). After exclusion of those in whom Cushing's syndrome had been diagnosed, this difference became significant (median 88 *vs* 58 nmol/24 hours, p=0.016).

Overnight 1 mg dexamethasone-suppression test

Test results were available for all patients. Median baseline cortisol was 440 (range <50 to 4400) nmol/l in group A and 415 (range 100 to 730) nmol/l in group B. Median baseline ACTH was 25 (range <1 to 310) ng/l in group A and 15 (range <1 to 210) ng/l in group B.

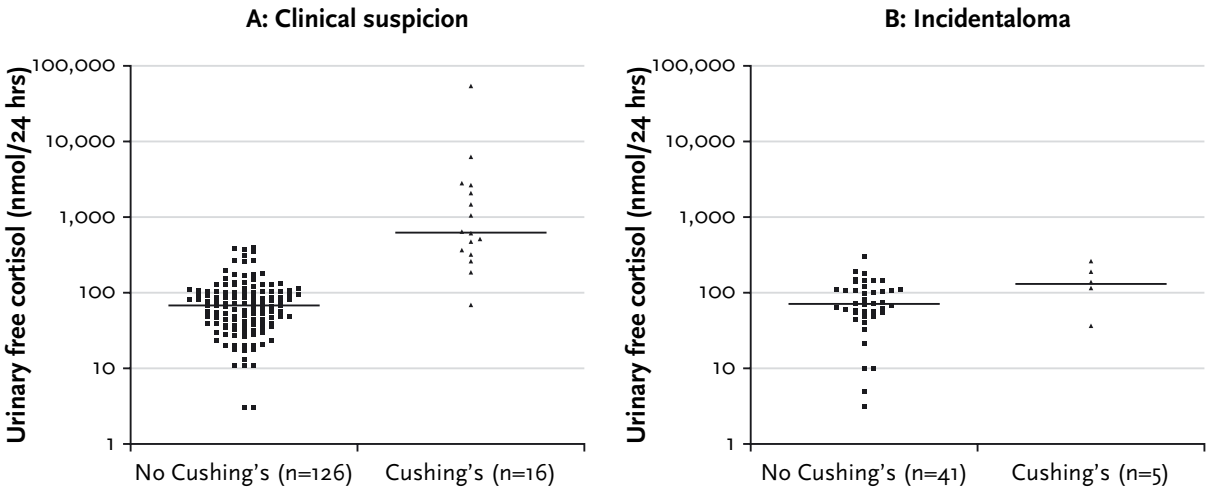
Data for post-dexamethasone cortisol are presented in *figure 2*. Median post-dexamethasone cortisol was <50 (range <50 to 4900) nmol/l in group A and 55 (range <50 to 720) nmol/l in group B. In group A (but not in group B) the difference in post-dexamethasone cortisol between those without and those with Cushing's syndrome was significant (median <50 and 890 nmol/l, respectively, p<0.001 Mann-Whitney U test).

Table 1 *Clinical characteristics of all patients evaluated for hypercortisolism*

	Clinical suspicion			Incidentaloma		
	All	Cushing's	No Cushing's	All	Cushing's	No Cushing's
N	144	17	127	50	5	45
Sex (m/f)	31/113[&]	4/13	27/100	18/32[&]	2/3	16/29
Males (%)	22%	24%	21%	45%	40%	36%
Age	40 ± 13[$]	40 ± 12	40 ± 13	59 ± 13[$]	59 ± 13	59 ±13
Systolic BP	150 ± 25	159 ± 23	148 ± 25	152 ± 23	153 ± 17	152 ± 24
Diastolic BP	92 ± 15	102 ± 17[#]	91 ± 15[#]	90 ± 12	91 ± 10	90 ± 12
BMI	30 ± 7[*]	28 ± 5	31 ± 7	28 ± 7[*]	28 ± 4	28 ± 7
Oral contraceptive users	30[&]	2	28	2[&]	0	2

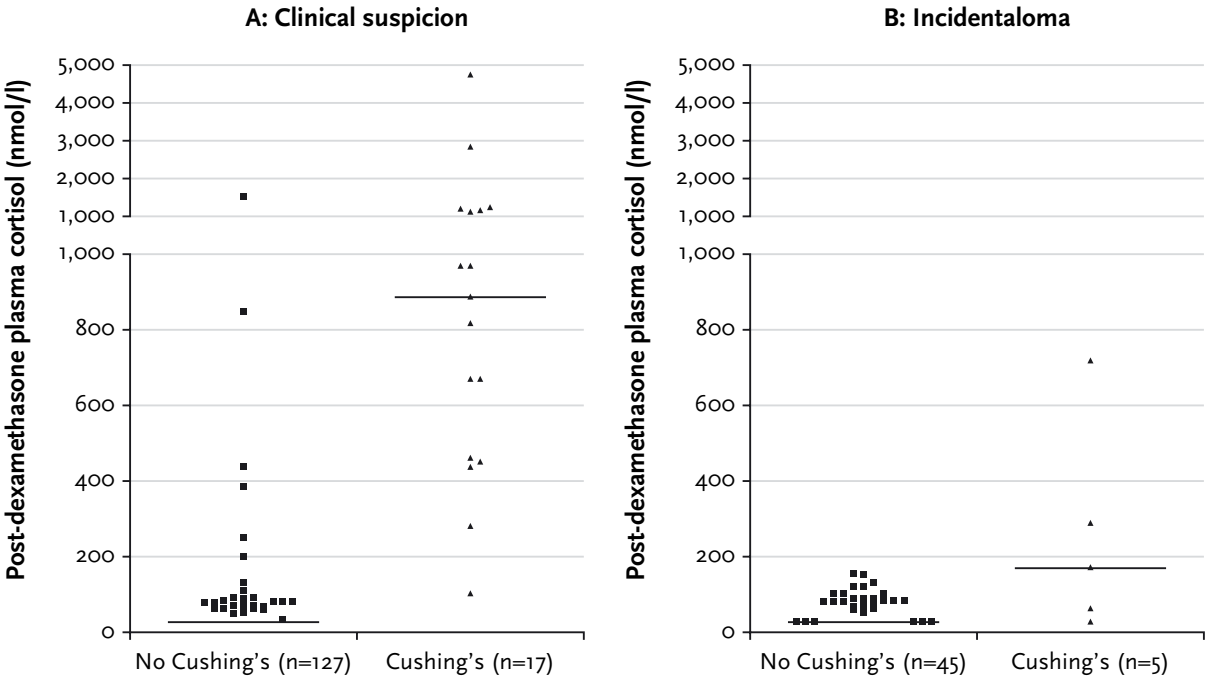
[*]p≤0.05 clinical suspicion *vs* incidentaloma (independent samples T test); [$]p<0.001 clinical suspicion *vs* incidentaloma (independent samples T test); [#]p<0.01 Cushing's *vs* no Cushing's (independent samples T test); [&]p≤0.05 clinical suspicion *vs* incidentaloma (χ^2 test). BP = blood pressure; BMI = body mass index.

Figure 1 *24-hour urinary free cortisol (nmol/24 hours) in patients with clinical suspicion of hypercortisolism (A) and in patients with adrenal incidentaloma (B)*



Please note the logarithmic nature of the scale. The line represents the median of the distribution.

Figure 2 *Plasma cortisol levels (nmol/l) after 1 mg dexamethasone in patients with clinical suspicion of hypercortisolism (A) and patients with adrenal incidentaloma (B)*



The line represents the median of the distribution.

Within group A, there was a significant difference in post-dexamethasone cortisol between women using and those not using oral contraceptives (median 60 and <50 nmol/l, respectively, p=0.014). This difference remained after exclusion of those patients with Cushing's syndrome (median 55 *vs* <50 nmol/l, p<0.001).

Test characteristics

ROC curves for 24-hour urinary free cortisol and post-dexamethasone cortisol in patients with clinical suspicion of Cushing's syndrome are shown in *figure 3*. The areas under the ROC curve were 0.958 for 24-hour urinary free cortisol and 0.985 for post-dexamethasone cortisol.
Cut-off values and corresponding sensitivities and specificities are shown in *table 2*. When women who were using oral contraceptives were excluded from the analysis, cut-off levels for urinary free cortisol and post-dexamethasone cortisol remained the same, with little change in sensitivity or specificity (data not shown).

DISCUSSION

Even though testing for Cushing's syndrome has a long history, controversies persist about the optimal screening procedure and the test cut-off levels to be used.
In the last few years there have been several promising reports about the use of salivary cortisol measurements.[6-8] Likewise, a midnight cortisol has been used as an alternative screening test.[8,9] In our hospital the overnight dexamethasone-suppression test and 24-hour urinary free cortisol have been used for over a decade, with prospective recording of patient data and a long follow-up period. Therefore, we decided to study all patients referred to our

Figure 3 *ROC curves for 24-hour urinary free cortisol (A) and post-dexamethasone cortisol levels (B) in patients with clinical suspicion of hypercortisolism*

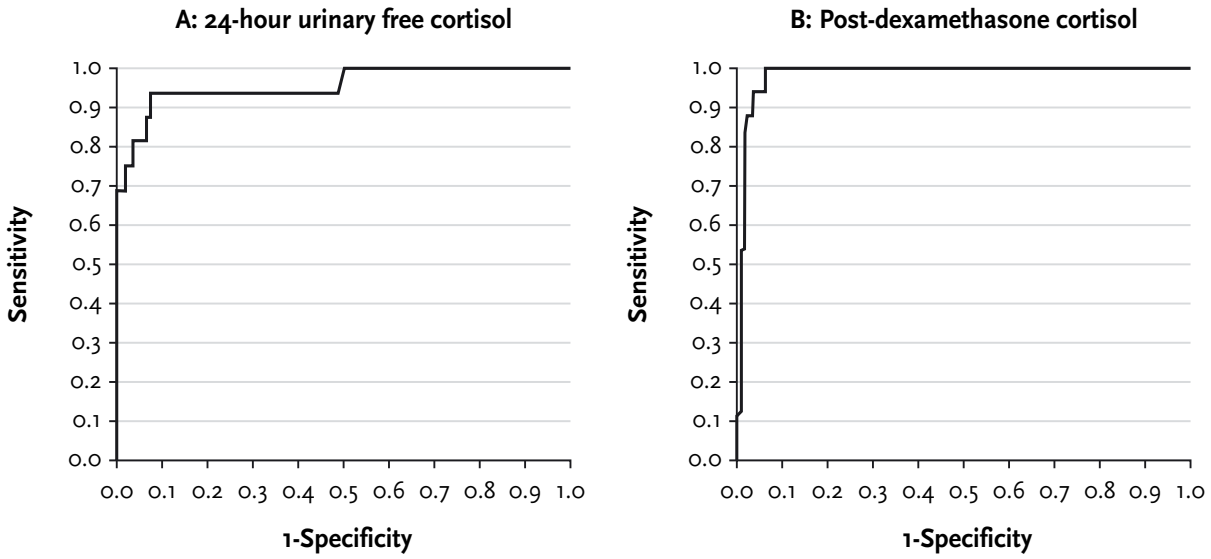


Table 2 *Cut-off values for 24-hour urinary free cortisol and post-dexamethasone plasma cortisol in patients with clinical suspicion of hypercortisolism*

	100% sensitivity	100% specificity	Optimal*
24-hour urinary free cortisol (nmol/24 hours)	68 (specificity 50%)	427 (sensitivity 69%)	180 (sensitivity 94%, specificity 93%)
Post-dexamethasone plasma cortisol (nmol/l)	95 (specificity 94%)	2225 (sensitivity 12%)	95 (sensitivity 100%, specificity 94%)

*The optimal cut-off value is the value that yields the highest sensitivity and specificity.

department for evaluation of putative hypercortisolism, in order to obtain optimal cut-off values for 24-hour urinary free cortisol and for the 1 mg dexamethasone-suppression test. There were two main reasons for referral: clinically suspected Cushing's syndrome and adrenal incidentaloma. While descriptive data are presented, we decided not to perform a formal analysis of the test characteristics in patients with an incidental adrenal mass for two reasons. Firstly, in these patients the test results form an integral part of the decision to operate and hence in the diagnosis, which makes it difficult to establish a 'gold standard'. At a recent National Institutes of Health (NIH) consensus conference a similar comment was made about the elusive nature of the diagnosis 'subclinical hypercortisolism'.[10] Secondly, only five patients were ultimately labelled as having Cushing's syndrome, too small a number to obtain reliable ROC curves.

Not surprisingly, in the group referred because of clinical suspicion of Cushing's syndrome, the range of values for urinary free cortisol and post-dexamethasone cortisol exceeded the reference range previously established in healthy volunteers.[4] While the optimal cut-off level for urinary free cortisol at 180 nmol/24 hours was above the upper normal limit of 145 nmol/24 hours, the 100% sensitivity level was much lower at 68 nmol/24 hours. This was associated with a very low specificity.

For post-dexamethasone cortisol the optimal level and the 100% sensitivity level were the same at 95 nmol/l, which was considerably lower than the upper limit of normal of 230 nmol/l previously established. This again underlines the fact that reference values established in healthy volunteers can not be equated to cut-off values for specific diagnostic groups.

The 100% sensitivity we found at 95 nmol/l compares favourably with data from Findling *et al.* who reported false-negative rates of 18% at a 135 nmol/l cut-off level and 8% at a 54 nmol/l cut-off level in a large series of patients with Cushing's syndrome.[11] While this may in part be explained by the fact that all measurements in our series were performed in one laboratory under standardised conditions, the number of patients with Cushing's disease in our study was limited and so some caution seems warranted in too rigorously interpreting our results.

Given the low prevalence of disease (12%) in the population studied for hypercortisolism, the dexamethasone-suppression test seems superior to 24-hour urinary free cortisol as a screening tool, with a greater area under the ROC curve and a far higher specificity at the 100% sensitivity level.

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Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Changes in antibiotic use in Dutch hospitals over a six-year period: 1997 to 2002

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ABSTRACT

Objective: To analyse trends in antibiotic use in Dutch hospitals over the period 1997 to 2002.
Methods: Data on the use of antibiotics and hospital resource indicators were obtained by distributing a questionnaire to all Dutch hospital pharmacies. Antibiotic use was expressed as the number of defined daily doses (DDD) per 100 patient-days and as DDD per 100 admissions.
Results: Between 1997 and 2002, the mean length of stay decreased by 18%. The mean number of admissions remained almost constant. Total antibiotic use significantly increased by 24%, from 47.2 in 1997 to 58.5 DDD per 100 patient-days in 2002 ($p<0.001$), whereas expressed as DDD per 100 admissions it remained constant. Antibiotic use varied greatly between the hospitals. Moreover, the mean number of DDD per hospital of amoxicillin with clavulanic acid, clarithromycin, cefazolin, clindamycin and ciprofloxacin increased by 16, 38, 39, 50 and 52%, respectively. Total antibiotic use was higher in university hospitals than in general hospitals.
Conclusion: Between 1997 and 2002, patients hospitalised in the Netherlands did not receive more antibiotics but, since they remained in the hospital for fewer days, the number of DDD per 100 patient-days increased. For macrolides, lincosamides and fluoroquinolones increases in both DDD per 100 patient-days and in DDD per 100 admissions were observed. It is arguable whether these trends result in an increase in selection pressure towards resistance in the hospitals. Continuous surveillance of antibiotic use and resistance is warranted to maintain efficacy and safety of antibiotic treatment.

KEYWORDS

Antibiotics, hospital, surveillance, the Netherlands, utilisation

INTRODUCTION

The increasing prevalence of antibiotic resistant micro-organisms poses a major threat to the health of hospitalised patients.[1,2] Its relationship with antibiotic use and misuse is well recognised. Specific criteria for appropriate use of antibiotics in order to avoid resistance should therefore be developed.[3] Quantitative and qualitative data on the use of antibiotics in hospitals are needed to evaluate strategies that are implemented to contain antimicrobial resistance. Obviously, resistance rates also need to be measured.
In Sweden, Denmark and the Netherlands, annual reports are issued in which resistance rates and antibiotic use data are reported.[4-6] In the Netherlands, Janknegt *et al.* collected data on the use of antibiotics in Dutch hospitals during the period 1991 to 1996.[7] In 1996 the Working Party on Antibiotic Policy (acronym is SWAB; www.swab.nl) was founded by the Dutch Society for Medical Microbiology (NVMM), the Society for Infectious Diseases (VIZ) and the Dutch Association of Hospital Pharmacists (NVZA). The main activities of SWAB are development of guidelines and educational programmes to promote appropriate use of antibiotics and the surveillance of antibiotic use and resistance. These activities are supported by a structural grant from the Dutch Ministry

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of Health, Welfare and Sport. In 2000 SWAB's working group on the use of antimicrobial agents started to collect national data on antibiotic use in hospitals. These data are presented in NethMap, the annual report of the SWAB.[6]
In a recent editorial in this journal it was stated that physicians would not directly benefit from these national reports in their daily practice, but that these reports may help to increase their general awareness of the problem of antibiotic resistance.[8] Furthermore these reports may provide a knowledge base for policy decisions, guidelines and research strategies.
The aim of this study was therefore to analyse and report on antibiotic use in Dutch hospitals between 1997 and 2002.

MATERIALS AND METHODS

Population

All Dutch hospitals, 94 general hospitals and 8 university hospitals, were asked to participate in SWAB's national surveillance system. Specialised hospitals, such as psychiatric and orthopaedic hospitals, and rehabilitation centres were excluded. Data on the use of antibiotics in acute care Dutch hospitals between 1997 and 2002 were collected by means of a questionnaire distributed to all Dutch hospital pharmacies by SWAB. Data from inpatient wards as well as day care wards had to be included, whereas outpatient use and dispensing to nursing homes was excluded from the data report.

Antibiotic use

Pharmacies were requested to report on the annual consumption of antibiotics for systemic use, group J01 of the Anatomical Chemical Classification (ATC) system. The use of different (sub)classes of antibiotics was expressed as defined daily doses (DDD) per 100 patient-days and per 100 admissions.[9]
The ATC/DDD classification from the World Health Organisation (WHO), version 2002, was used to calculate the number of DDD of the various antibiotics. The DDD was defined as the assumed average maintenance dose per day for a drug used for its main indication in an adult.[10]

Hospital resource data

For each hospital the annual number of admissions and days spent in the hospital (bed-days) were recorded. The number of patient-days was obtained by subtracting the number of admissions from the number of bed-days as the number of bed-days overestimates actual treatment-days by including both the day of admission and the day of discharge. The mean length of stay was calculated by dividing the mean number of patient-days by the mean number of admissions.

Statistical analysis

Regarding the period 1997 to 2002 an overall pooled mean (i.e. weighted mean) was calculated for each year by aggregating data on antibiotic use and patient-days from all the hospitals. Drug utilisation was compared between hospitals and over time by a mixed model for repeated measurements. The response variables applied were the number of DDD per 100 patient-days and the number of DDD per 100 admissions. P values less than 5% were considered statistically significant. All statistical analyses were performed by SAS 8.2 (SAS Institute, N.C., USA).

RESULTS

Hospital resource indicators

Between 1997 and 2002 a decrease in the mean length of stay was found in both the total cohort of hospitals and the subgroups of university and general hospitals (*table 1*). The mean number of admissions remained almost constant. As the mean number of patient-days is calculated by multiplying the mean number of admissions by the mean length of stay, a decrease was also found in the mean number of patient-days.

Hospital use

The number of hospitals that issued data on antibiotic use varied from 49 (48%) in 1997 to 59 (58%) in 2002. The reasons given for not participating were other priorities (56%), not being able to generate data on antibiotic use (25%) or no interest (19%).
In 1997 total systemic use in hospitals was 47.2 DDD per 100 patient-days and significantly increased by 24% to 58.5 DDD per 100 patient-days in 2002 ($p<0.001$) (*table 2*). However, total systemic use expressed as DDD per 100 admissions remained almost constant at 385.9 in 1997 and 391.6 in 2002 ($p=0.866$) (*table 3*).
The mean number of total DDD per hospital did not change between 1997 and 2002 (67,176 and 66,714 DDD in 1997 and 2002, respectively).
Regarding trends in antibiotic use over the years, five main categories can be distinguished:

- For macrolides, lincosamides and fluoroquinolones we found a significant increase over the years for both units of measurement;
- For amphenicols and monobactams a significant decrease in both units of measurement was found;
- For tetracyclines, β-lactamase-resistant penicillins, carbapenems, trimethoprim and derivatives, intermediate-acting sulfonamides, aminoglycosides and imidazole derivatives, a constant use in both units of measurement was found;
- For total systemic use, combinations of penicillins including β-lactamase inhibitors, β-lactamase-sensitive

Table 1 *Resource indicators of Dutch hospitals, 1997 to 2002*

	Hospitals		Admissions			Patient-days			Length of stay		
	1997 (n)	2002 (n)	1997 (mean)	2002 (mean)	% change 1997-2002	1997 (mean)	2002 (mean)	% change 1997-2002	1997 (mean)	2002 (mean)	% change 1997-2002
All hospitals	49	59	17,405	17,038	-2.1	142,339	114,038	-19.9	8.2	6.7	-18.3
University hospitals	8	7	25,670	24,441	-4.8	226,264	191,374	-15.4	8.8	7.8	-11.4
General hospitals	41	52	15,793	16,041	+1.6	125,963	103,628	-17.7	8.0	6.5	-18.9

Table 2 *Antibiotic use in Dutch hospitals (DDD per 100 patient-days), 1997 to 2002*

ATC code	Antimicrobial group	Relevant example antibiotic(s)	DDD per 100 patient-days			Average change per year (%)	Trend 1997-2002 (p value)
			1997	2002	Absolute change 1997-2002		
J01AA	Tetracyclines	Doyxcycline	1.6	1.6	0.00	0.071	0.933
J01BA	Amphenicols	Chloramphenicol	0.017	0.0039	0.00	-62.1*	0.007
J01CA	Penicillins with extended spectrum	Amoxicillin	6.5	6.2	-0.34	-1.1	0.212
J01CE	β-lactamase-sensitive penicillins	Benzylpenicillin	1.2	1.2	0.082	1.4	0.004
J01CF	β-lactamase-resistant penicillins	Flucloxacillin	4.1	4.5	0.36	1.7	0.116
J01CR	Combinations of penicillins, incl. β-lactamase inhibitors	Amoxicillin with clavulanic acid, piperacillin with tazobactam	14.4	20.6	6.2	7.4	<0.001
J01DA	Cephalosporins and related substances	Cefazolin, cefuroxim, ceftazidim	5.1	6.3	1.1	4.0	<0.001
J01DF	Monobactams	Aztreonam	0.011	0.0021	-0.009	-27.7*	0.018
J01DH	Carbapenems	Imipenem, meropenem	0.43	0.46	0.034	1.6	0.246
J01EA	Trimethoprim and derivatives	Trimethoprim	0.46	0.48	0.021	0.90	0.353
J01EC	Intermediate-acting sulfonamides	Sulfadiazine	0.061	0.00013	-0.061	-70.8*	0.229
J01EE	Combinations of sulfonamides and trimethoprim	Sulfamethoxazole with trimethoprim	2.6	2.4	-0.22	-1.7	0.0715
J01FA	Macrolides	Clarithromycin	1.9	2.7	0.77	7.1	<0.001
J01FF	Lincosamides	Clindamycin	0.80	1.5	0.67	12.9	<0.001
J01GB	Aminoglycosides	Gentamycin, tobramycin	2.0	2.1	0.13	1.3	0.334
J01MA	Fluoroquinolones	Ciprofloxacin	4.0	5.7	1.7	7.3	<0.001
J01MB	Other quinolones	Pipemidic acid	0.030	0.077	0.046	20.4*	#
J01XA	Glycopeptides	Vancomycin	0.42	0.51	0.092	4.1	<0.001
J01XD	Imidazole derivatives	Metronidazole	1.2	1.4	0.26	4.1	0.622
J01XE	Nitrofuran derivatives	Nitrofurantoin	0.21	0.52	0.31	20.4*	#
J01	Antibiotics for systemic use (total)		47.2	58.5	11.3	4.4	<0.001

P<0.05 = statistically significant; #unable to calculate p value due to too small a number of observations; *due to the low absolute use of these compounds the average change per year bears little practical importance.

Table 3 *Antibiotic use in Dutch hospitals (DDD per 100 admissions), 1997 to 2002*

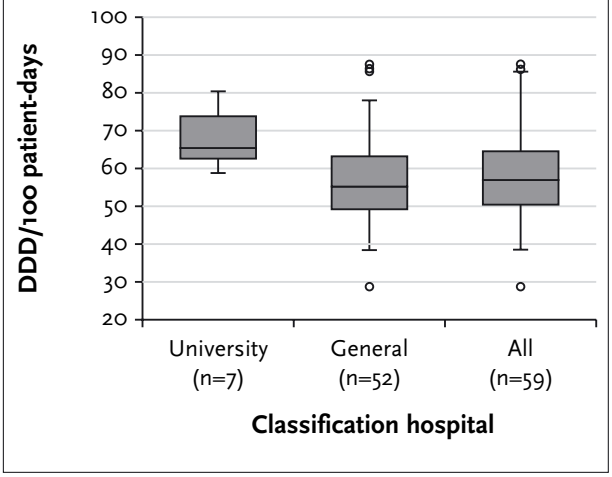
ATC code	Antimicrobial group	Relevant example antibiotic(s)	DDD per 100 admissions			Average change per year (%)	Trend 1997-2002 (p value)
			1997	2002	Absolute change 1997-2002		
J01AA	Tetracyclines	Doyxcycline	13.4	11.0	-2.4	-3.9	0.482
J01BA	Amphenicols	Chloramphenicol	0.14	0.03	-0.1	-28.1*	0.001
J01CA	Penicillins with extended spectrum	Amoxicillin	53.1	40.1	-13.0	-5.4	<0.001
J01CE	β-lactamase-sensitive penicillins	Benzylpenicillin	9.4	8.0	-1.4	-3.2	0.080
J01CF	β-lactamase-resistant penicillins	Flucloxacillin	33.6	28.9	-4.7	-2.9	0.265
J01CR	Combinations of penicillins, incl. β-lactamase inhibitors	Amoxicillin with clavulanic acid, piperacillin with tazobactam	117.6	135.5	17.9	2.9	0.159
J01DA	Cephalosporins and related substances	Cefazolin, cefuroxim, ceftazidim	41.9	41.8	-0.1	-0.05	0.415
J01DF	Monobactams	Aztreonam	0.09	0.01	-0.07	-30.5*	0.007
J01DH	Carbapenems	Imipenem, meropenem	3.5	3.1	-0.4	-2.4	0.754
J01EA	Trimethoprim and derivatives	Trimethoprim	3.7	3.2	-0.5	-3.1	0.902
J01EC	Intermediate-acting sulfonamides	Sulfadiazine	0.5	0.00087	-0.5	-71.9*	0.268
J01EE	Combinations of sulfonamides and trimethoprim	Sulfamethoxazole with trimethoprim	21.1	15.9	-5.3	-5.6	<0.001
J01FA	Macrolides	Clarithromycin	15.4	17.8	2.4	2.9	0.012
J01FF	Lincosamides	Clindamycin	6.6	9.8	3.3	8.5	<0.001
J01GB	Aminoglycosides	Tobramycin	16.0	13.9	-2.0	-2.7	0.458
J01MA	Fluoroquinolones	Ciprofloxacin	32.7	38.0	5.3	3.1	<0.001
J01MB	Other quinolones	Pipemidic acid	0.25	0.51	0.3	15.7*	#
J01XA	Glycopeptides	Vancomycin	3.4	3.4	0.0	-0.01	0.026
J01XD	Imidazole derivatives	Metronidazole	9.6	9.5	-0.01	-0.01	0.458
J01XE	Nitrofuran derivatives	Nitrofurantoin	1.7	3.5	1.8	15.7*	#
J01	Antibiotics for systemic use (total)		385.9	391.6	5.6	0.3	0.866

P<0.05 = statistically significant; #unable to calculate p value due to too small a number of observations; *due to the low absolute use of these compounds the average change per year bears little practical importance.

penicillins, cephalosporins and glycopeptides, a significant increase in DDD per 100 patient-days and a constant use in DDD per 100 admissions was observed;
- For penicillins with extended spectrum and combinations of sulfonamides and trimethoprim we found a constant use when expressed in DDD per 100 patient-days; a significant decrease in the number of DDD per 100 admissions was also found.

The proportion of all penicillins combined represented 55% of total systemic use in both 1997 and 2002. In an in-depth study of the individual antibiotics we found that the mean number of DDD per hospital of amoxicillin with clavulanic acid, clarithromycin, cefazolin, clindamycin and ciprofloxacin increased by 16, 38, 39, 50 and 52%, respectively.
In university hospitals, total systemic antibiotic use increased significantly by 16.5%, from 57.6 in 1997 to 67.1 DDD per 100 patient-days in 2002 (p=0.002), whereas in general hospitals total use increased significantly by 29.4%, from 43.6 in 1997 to 56.4 DDD per 100 patient-days in 2002 (p<0.001). However, total systemic antibiotic use expressed as DDD per 100 admissions in university hospitals remained almost constant at 507.4 in 1997 and 525.2 in 2002. In general hospitals no increase was found either when use was expressed as DDD per 100 admissions: 347.4 in 1997 and 364.2 in 2002. In university hospitals the mean number of DDD per hospital decreased by 1.5%, whereas in general hospitals an increase of 6.5% was observed.
Moreover, a large variation in quantitative antibiotic use was found between the participating hospitals, in particular in general hospitals (*figure 1*).

Figure 1 *Variance in total use of antibiotics for systemic use (J01) in Dutch hospitals, 2002: university vs general hospitals*



DISCUSSION

Our data showed a decrease in the mean length of stay during the study period and a more or less constant mean number of admissions. These trends in hospital resource indicators are consistent with the demographics of all the hospitals as registered by Statistics Netherlands (www.cbs.nl). In addition, we found that trends over time in DDD per 100 patient-days did not consistently correlate with trends in DDD per 100 admissions.
In the present study total antibiotic use significantly increased by 24%, from 47.2 in 1997 to 58.5 DDD per 100 patient-days in 2002. The total number of DDD and admissions remained almost constant between 1997 and 2002. However, length of stay decreased significantly during this period. This means that on average patients used the same number of DDD in a shorter period of time, which might be interpreted in different ways. Firstly, no changes in treatment policies occurred since most patients were already treated with antibiotics during the first days of hospitalisation. Due to intensification of general care, the length of stay decreased. Another explanation might be that antibiotic courses are completed at home with antibiotics supplied by the hospital.
Between 1991 and 1996 total antibiotic use in Dutch hospitals increased by 14% from 37.2 to 42.5 DDD per 100 patient-days in 1996.[7] This might also be the result of a decreasing length of stay over the years (12%) rather than an increase in DDD per admission. The first results of a European surveillance programme demonstrated that the Nordic countries and the Netherlands all show a low total antibiotic use compared with other European countries.[11]
In both university and general hospitals we found a constant use in DDD per 100 admissions and an increase in DDD per 100 patient-days as well. Total systemic antibiotic use was notably higher in university hospitals than in general hospitals. This might be explained by the admission of patients with more complex infections or undergoing complex surgery and transplantations requiring prophylaxis.
In the total cohort of hospitals the mean number of DDD per hospital of amoxicillin with clavulanic acid, clarithromycin, cefazolin, clindamycin and ciprofloxacin increased with 16, 38, 39, 50 and 52%, respectively. As the number of admissions remained almost constant over the years this means an increase in the consumption of these antibiotics per admission. The increase in the use of cefazolin, an agent that is only used for perioperative prophylaxis, may be explained by the publication of a national guideline on perioperative antibiotic prophylaxis in 2000. This guideline strongly recommends the use of cefazolin for surgical prophylaxis.[12] In our cohort of hospitals the percentage of hospitals using cefazolin increased from 37% in 1997 to 69% in 2002 (p=0.001). It is not

clear why the use of the other antibiotics is increasing. Audits on antibiotic prescribing practices at the individual patient level are needed to clarify the increasing use of these antibiotics.

We distinguished five categories concerning trends in antibiotic use over the years. With regard to resistance development it appears that an increase in both the number of DDD per 100 patient-days and the number of DDD per 100 admissions (category 1) is a cause for concern and that no significant change or a significant decrease in both units of measurement (category 2, 3 and 5) is not. The trend in category 4 is less easy to interpret. An increase in the number of DDD per 100 patient-days may be interpreted as an increase in the selection pressure towards resistance. However, this is arguable since the number of admissions and the total number of DDD has remained almost constant over the years. Moreover, an intensification of antibiotic therapy suggests a shortening of duration of antibiotic treatment. Short duration of therapy may lead to less selection of resistant microorganisms.[13,14]

In the present study some methodological problems were encountered. Firstly, one possible source of bias was the variety of methods used by the different Dutch hospital pharmacies to quantify their antibiotic use. The majority of hospitals delivered data based on hospital purchases, while only a few hospitals provided actual dispensing data. Ideally, actual administration data should be used as a source to measure antibiotic use in hospitals, with every dose actually administered to a patient recorded electronically.

Secondly, we aimed to provide census data, covering at least 90% of the acute care hospital population in the Netherlands. The overall response to the enquiry was, however, 58%. In contrast with Denmark, for example, the Dutch government does not make it compulsory for hospitals to deliver their data on the use of antibiotics.[15] Consequently aiming at 90% coverage will be unrealistic. Since the variance in antibiotic use is very large between the hospitals, a representative selection of hospitals is only possible when insight is obtained in the determinants of hospital antibiotic use.

Another possible source of bias may be that as a result of earlier discharge of the less ill patients, patient-days may increasingly originate from sicker patients who more often require antibiotic treatment. However, this is not likely, as the total number of DDD remained constant.

In this survey, data were collected by a questionnaire and processed manually, which is a relatively slow process. In the near future the SWAB wishes to start a national project in order to collect data on hospital drug use in a central data warehouse. This will facilitate the collection of data and the conversion to DDD per 100 patient-days. Data on the use of antibiotics at hospital level might be too crude for identifying subtle trends in antibiotic use of specific patient populations. Therefore, monitoring antibiotic use patterns by specific populations within the hospital (e.g. intensive care and general ward patients; surgical and nonsurgical patients) is warranted. In this way substantial changes can be demonstrated that would be overlooked if hospital-wide data are aggregated into national trends.

In conclusion, patients hospitalised in the Netherlands did not receive more antibiotics but, since they remained in the hospital for fewer days, the number of DDD per 100 patient-days increased. It is arguable whether this results in an increase in selection pressure towards resistance in the hospitals, since the total number of DDD remained almost constant over the years. For macrolides, lincosamides and fluoroquinolones increases in both DDD per 100 patient-days and DDD per 100 admissions were observed between 1997 and 2002. This might be a cause for concern since this trend is more likely to be associated with an increase in the selection pressure. Further research is needed to determine the relationship between antibiotic use, selection pressure and the emergence of resistance. To maintain efficacy and safety of antibiotic treatment, continuous surveillance of antibiotic use and resistance is necessary.

ACKNOWLEDGEMENT

We thank the pharmacists of the participating hospitals for providing data on antibiotic use. This study was supported with a structural grant from the Ministry of Health, Welfare and Sport to the SWAB, no. 366950.01.

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ABOUT THE COVER

'Untitled'

Jochen Proehl

This print is a brush technique on handmade paper by Jochen Proehl. Born in Lübeck, Germany, in 1958, Jochen Proehl was raised in Istanbul. From 1982 to 1988 he attended the Academy of Arts in Berlin. After graduation, he has received many assignments for different institutions. He exhibits his work in many group and solo exhibitions in Germany. Proehl alternates where he lives and works between Berlin, am Niederrhein and Istanbul. Inconspicuous views of shapes that materialise when man encroaches upon territories, such as holes, pits or puddles, are the catalysts for Jochen Proehl's etchings. These unspectacular traces of human intervention appear in his pictures as escapist scenery clippings and – characteristic for his work – as an elementary concept of power and tranquillity.

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Netherlands
The Journal of Medicine

Acute lymphoblastic leukaemia in pregnancy

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ABSTRACT

Two cases of pregnant patients with acute lymphoblastic leukaemia (ALL) are presented. ALL is rare in pregnancy. The basic principle of ALL treatment is combination chemotherapy with sequential administration of induction, consolidation and maintenance therapy, and this also holds for ALL in pregnancy. The prognosis of ALL in pregnancy is poor and termination of the pregnancy needs to be considered.

KEYWORDS

Acute lymphoblastic leukaemia, pregnancy, termination

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is rare in pregnancy. The overall incidence of ALL is 1.3 per 100,000, with a slight male predominance.[1] In nonpregnant adult patients treatment results in a complete remission in 80% of the cases. Forty percent of adults are cured by modern treatment strategies (disease-free survival for at least ten years). In the past 20 years major advances in terms of biological characterisation and outcome of adult ALL have been achieved. The basic principle of ALL treatment is combination chemotherapy with sequential administration of induction, consolidation and maintenance therapy.[2]
We present two cases of pregnant patients with ALL.

CASE REPORT

Patient A
A 30-year-old female patient presented to the emergency department because of a collapse. An acute lymphoblastic leukaemia (common B cell type) was diagnosed, and a pregnancy test was positive. The white blood cell (WBC) count was 206,000/μl. Vaginal ultrasound revealed an intact intrauterine pregnancy of six weeks gestation. It was her third pregnancy; she had two children from two uneventful pregnancies, the youngest ten months old. Furthermore she had a negative medical history.

Treatment for ALL with prednisone, vincristine, asparaginase, daunorubicin and methotrexate (intrathecal) was started. Cytogenetic analysis revealed a t(9;22) (Philadelphia chromosome). At day 28 after the start of the first course, bone marrow analysis showed persistent leukaemia. After five weeks a missed abortion was diagnosed by abdominal ultrasound. Because of bone marrow depression due to the chemotherapy with concomitant strict isolation, medical rather than surgical treatment for the missed abortion was considered to be the first option, since especially profuse bleeding due to a surgical procedure was feared. Misopristol (800 μg) was given vaginally followed by mifepristone (600 mg) orally. Within 12 hours a complete abortion with little blood loss occurred which was confirmed by vaginal ultrasound. After the second course of high-dose cytarabine, the patient reached a complete remission (CR). An HLA-identical sib was found. Awaiting allogenic transplantation, we prescribed imatinib 800 mg once daily. Three weeks after CR, she was admitted for an allogenic stem cell transplantation. This procedure was complicated by severe sepsis and

adult respiratory distress syndrome (ARDS). The patient died in the ICU.

Patient B

A 37-year-old patient was admitted to the haematology department, where an acute lymphoblastic leukaemia was diagnosed. The WBC was 166,000/μl. The patient was treated with the same high-dose chemotherapy schedule as patient A. Cytogenetic analysis revealed a t(9;22) (Philadelphia chromosome). At the time of diagnosis she was 15 weeks pregnant in her first pregnancy. Termination of the pregnancy was discussed and rejected. Three weeks after the first course of chemotherapy the peripheral blood smear showed 3% lymphoblasts. She was given high-dose cytarabine. At 22 weeks gestation she started having abdominal cramps with the loss of clear fluid and the same day a spontaneous delivery of a stillborn foetus of 400 g occurred. The placenta followed spontaneously and was complete, the blood loss was 500 cc. Because of low platelets (24,000/μl) a platelet transfusion was given. At day 28 after the start of cytarabine we found 65% lymphoblasts in the bone marrow smear. No HLA-identical sib or matched unrelated donor was found. At the patient started imatinib 400 mg twice a day and was discharged. She died a few weeks later.

DISCUSSION

The prognosis of ALL depends on several clinical and biological features. Younger age (<30 years), WBC <30,000/μl, the presence of a mediastinal mass, T-cell or TMy immunophenotype, and absence of the Philadelphia chromosome are positive prognostic factors. Both our patients had Ph+ ALL, WBC >30,000/μl and were ≥30 years. Without any adverse features three-year survival is 91%. Philadelphia chromosome + ALL (Ph+ ALL) has a 76% chance of CR after chemotherapy; of this 76%, only 17% remain in remission after three years.[3] Allogenic transplantation results in higher survival rates.[4] With regard to pregnancy the overall literature is moderately positive about acute leukaemia, but a recent report shows a less favourable outcome.[5] In the first trimester a teratogenic effect of the chemotherapeutic agents used for the treatment of leukaemia can occur.[6] In the second and third trimester of pregnancy, chemotherapy may provide a greater risk of stillbirth, growth retardation, premature birth and maternal and foetal myelosuppression.[7] The treatment during pregnancy does not appear to have a significant impact on the future growth and development of the child.[8]

However, most of the literature deals with acute myeloblastic leukaemia (AML) instead of ALL. Both of our patients suffered from ALL. Some pregnancies have ended uneventfully, although there are few data on long-term follow-up, but severe pre-eclampsia, sudden intra-uterine death, pancytopenia and normal karyogram with a ring chromosome and gaps without clinical consequence have also been reported in pregnant patients with ALL.[9]

Acute leukaemia requires immediate treatment, irrespective of the gestational age.[10] Pregnancy does not alter the course of acute leukaemia, but the outcome is far worse when treatment is delayed.[11] Pregnant women should receive weight-based doses similar to those given to women who are not pregnant, adjusted to the continuing weight gain.[10] Because of the high risk of teratogenic effects of chemotherapy during the first trimester, termination of the pregnancy should be considered. After the first trimester the decision to terminate the pregnancy needs to be discussed with the patient. Vinca alkaloids, anthracyclines, cytarabine and steroids are the cornerstone of remission induction regimens. Vinca alkaloids are not potent teratogens. During pregnancy, 111 exposures have been reported. With administration after the first trimester 8% intrauterine growth retardation (IUGR), 6% preterm delivery and 2% pre-eclampsia occurred. In 28 pregnancies exposed to anthracyclines, 21 were uneventful. Cytarabine can induce limb abnormalities when used in the first trimester. Eighty-nine cases have been reported in which cytarabine was used in all trimesters, with six intrauterine foetal deaths (IUFD) and two neonatal deaths.[10]

A dilatation and curettage is usually considered the first option, but to terminate pregnancies of up to 63 days of amenorrhoea, and increasingly at all gestations, the antiprogesterone mifepristone in combination with a prostaglandin analogue (misoprostol) provides a suitable nonsurgical method.[12-14]

In our first patient timely induction was needed, because she had a high-risk ALL. In patients in the middle of chemotherapy with a very low platelet count, a spontaneous abortion might result in profuse bleeding. Platelets are given if their numbers fall to less than 10,000/μl; in pregnancy transfusions are required at higher levels.[1] In our second patient an immature delivery occurred spontaneously. But again, also in the case of a viable pregnancy, termination of the pregnancy can be considered because of the adverse effects of the chemotherapeutic agents.

CONCLUSION

Our two cases show the poor prognosis of ALL in pregnancy. Both patients had Ph+ ALL, WBC >30,000/μl and were ≥30 years, which are all negative prognostic factors. Acute leukaemia requires immediate treatment, irrespective of the gestational age. Termination of the pregnancy and the risks of chemotherapy during pregnancy, especially in the first trimester, need to be discussed with the patient with ALL. The combination of oral mifepristone and vag-

inally inserted misoprostol is a safe and effective method for abortion. Our first case showed that this method can also be used in patients less suitable for surgical treatment and might be considered the first choice for these patients. Although the literature is moderately positive about the prognosis of acute leukaemia, this does not seem to be the case for ALL in pregnancy. More studies are required to establish the prognosis of acute (lymphoblastic) leukaemia in pregnancy, but this is difficult, because of the low prevalence.

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The Journal of Medicine

CASE REPORT

Early onset of oral aphthous ulcers with weekly docetaxel

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ABSTRACT

Two patients with metastatic breast cancer developed oral aphthous ulcers after only two administrations of weekly docetaxel without any other toxicity. A treatment delay and dose reduction appears to be an effective management strategy.

KEYWORDS

Docetaxel, oral aphtous ulcer

INTRODUCTION

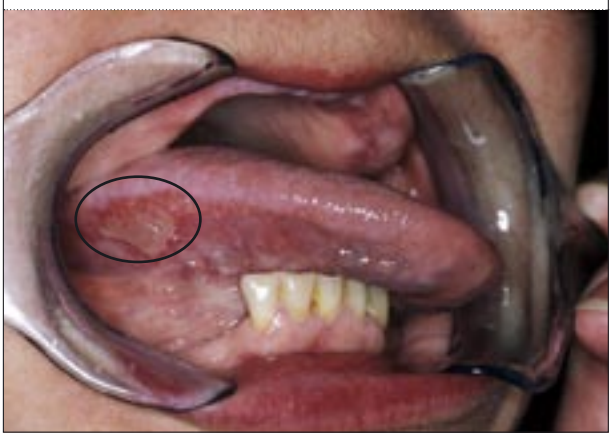
Weekly administration of docetaxel can be effective in the treatment of metastatic breast cancer and has a relatively low toxicity in comparison with docetaxel given once every three weeks. Grade 3/4 myelosuppression is uncommon (percentages of 14 to 20% have been reported). Fatigue and asthenia are the most frequent nonhaematological toxicities (also observed in 14 to 20% of the patients). Grade 3/4 mucositis is seldom described in weekly docetaxel.[1,2] We report two patients with unusual oral aphthous ulcers after only two applications of weekly docetaxel.

CASE REPORT

Patient A

A 73-year-old woman who presented with breast cancer and skeletal metastases in 2000 was treated with pamidronate and tamoxifen. In 2001, radiotherapy was administered because of progressive disease with compression of the spinal cord. Simultaneously, she developed liver metastases, for which first-line palliative chemotherapy consisting of six cycles of doxorubicin and cyclophosphamide was given. This therapy led to regression of the liver metastases. Subsequently, treatment with anastrozole was started as consolidation therapy. After four months the patient developed progressive liver metastases. Laboratory findings showed grade 2 hepatic dysfunction: bilirubin 24 μmol/l (<16 μmol/l), alkaline phosphatase 595 U/l (40 to 120 U/l), serum glutamic oxaloacetic transaminase (SGOT) 178 U/l (<40 U/l) and serum glutamic pyruvic transaminase (SGPT) 76 U/l (<45 U/l). Second-line treatment with weekly docetaxel for three weeks, followed by a one-week rest, was initiated. Because of the hepatic dysfunction the dose was reduced to 25 mg/m²/week (normal dose is 36 to 40 mg/m²/week). After only two applications of docetaxel grade 3, painful, grey aphthous ulcers developed on the lateral aspects of the tongue (*figure 1*). There were no other signs of mucositis. There was no bone marrow suppression either, or any other toxicity. The patient had not experienced stomatitis aphtosa or oral herpes before. Diagnostic polymerase chain reaction for herpes simplex virus was negative. The cultures of oral lesions showed only a trace of *Candida albicans*. Treatment with acyclovir and fluconazole had already been started but did not lead to any noticeable improvement, also suggesting docetaxel-associated oral toxicity. The next chemotherapy course was delayed for one week, in which time the aphthous ulcers improved. Weekly docetaxel applications were

Figure 1 *Aphthous ulcer on the lateral side of the tongue*



continued in a reduced dose of 15 mg/m², without recurrence of aphthous ulcers. Evaluation by CT abdomen after six weeks and 12 weeks showed a reduction in the liver metastases. Because of the development of meningitis carcinomatosa, the docetaxel therapy was discontinued after a total of 16 weeks of treatment.

Patient B

A 45-year-old woman was found to have breast cancer T2N1M0 in 2002. She was treated with breast-conserving therapy and adjuvant chemotherapy with doxorubicin and cyclophosphamide. After the fifth course, progressive cancer infiltration of the chest wall was observed and loco-regional radiotherapy was given. In 2003, a local relapse in the breast was treated with salvage surgery followed by radiotherapy and hyperthermia. Subsequently, she developed progressive disease in the contralateral breast, with metastases in lymph node, pleura and lung. Laboratory findings showed a grade 1 liver dysfunction: bilirubin 11 µmol/l (<16 µmol/l), alkaline phosphate 240 U/l (40 to 120 U/l), SGOT 65 U/l (<40 U/l) and SGPT 81 U/l (<45 U/l). The standard dose of weekly docetaxel of 40 mg/m² was started, because the bilirubin was not elevated. Following the second administration of docetaxel, the patient developed grade 3, painful, grey aphthous ulcers covered with white plaques, which she had never experienced before. Acyclovir and miconazole were administered for supposed fungal or viral infection. A third application of docetaxel was given in a slightly lower dose of 35 mg/m²/week. Six days later, the patient was admitted to the hospital with severe ulcerative pharyngitis. The docetaxel was suspended; the patient developed neutropenic fever and was treated with parenteral ceftriaxone, fluconazole and valaciclovir. Cultures were negative for herpes simplex and for candida. In two weeks the oral lesions had improved. Docetaxel was reintroduced at a lower weekly dose of 25 mg/m²/week. Seven weekly doses of docetaxel were administered without recurrence of the aphthous ulcers. Evaluation after six applications of docetaxel showed regression of pleuritis carcinomatosa and stable disease of liver metastases. After a total of 11 weeks of therapy, the docetaxel was stopped because of progression, which manifested as cerebral metastases.

DISCUSSION

Weekly docetaxel therapy is an active regimen that is generally well tolerated by patients with metastatic breast cancer.[1,2] The usual dose of weekly administration of docetaxel ranges from 36 to 40 mg/m². Hepatic dysfunction may cause a significant reduction in docetaxel clearance, which can result in a higher risk of toxicity. A 25% dose reduction is commonly recommended if there are abnormalities in the alkaline phosphatase (>2.5 x upper limit of normal (ULN)) and transminase values (>1.5 x ULN), even in the presence of normal bilirubin levels.[3] Stomatitis is seen in about 5 to 20% of patients receiving docetaxel in a three-weekly schedule. With weekly docetaxel use, stomatitis is infrequent and less severe.[3-9] In stomatitis the mucosa initially becomes diffusely reddened and swollen, followed by ulceration which may be covered with fibrinous exudate. In these two cases the patients only developed solitary oral aphthous ulcers, with otherwise normal mucosa. There are a number of reasons why we suppose that these oral aphthous ulcers were caused by the docetaxel treatment. First, in both cases there is a clear relation in time between the start of docetaxel administration and the development of the oral ulcers. Second, there were no signs of other causes of oral ulcers in either of the patients. Neither of the patients had history of aphthous ulcers or herpes infection. The cultures for candida and herpes were negative. Moreover antifungal and antiviral therapy gave no improvement. Third, in both cases the oral ulcers disappeared in only two weeks after cessation of docetaxel and after reintroduction of docetaxel in a lower dose there was no recurrence of the aphthous ulcers. Remarkable is that the grade 3 oral aphthous lesions developed in these two patients with only mild hepatic dysfunction and even though the dose of docetaxel was reduced in patient A. To our knowledge, early onset of severe solitary oral aphthous ulcers without any other toxicity has not been reported before in patients on weekly low-dose docetaxel. Physicians treating patients with weekly docetaxel should be aware of the possibility of this side effect developing, even with mild impairment of liver function. A treatment delay and dose reduction appears to be an effective management strategy. We are curious whether other physicians have also noticed this toxicity of docetaxel.

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Netherlands
The Journal of Medicine

Fever from the USA or Portugal?

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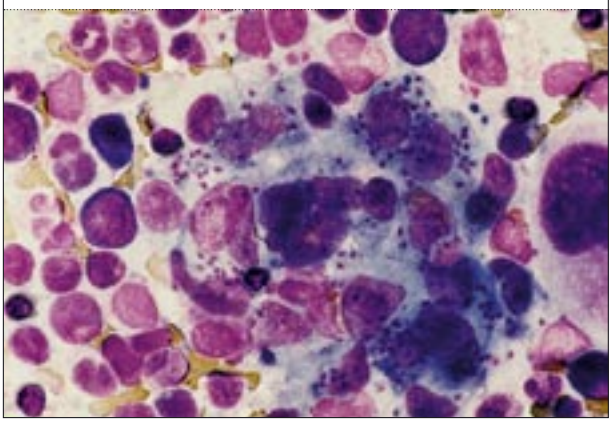
CASE REPORT

A 54-year-old woman presented with a long-standing high fever of four weeks. The daily fever reached 40°C every night without cold chills. She had just returned from a family visit to Florida (USA) one month ago. The family included three children in their teens. For the past three years she had lived in Portugal with her husband and visited the Netherlands regularly, several times each year. She did not have any other complaints. Physical examination was normal and the laboratory examination showed a BSE of 52 mm/hour and a C-reactive protein of 75 mg/l. The haemoglobulin count was 7.3 mmol/l, the thrombocyte count was 90 x 10^9/l and the leucocyte count was 2.8 x 10^9/l. The lymphocytes showed an atypical morphology and the Monosticon (Pfeiffer) test was weakly positive. The serology for Ebstein-Barr virus (EBV) was positive for IgM against early antigen and the IgG was negative. Cytomegalovirus serology was also unreactive. X ray of the chest did not show any abnormalities. An ultrasound of the abdomen showed a slightly enlarged spleen of 13.5 cm but was otherwise normal. The first working hypothesis was an acute EBV infection possibly related to her visit to Florida. However, two weeks later the clinical picture and laboratory abnormalities did not change at all and the second serological test for EBV did not show the formation of IgG early antigen. Further analysis was performed by bone marrow aspiration and bone biopsy because of the persistent pancytopenia. The microscopic examination is shown in *figure 1*.

Figure 1 *Bone marrow aspirate shows numerous intracellular pathogens in macrophages*



WHAT IS YOUR DIAGNOSIS?

See page 372 for the answer to this photo quiz.

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Dutch medical oath

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ABSTRACT

In the first part of this article, the booklet *Dutch Medical Oath* is reviewed.
The content of the new oath is discussed as are the reasons for revision of the previous version of the oath. This is followed by a short history of the oath.
In the second part of the article the oath is compared with the seven competencies of a medical specialist. The new oath contains elements of six of these seven competencies. This demonstrates that the oath is in keeping with the new medical educational demands.

KEYWORDS

Competencies, Dutch medical oath, Hippocrates

DUTCH MEDICAL OATH 2003

I swear/promise to practise the art of medicine as well as I can for the benefit of my fellow man. I will take care of the ill, promote health and relieve suffering. I put the interest of the patient first and respect his convictions. I will not harm the patient. I will listen and will inform him well. I will keep secret what has been entrusted to me. I will further the medical knowledge of myself and others. I acknowledge the boundaries of my possibilities. I will adopt an open and testable attitude and I know my responsibilities towards society. I will further the availability and accessibility of health care. I will not misuse my medical knowledge, not even under pressure. This is how I will honour the profession of medical doctor.

I promise
Or
So help me God[*]

[*]The choice was made to use the general term 'God', so students may, depending on their religion, have the name of their own God in mind.

INTRODUCTION

In the Netherlands, as in many other countries, taking a vow is the usual way to declare dedication to the values of the medical profession.[1,2] The medical oath does not have any legal value. Whether or not one can practise medicine depends on registration with the BIG act, the Individual Healthcare Professions Act. Besides BIG, the rights and obligations of a medical doctor have been laid down in several laws.
However, the medical oath is still important. It marks the moment of joining the group of medical professionals and it is a moment of reflection on the values of the medical profession. The oath used until September 2003 was based on the law of practising the art of medicine from 1865, which is no longer in force, and the Hippocratic oath from 400 years BC. The position of doctors within society changed so much in the second half of the last century that it was time for a new version of the oath.[3] The oath has been modernised by a committee made up of doctors, a medical student, a lawyer, a historian and an ethicist. Since September 2003 all medical faculties in the Netherlands have been using the new medical oath.[4] In the next paragraphs the history of the oath and the development of the new oath will be briefly discussed. Furthermore the new oath will be compared with the latest requirements for medical specialisms.

THE HISTORY OF THE OATH

The classic oath of Hippocrates dates back to approximately 400 BC. This original oath, which is assumed not to have been written by Hippocrates himself, was not meant as a religious or ethical manifest. It served as a description of the practices of a group of doctors who wanted to distinguish themselves from quacks, which means it was a certifying code rather than an ethical code. Abortion, for example, was something only quacks did and it often went wrong so it had no place within the code. This had nothing to do with ethical views on abortion, which was common practice. In ancient times, the oath was not an authorative document; there were several other medical writings in circulation. The Hippocratic oath did not become important until the Renaissance. The dismissal of abortion and euthanasia was then embraced as an ethical position that was well in keeping with the Christian faith of that period. After 1500, swearing the oath was established at universities in Europe and later also in North America.
The function of the oath changed again after 1800 when it became a document that described the relationship between doctor and patient and the relation between doctor and society. In 1865 the oath was incorporated into the law of practising the art of medicine. That version of the oath focused on the obligation of secrecy and the obligations of the doctor towards society. That same version of the oath was also the base for the oath that was used by medical faculties in the Netherlands until 2003.

NEW TIMES, NEW OATH

The misuse of medical knowledge during World War II made it clear that besides Hippocratic ethics, there was a need for codes of conduct that would place the work of the doctor within the broader context of human rights, the interest of patients and informed consent. Examples of this are the declaration of Geneva (1948) and the declaration of Helsinki (1964), both from the World Medical Association (www.wma.net).[4] There was another development too. Over the course of the last decennia the relationship between doctor and society had slowly but surely shifted.[5] The old contract between doctor and society was implicit and based on a strong autonomy of the professional group. The professional group set its own standards, doctors did the best they could and knew what was right for a patient. The patient was expected to have blind faith in the doctor, after all, he did the best he could. The quality of the doctor was never doubted and did not have to be established, it was a given.
This blind faith in doctors disappeared with the rise of well-informed, emancipated patients united in patient organisations, and because medical mistakes became public. At the same time the government started to interfere more with healthcare on a financial level, an organisational level and where content was concerned. These developments caused the old implicit contract, with autonomy of the professional group, to make way for a new situation where patients, government and doctors work together on professional standards and quality controls. Within these standards and controls as much as possible will be made explicit and will be established in standards.

The medical professional group had a need for reorientation within these developments. While looking for a new professional identity and ideology, many new rules of conduct and professional codes were formulated, nationally as well as internationally. Those rules and codes existed alongside the legislation and describe the contract between doctor and society. Examples of this in the Netherlands are the rules of conduct, drawn up by the Royal Dutch Medical Association (Koninklijke Nederlandsche Maatschappij tot bevordering der Geneeskunst; KNMG; www.knmg.nl). The Duties of a doctor,[4] drawn up by the British Medical Association (BMA), are a short and good example of this in the UK. 'The charter on professionalism',[6] an international example, is also worth mentioning. This joint European-American project describes three fundamental principles and ten core responsibilities of a doctor. Simultaneous publication in the Lancet and the Annals of Internal Medicine underscores the importance of this kind of project to describe medicine's contract with society.
The changing position of doctors in society, combined with the new legislation, were reasons to revise the text of the medical oath.

DUTCH MEDICAL OATH

When the new oath was formulated, the classic Hippocratic oath, the declaration of Geneva, the rules of conduct of the KNMG, the charter of professionalism and the 'Duties of a doctor' of the BMA were used.
An important new aspect of this oath is that it does not focus solely on the professional group it is written for, but also on society. A future doctor promises to keep an open mind towards possible criticism and to watch over the accessibility of healthcare. He acknowledges the boundaries of his possibilities. What is also new is that the future doctor promises not to misuse his medical knowledge, *not even under pressure*. This is based on the 'Declaration of Geneva', drawn up in 1948 to avoid misuse of medical knowledge as happened during World War II. But it also refers to more subtle pressure, such as potential temptations for doctors from pharmaceutical industries and

Table 1 *Competences contained in new and old oath*

General competences of a medical specialist	Dutch medical oath 2003	In 1878 oath
Medical performance		
Adequate knowledge and skills according to the profession's current standards		
Adequately applying the diagnostic, therapeutic and preventive possibilities of the discipline in an evidence-based way wherever possible		
Delivering effective and ethical patient care	Taking care of the ill Relieving suffering Pledging secrecy Not doing harm Honouring the views of patients	Pledging secrecy
Finding necessary information and applying it adequately		
Communication		
Establishing adequate therapeutic relationships with patients	Putting the interests of the patient first	
Listening carefully and obtaining relevant patient information effectively	Listening	
Adequately discussing medical information with patients and their families	Informing well	
Adequately reporting on patient cases orally and in writing		
Collaboration		
Effectively consulting with other physicians and healthcare providers		
Adequately referring to other healthcare professionals		
Adequately delivering collegial advice		
Supporting effective interdisciplinary collaboration and chain care		
Knowledge and science		
Receiving medical information critically		
Contributing to the development of professional, scientific knowledge		
Developing and maintaining a personal continuous educational plan	Furthering one's medical knowledge	
Contributing to the education of students, residents, colleagues, patients and others involved in healthcare	Furthering the medical knowledge of others	
Community performance		
Knowing and identifying the determinants of illnesses		
Contributing to the health of patients and the community	Knowing one's responsibility towards society	
Acting according to relevant legislation	Adopting an open and testable attitude	Following legal regulations
Acting adequately in case of incidents in healthcare		
Management		
Finding an adequate balance between professional patient care and personal development		
Working effectively and efficiently in a healthcare organisation		
Allocating available healthcare resources wisely	Furthering the availability and accessibility of healthcare	
Using information technology to optimise patient care and life-long learning		
Professionalism		
Delivering high-quality patient care with integrity, honesty and compassion	Practising the art of medicine as well as possible (in honour of one's fellow man)	Performing the art of medicine, surgery and obstetrics as well as possible
Exhibiting appropriate personal and interpersonal professional behaviour		

Table 1 *Continued*

General competences of a medical specialist	Dutch medical oath 2003	In 1878 oath
Professionalism		
Being conscious of one's personal limits and acting within them	Knowing the boundaries of one's own possibilities	
Practising medicine consistent with the ethical standards of the profession	Not misusing one's medical knowledge, not even under pressure	

commercial organisations. Elements from the classic Hippocratic oath that are still relevant have been maintained such as 'I will not harm the patient' (nil nocere) and the pledge of secrecy.

The oath was formulated as simply, timelessly and concisely as possible. The oath comes equipped with a short explanatory brochure (which can be downloaded from www.vsnu.nl), which is handed out to every student taking the oath. In the brochure an overview is given of the meaning of the oath throughout the ages. The legal and ethical frames doctors have to work within are also generally outlined.

THE OATH IN RELATION TO EDUCATION

The redefining of the role and position of doctors is also reflected in the new educational requirements of medical specialisms, which have been discussed in a previous issue of this journal.[7] The new medical trainee specialist is aware of the fact that more is expected of him than just competence in medical performing. Adequate medical performance is only one of seven competencies the Central College of Medical Specialisms formulated for the new training of medical specialists. These competences will be the guide for specialist educations in the Netherlands from 2006 and will, within the concept of a medical educational continuum, influence the medical curricula.

Analyses of the new medical oath in light of these seven general competences of a medical specialist shows that aspects of six competences – medical performance, communication, knowledge and science, social performance, organisation and professionalism – can be found back in the oath (*table 1*). It is only the competence 'collaboration' that does not appear in the oath. It has been suggested that this competence is entered into the next version of the oath.
In comparison: in the old Dutch medical oath only two of the seven competences could be found (*table 1*).
The fact that six out of seven competences appear in the new oath demonstrates that the oath is in keeping with the new medical educational demands.

Taking the oath could take place at the end of the education but also at an earlier stage, for example when starting the internships, before students first start working with patients. This is the standard procedure in the US, called the 'white coat ceremony'.[2] The oath can also be used during the medical education in classes on medical ethics.

CONCLUSION

The new Dutch medical oath is based on the new position of doctors in society and is in keeping with the new educational demands for medical specialisms.

ACKNOWLEDGEMENT

The authors would like to express their grateful thanks to Professor D.W. Erkelens, initiator and chairman of the Committee for Revision of the Medical Oath.

NOTE

Revision of the Dutch medical oath was project of the Association of Universities in the Netherlands (VSNU).

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ANSWER TO PHOTO QUIZ (ON PAGE 367)
FEVER FROM THE USA OR PORTUGAL?

DIAGNOSIS

The diagnosis of visceral leishmaniasis (kala-azar) was made. The bone marrow aspirate showed numerous intracellular parasites in macrophages. These parasites have a large dark-purple, eccentric nucleus with blue-staining cytoplasm and a small rod-shaped mitochondrial structure known as the kinetoplast, which is characteristic for *Leishmania amastigotes*. This infection is spread by the sandfly in numerous parts of the world including the Mediterranean area. In Portugal visceral leishmaniasis is due to an infection with *Leishmania infantum* and frequently diagnosed in patients with defective cellular immunity by HIV.[1] The incubation time of this infection is one to three weeks. Our patient probably acquired this infection during her stay in Portugal. The most characteristic finding is usually hepatosplenomegaly which was almost absent in this case. The pancytopenia showed us the right way to the diagnosis of leishmaniasis. She was treated with liposomal amphotericine B and recovered completely.[2,3]

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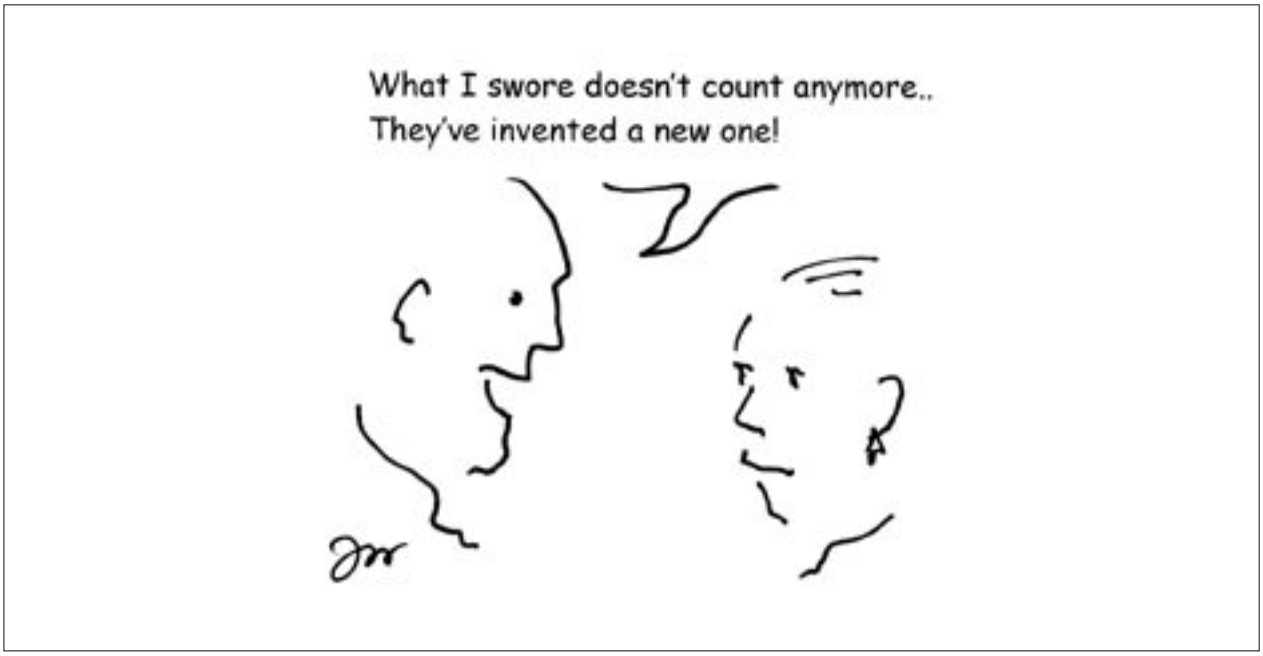

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2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

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