Netherlands
# The Journal of Medicine
PUBLISHED IN COLLABORATION WITH THE NETHERLANDS ASSOCIATION OF INTERNAL MEDICINE

Echinococcal disease

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Recurrent erysipelas

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Hyperglycaemia in nondiabetic patients with myocardial infarction

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Low-dose fondaparinux in suspected HIT

MARCH 2007, Vol. 65, No. 3, ISSN 0300-2977

VAN ZUIDEN COMMUNICATIONS

Netherlands
# The Journal of Medicine

PUBLISHED IN COLLABORATION WITH THE NETHERLANDS ASSOCIATION OF INTERNAL MEDICINE

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EDITORIAL

# Treatment of cystic echinococcosis: a combination of general goals and rules, individual decisions and indications

**D.A. Vuitton[1*], H. Wen[2]**

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The four papers published in this issue of the Netherlands Journal of Medicine on cases of cystic echinococcosis (CE) [1-4] remind us of several important points: 1) CE/hydatid disease, due to the larval development of *Echinococcus granulosus*, is less benign than often claimed; 2) its surgical treatment may be at the origin of dissemination and complications; 3) CE should be evoked for a variety of presenting signs and symptoms when the patient comes from an endemic area; 4) the treatment of CE complications needs to adapt the individual condition of the patient while following general rules that aim at removing or inactivating the parasitic cysts and preventing parasite recurrence.[5-7] Both clinical cases of CE presentation, with aching hands and urticaria in an 18-year-old girl,[4] and with gastrointestinal symptoms in a Kyrgyz 44-year-old veterinarian,[2] well illustrate the variety of presenting signs and symptoms. The observation of a quite unusual hydatid cyst location with complete obstruction of the pulmonary artery and destruction of the lung[1] fully supports both the risk of surgery and the usefulness of an appropriate surgical procedure combined with chemotherapy to treat CE complications. It is likely that the first surgical operation on the liver cyst was responsible for the pulmonary embolism. A description of the first operation (type of operation, possible mistakes) could have explained the occurrence of protoscolex and/or cyst fragment migration from the hepatic veins to the pulmonary arteries through the cardiac right cavities.

Surgery has long been considered the only treatment for all cases of hydatid cysts. In 1996, treatment guidelines published by the WHO-Informal Working Group on Echinococcosis (IWGE) stated that the therapeutic strategy should consider combined or alternative treatments.[8] Since then, results of long-term evaluation have been made available and updated guidelines are currently being discussed by the WHO-IWGE and should be published soon. There are very few available controlled trials designed to assess CE treatment. A recent meta-analysis aimed at finding 'evidence-based' answers to the main questions about treatment strategy in cystic echinococcosis.[9] The main results, graded according to the Cochrane system, were as follows: 1) chemotherapy is not the ideal treatment for uncomplicated hydatid cysts of the liver when used alone; 2) the level of evidence is too low to help decide between radical or conservative treatment; 3) omentoplasty associated with radical or conservative treatment is efficient in preventing deep abscesses; 4) drug treatment associated with surgery requires further studies; 5) the laparoscopic approach is safe; 6) percutaneous drainage associated with albendazole therapy is safe and efficient in selected patients; 7) the level of evidence is low concerning treatment of complicated cysts. Thus, several key questions regarding CE treatment are obviouly not answered.

The objective of surgery is to remove parasitic cysts and fluid completely, a major advantage compared with other types of treatment. However, when discussing surgery regard should be given to cyst location in the liver, lung and/or other organs, number of cysts, presence of other cysts in other organs, anatomical/clinical complications, clinical status of the patient, but also surgical facilities, expertise of the surgical team and quality of follow-up.[8] Controversies still exist about the preferred operating technique. Many operations and variants have been published.[5-7,10-13] Hepatic resection is usually only recommended for central cysts of a left lateral segment. Liver transplantation has been exceptionally performed in patients with acute Budd-Chiari syndrome and secondary biliary cirrhosis.[14] Various types of cystectomy, with or without pericystectomy, permit the complete removal of the parasite. A modified technique of endocystectomy *vs*

pericystectomy has recently been evaluated in one of the very rare randomly controlled surgical trials which showed the advantage of the former for cysts ≤8 cm in diameter.[15] Total subadventitial cystectomy has also recently been proposed to excise the laminated membrane intact, by following the virtual gap which exists between the inner and outer fibrous layer surrounding the cyst.[16] Such a procedure might have prevented entry of parasitic material into hepatic veins in the case described by Aribas *et al*.[1] In order to avoid spillage of the cyst content, the peritoneal cavity must be carefully protected and the cyst content and germinal layer sterilised by protoscolicides: 3% hydrogen peroxyde, 80 to 95% alcohol, 15 to 20% saline solution, 0.15 chlorhexidine/1.5% cetrimide and/or 10% polyvinyl pirrolidone iodine.[17] Formalin and >20% hypertonic saline should not be used because of the risk of sclerosing cholangitis. Despite the high number of hydatid cysts surgically removed worldwide, few large reviews of surgical cases with a significant follow-up are available, and the number of recurrences is generally underestimated. It ranges from 2 to 25%, depending on the size, location, number, or peroperative rupture of the cysts, as well as expertise of the surgical team.[11-13] The high number of repeated operations in a single patient in most of the published reports is indirect evidence for the frequency of recurrence; of course, the authors often stress that the first operation was performed 'elsewhere'. This emphasises the necessity of long-term follow-up.

Since 1986, Puncture Aspiration Injection Reaspiration (PAIR) has been proposed as an alternative to surgery.[18] After percutaneous puncture under ultrasonographic guidance, a complete aspiration is performed; the residual cavity is then filled with a protoscolicide, usually ethanol, reaspired 10 minutes later. Detailed practical guidelines have been published after a careful evaluation of the technique by the WHO-IWGE.[19] Long-term follow-up of patients is now available.[20,21] A meta-analysis has established the efficiency, safety and usefulness of the procedure in selected indications.[22] A very limited number of anaphylactic shocks and secondary dissemination, lower than after surgery in most series, have been reported.[10] PAIR can be proposed for type CE1, and selected cases among CE2, and CE3 cysts according to WHO classification.[23] It is contraindicated if there is a communication between the cyst and the biliary tree. Deep location in the liver is not, per se, a contraindication to PAIR since in such cases surgical dissection of the cyst is difficult and may lead to peroperative parasitic embolism in the vessels or damage to the bile ducts. Drainage may be associated with PAIR in large cysts.[21] To treat cysts with numerous daughter cysts, a PAIR-like technique using larger tubes and vacuum aspiration through a small surgical incision was first described in a huge series of cases in western China;[24] similar procedures have then been published in European countries.[25,26] Laparoscopic treatment of the cysts is also feasible but, however, more frequently associated with spillage and recurrence.[27]

Treatment of complications and recurrences is always difficult and needs a multidisciplinary approach to define the best option adapted to the patient's condition. With multiple cysts and multiple initial locations, recurrence in multiple organs and especially in the peritoneum represents a good indication of chemotherapy alone,[28] which may also be the first step before a hazardous operation in complicated cases. Albendazole is usually preferred at an average daily dosage of 15 mg/kg/day; it must be given continuously, without those treatment interruptions which were recommended in the past. Blood count and transaminases must be checked every week for the first month and every month thereafter.[7,8,28] Combination of chemotherapy and surgery or PAIR is increasingly being used. Presurgery treatment with albendazole may facilitate a complete removal of the germinal layer, as shown in this issue by Genetzakis *et al*.[3] A recent report of 52 CE cases treated with surgery and pre- and postsurgery albendazole showed the efficacy of chemotherapy to prevent recurrence, assessed within a 5 to 92 month follow-up.[29] Praziquantel, which is protoscolicidal but has no efficacy on germinal layer cells, may be added, especially after surgery when the risk of spillage is high.[28] However, no controlled long-term studies have ever evaluated chemotherapy efficacy to prevent recurrence after surgery, as well as the optimal schedule before and after surgery or PAIR and the risk/benefit of a combined treatment with praziquantel. Depending on the team, duration of albendazole therapy ranges between one and eight days before and one and three months after PAIR. It is noteworthy that in the four papers published in this issue, the schedule and duration of albendazole treatment were quite variable: only after surgery for an unknown duration,[1] three sequences of 28 days, with treatment interruptions, before PAIR, and apparently no treatment after the puncture despite the failure of fluid aspiration and ethanol reinjection,[2] 28 days, only before surgery,[3] and six months, only after surgery.[4] This clearly indicates the absence of consensus and the need for guidelines.

Assessment of treatment efficacy relies mainly on the morphology and size of the cyst(s), appreciated by repeated ultrasound examinations. A major endpoint is the disappearance of the cyst; however, persistence of ultrasound or CT-scan image may well be associated with parasite death and thus response to the treatment. Serology is of little use to assess cyst viability; specific IgG4 could be good indicators of treatment efficacy but are not widely available.[15]

The search for new drugs is ongoing. Attempts at increasing serum concentrations of albendazole have given promising results.[30,31] Amphotericin B was proposed as salvage treatment in alveolar echinococcosis, due to

*Echinococcus multilocularis*, but does not seem to work in CE.[32] The parasitocidal effect of nitazoxanide was recently proven *in vitro* but has never been tested in human CE.[33] New therapeutic approaches such as radiothermal ablation are currently under investigation.[34] However, what is most urgently needed in order to make progress in the treatment of this disease, which still occurs frequently worldwilde, is to construct controlled studies aimed at more clearly specifying the respective place of the various treatment options, including a 'watch and wait' attitude for asymptomatic cysts which may be cured spontaneously.[35,36]

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REVIEW ARTICLE

# Recurrent erysipelas despite antibiotic prophylaxis: an analysis from case studies

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## ABSTRACT

**Background: Erysipelas is a distinctive type of superficial cellulitis of the skin with prominent lymphatic involvement, generally caused by group A streptococci. A substantial proportion of patients experience recurrences of erysipelas, and this may be a reason to install prophylactic antibiotic treatment. Despite such prophylaxis, further recurrences are occasionally encountered.**

**Objectives: To investigate recurrences of erysipelas during prophylactic antibiotic treatment and to delineate the reasons for such failure.**

**Methods: Retrospective chart review of 117 adult patients with episodes of erysipelas known in our institution between 1990 and 2004.**

**Results: Recurrent episodes of erysipelas, despite prophylactic treatment, were found in eight patients. Our analysis indicated noncompliance, incorrect selection and insufficient dosing of antibiotics, and causative pathogens other than streptococci as demonstrable causes of the recurrence of erysipelas. In three patients, a reason for failure could not be identified.**

**Conclusions: In a minority of cases, erysipelas recurs despite antibiotic prophylaxis. Based on these cases, we first recommend that all efforts are made to (re)confirm the diagnosis of erysipelas and search for the causative micro-organism. Based on this information, the right antibiotic with adequate dosing and timing can be selected. The issue of compliance with the prophylactic treatment should be addressed and finally, the clinician should be aware that prophylaxis does not prevent erysipelas in all cases.**

## KEYWORDS

Antibiotic prophylaxis, erysipelas, prevention, recurrent erysipelas

## INTRODUCTION

Erysipelas is an acute inflammation of the skin, with marked involvement of cutaneous lymphatic vessels. It is a clinically recognisable entity, with sudden onset of fever and a painful erythematous swollen lesion, sharply demarcated from the normal skin. Erysipelas is most commonly caused by β-haemolytic streptococci of group A, less so by group B, C, or G streptococci, and occasionally by *Staphylococcus aureus*.[1,2] In many patients, factors are present that facilitate the development of erysipelas. The major risk factors in erysipelas are disruption of the skin and lymphoedema.[3] Erysipelas can be treated successfully with narrow-spectrum penicillins, such as benzylpenicillin and feneticillin. Patients who are allergic to penicillin may be treated effectively with macrolides.

The recurrence rate of erysipelas is high: nearly 30% has been noted within a two to four year period.[4] Unfortunately, once erysipelas occurs, damage to the cutaneous lymph vessels often leads to susceptibility for further relapses. To prevent a vicious circle of recurrent erysipelas and vulnerability to subsequent episodes, long-term antibiotic prophylaxis is advocated. Studies have suggested an effect of such prophylaxis, using various antibiotic regimens.[4-7]

A neglected aspect in studies on prophylaxis for erysipelas is that a few patients still have attacks of erysipelas during antibiotic prophylaxis.[7,8] In line with this notion, we have encountered patients with recurrent erysipelas despite antibiotic prophylaxis. In this paper, we review these cases and examine the reasons for failure of prophylaxis.

## PATIENTS AND METHODS

Patients with one or more episodes of erysipelas during antibiotic prophylaxis were identified and retrospectively analysed to examine the incidence of recurring erysipelas

despite prophylactic antibiotic treatment and the factors associated with this failure. Patients were identified by searching two databases for the clinical diagnosis of erysipelas: the first database contains data on infectious disease consultations performed in our university medical centre between 1990 and 2004; the second contains the diagnoses of patients at the outpatient clinic for internal medicine from 1999 until 2003. In addition, infectious disease specialists were asked whether they were aware of additional patients.

From the charts of patients with attacks of erysipelas during antibiotic prophylaxis, the following data were collected: 1) personal characteristics: gender, age, weight; 2) underlying diseases and/or factors predisposing for erysipelas; 3) attacks of erysipelas before prophylactic treatment; 4) results of diagnostic tests, such as cultures, antistreptolysin titres and anti-DNAse B; 5) treatment of the episodes of erysipelas; 6) prophylactic regimens; 7) the effect of the antibiotic prophylaxis.

## RESULTS

In this study, 117 patients with erysipelas were identified. Five patients had an attack despite antibiotic prophylaxis. Three more patients were retrieved from infectious diseases specialists. The characteristics of these eight patients, the sites of erysipelas, and underlying conditions are provided in *table 1*.

The phenomenon of recurrent erysipelas under antibiotic prophylaxis will further be described on the basis of three illustrative cases.

### Patient C

This 29-year-old male had suffered from several episodes of erysipelas affecting the right leg since the age of 17. At 15 years, he underwent an epiphysiodesis of the femur and tibia of his right leg to correct a difference in length. He had been treated with benzathine penicillin 1.2 MU intramuscularly every four weeks as prophylaxis. Despite this treatment, frequent attacks of erysipelas recurred. It turned out that relapses occurred shortly before the next injection was planned.

At the age of 20, the patient was hospitalised for another episode of erysipelas, which was treated with penicillin G. On this occasion, interdigital mycosis was found as a potential portal of entry. In an attempt to reduce the risk of another attack, antimycotic treatment and elastic stockings were prescribed, but despite this, episodes of erysipelas still recurred. The attacks responded well to therapy with roxitromycin.

The patient was first seen at our department at the age of 22. He was put on a prophylactic regimen of benzathine penicillin 1.2 MU every two weeks and this preventive treatment was successfully continued for two years. Six months after stopping, a new episode occurred, and the two-weekly preventive regimen was reinstituted. Despite the prophylaxis, a new attack occurred three months later. This episode probably occurred because the penicillin injection was delayed until 3.5 weeks after the previous dose.

The next episode of erysipelas developed 16 days after the injection of benzathine penicillin. After treatment, a prophylactic regimen of injections strictly administered every two weeks was installed. This prevented recurrences for 2.5 years. On the patient's request, the frequency of administration was again reduced to every three weeks and this led to new episodes of erysipelas. Antibiotic prophylaxis every two weeks has prevented further attacks of erysipelas, for one year of follow-up.

### Patient E

This 24-year-old female experienced a minor trauma of her chin at the age of five. The first episode of erysipelas at the age of 14 affected her chin and lower lip. During the following years she had several attacks of erysipelas. After her second hospitalisation at the age of 18, she received

**Table 1.** *Patients characteristics*

| Patient | Age (years) | Sex | Weight (kg) | Location | Underlying condition | Site of entry | Age at first episode (years) | Age at start of prophylaxis (years) |
|---|---|---|---|---|---|---|---|---|
| A | 45 | m | 113 | Right and left leg | Trauma: spinal cord lesion, multiple fractures left leg | Intertrigo | 33 | 39 |
| B | 56 | m | – | Left leg | Spinal muscular atrophy, fracture left femur | | 47 | 52 |
| C | 29 | m | 108 | Right leg | Epiphysiodesis right leg | Dermatomycosis | 17 | 19 |
| D | 53 | f | 86 | Left arm | Post-breast cancer surgery | Eczema | 44 | 47 |
| E | 24 | f | 72 | Face | Trauma chin | | 14 | 18 |
| F | 38 | m | 74 | Right and left leg | Short-bowel syndrome, arterial insufficiency right leg | Intertrigo | 34 | 35 |
| G | 55 | f | 62 | Right arm | Post-breast cancer surgery | Skin lesion | 45 | 53 |
| H | 39 | f | 63 | Face, neck | Recurrent herpes simplex | Herpetic lesions | 29 | 30 |

prophylactic treatment, consisting of benzathine penicillin 1.2 MU intramuscularly every four weeks.
She remained free from episodes of erysipelas for 11 months until a new attack at the same site occurred during antibiotic prophylaxis. During this episode, the serology was suggestive for a streptococcal origin: aspartate aminotransaminase (AST) (332 U $ml^{-1}$) and anti-DNAse (B 879 U $ml^{-1}$) were both elevated, whereas the antistaphylolysin titre was 0.71 U $ml^{-1}$. She was referred to our clinic.
The prophylactic regimen was changed to clindamycin 300 mg three times a day. Five months after starting with this regimen, another episode of erysipelas occurred. As the patient was not critically ill, we felt confident to try and see whether it was a dose or a resorption problem. So we switched to intravenous clindamycin 3 x 600 mg. The response to therapy with intravenous clindamycin was rapid. Hereafter, the dose of prophylactic treatment was raised to 300 mg four times a day. Measurement of serum clindamycin showed concentrations of 1.69 and 4.12 mg $l^{-1}$, which are considered appropriate. Even with the higher oral dose of clindamycin, another episode of erysipelas occurred three months later. Prophylaxis was stopped, and nine months later, she again developed erysipelas.

**Patient G**

This 55-year-old female was healthy until the age of 44, when breast cancer was diagnosed. A modified radical mastectomy with axillary lymph node dissection was performed. A year later, a tumour was found in her other breast, and a mastectomy with axillary lymph node dissection was performed followed by radiotherapy. Tamoxifen was continued for 2.5 years.
Since the second mastectomy, she experienced several episodes of erysipelas. These episodes would usually follow a small skin defect on the right hand and were characterised by a fiery red, sharply demarcated lesion on one side of the thorax and the right arm, high fever, and systemic toxicity. Response to treatment with either amoxicillin or flucloxacillin was rapid.
Five years after surgery, a reconstruction by a latissimus dorsi muscle flap combined with breast implants was performed, complicated by oedema of the right arm. The episodes of erysipelas increased in frequency. After multiple attacks, the patient was put on benzathine penicillin 1.2 MU intramuscularly every four weeks. The attacks decreased but were not completely prevented. Even injections given every two weeks did not prevent the episodes of erysipelas. There was no clear correlation between the time of injection and the occurrence of erysipelas.
After stopping the prophylactic treatment, the frequency of erysipelas increased to once every one or two months. She was put on a prophylactic regimen of clindamycin 600 mg twice daily, and several months later the dose was decreased to 600 mg once daily. This treatment prevented further episodes of erysipelas for three months, but thereafter breakthroughs occurred.

An overview of the cases of recurrent erysipelas during antibiotic prophylaxis is provided in *table 2*. In most cases, it is not possible to judge whether these recurrent episodes represent relapses from foci within the body or exogenous reinfections.
In a number of cases, a plausible explanation for the failure of prophylaxis and subsequent recurrences could be given on the basis of chart review. These were: 1) noncompliance; 2) incorrect antibiotic; 3) other causative micro-organism; and 4) insufficient antibiotic concentration.

**Noncompliance**

Two patients experienced an episode of erysipelas when they extended the interval time of the prophylactic regimes. Patient C exceeded the prophylactic schedule by 1.5 weeks, when erysipelas recurred. Patient A had a new attack of erysipelas ten weeks after the last injection.

**Incorrect antibiotic**

Instead of benzathine penicillin, patient B received a combination of benzathine and procaine-benzylpenicillin. This agent only contains 0.6 MU of benzathine penicillin. Penicillin concentrations in serum are therefore only detectable for about one week.

**Other causative micro-organism**

Although no culture samples could be obtained, it is likely that the recurrences in patients D and B during antibiotic prophylaxis were not caused by group A streptococci, but by *Staphylococcus aureus*. Patient D developed a skin infection of the left arm four days after the injection of benzathine penicillin. The infection responded to flucloxacillin. Patient B developed an attack of erysipelas one week after the injection of benzathine penicillin 1.2 MU. The initial treatment consisted of feneticillin 1000 mg four times a day. Despite an initial improvement, treatment was unsuccessful. After two weeks, the treatment was changed to clindamycin 600 mg three times a day, which led to an improvement.

**Insufficient antibiotic concentration**

In three patients, the serum concentrations of the antibiotic agent were probably insufficient. Patient B received clarithromycin 250 mg daily to prevent further episodes of erysipelas. This did not prevent the episode 1.5 weeks later. The recommended therapeutic dose for an adult should be at least 250 mg twice daily. Patients C and H experienced several episodes during prophylaxis with benzathine penicillin 1.2 MU. The occurrence of episodes of erysipelas occurred just before the dose was to

**Table 2.** *Recurrences during antibiotic prophylaxis*

| Patient | Recurrence | Antibiotic | Dosage | Time to recurrence | | Treatment of erysipelas | Reasons for failure of prophylaxis: Non-compliance | Incorrect antibiotic | Other causative micro-organism | Insufficient antibiotic concentration | No explanation |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A | 1 | benzathine penicillin | 1.2 MU/ 4 wk | 15 | mo | penicillin, feneticillin | v | | | | |
| B | 1 | procaine penicillin | 1.2 MU/ 4 wk | | | | | v | | | |
| | 2 | clarithromycin | 250 mg/day | 1.5 | wk | | | | | v | |
| | 3 | benzathine penicillin | 1.2 MU/ 3 wk | 1 | wk | feneticillin failed | | | v | | |
| C | 1 | benzathine penicillin | 1.2 MU/ 4 wk | * | | | | | | v | |
| | 2 | benzathine penicillin | 1.2 MU/ 2 wk | 3.5 | wk | | v | | | v | |
| | 3 | benzathine penicillin | 1.2 MU/ 2 wk | 2 | wk | feneticillin | | | | | v |
| | 4 | benzathine penicillin | 1.2 MU/ 3 wk | | | penicillin, feneticillin | | | | | v |
| D | 1 | benzathine penicillin | 1.2 MU/ 4 wk | 2 | wk | flucloxacillin | | | v | | |
| | 2 | benzathine penicillin | 1.2 MU/ 3 wk | 1.5 | wk | amoxicillin | | | | | v |
| E | 1 | benzathine penicillin | 1.2 MU/ 4 wk | 9 | mo | amoxicillin | | | | | v |
| | 2 | clindamycin | 300 mg t.i.d. | | | clindamycin *iv* | | | | | v |
| | 3 | clindamycin | 300 mg q.i.d. | | | clindamycin *iv* | | | | | v |
| F | 1 | benzathine penicillin | 1.2 MU/ 4 wk | | | | | | | | v |
| G | 1 | benzathine penicillin | 1.2 MU/ 4 wk | | | | | | | | v |
| | 2 | benzathine penicillin | 1.2 MU/ 2 wk | | | | | | | | v |
| H | 1 | benzathine penicillin | 1.2 MU/ 4 wk | 9 | mo | penicillin ** | | | | v | |

* **shortly before the next injection was planned;** ** **plus valaciclovir prophylaxis; wk = week; mo = month; t.i.d. = three times a day; q.i.d = 4 times a day.**

be administered, which may indicate insufficient levels of the antibiotic during the last phase of the administration interval. Indeed, in patient B injections every two weeks and in patient H every three weeks prevented relapses.

**No explanation**

Recurrences of erysipelas during antibiotic prophylaxis in patients E, F, and G could not be explained. Furthermore, no explanation was available for one episode of erysipelas in patients C and D.

## DISCUSSION

Our review of the literature and analyses of case reports clearly indicate that despite antibiotic prophylaxis, erysipelas still recurs.[7,8] Recurrent erysipelas despite prophylaxis has gone unnoticed, because cases are rare. A survey in our tertiary care centre among 117 cases of erysipelas yielded eight such cases. It is not usually possible to judge whether these recurrent episodes represent relapses from foci within the body (e.g., within the lymphatic system) or exogenous reinfections.

The analysis of the reasons for failure of preventive therapy in our sample indicates that the recurrence of erysipelas had multiple causes: 1) noncompliance; 2) incorrect antibiotic; 3) other causative micro-organism; 4) insufficient antibiotic concentrations. Importantly, in half of the cases, no valid explanation could be obtained. Thus, the reasons for failure of prophylaxis in these cases remain unclear. We tend to conclude that in such cases, erysipelas may recur despite concentrations of antibiotics that are otherwise considered adequate. We have not been able to find many similar cases in the literature.

An important question is whether evidence exists that antibiotic prophylaxis is effective in preventing recurrences of erysipelas. In the older literature, case reports suggested that prolonged antibiotic prophylaxis successfully reduces the frequency of attacks in all patients with recurrent erysipelas.[8,9] In addition, several clinical studies have addressed this problem. In the study by Duvanel *et al.*[5] benzathine penicillin 2.4 MU every three weeks was given intramuscularly to 12 patients for six months, after the first attack of erysipelas. There where no recurrences during the period of prophylaxis, but after discontinuation of prophylaxis, three patients experienced a recurrence.

Jorup-Rönström *et al.*[4] included 143 patients with erysipelas; 29% had recurrences during a follow-up period of two to four years. Only nine patients received antibiotic prophylaxis, which prevented further episodes of erysipelas. After the second recurrence, the calculated cost of prophylaxis with phenoxymethylpenicillin or erythromycin was only marginally lower then the cost of therapy for erysipelas attacks.

Kremer *et al.*[6] studied erythromycin as a preventive antibiotic in 32 patients who had suffered two or more episodes of erysipelas or cellulitis during a follow-up period of 18 months. Only 11 of 36 patients were included because of recurrent erysipelas. There were no recurrences in the study group, compared with a relapse rate of 50% in the control group.

Sjöblom *et al.*[7] prescribed antibiotic prophylaxis to 20 patients with a history of two or more attacks of erysipelas. Phenoxymethylpenicillin was given in most cases. A few patients received erythromycin because of a known allergy to penicillin. Despite the antibiotic prophylaxis, two patients had a recurrence, compared with eight patients in the control group. The median follow-up period was 15 months.

Our study has a number of implications for clinicians dealing with recurrent erysipelas (summarised in *table 3*). First, we would recommend that the diagnosis is as certain as it can possibly be. Cultures and serology may be of help to ascertain the cause. Not only should the question be raised whether it is a streptococcal or a staphylococcal infection, but also more rare causes, such as *Campylobacter jejuni*, especially in patients with compromised host defences (e.g., hypogammaglobulinaemia) and *Campylobacter fetus* in patients with other underlying illnesses,[10-12] should be considered. Secondly, the clinician should make sure that the correct antibiotic is selected, based on the most likely causative micro-organism. Thirdly, dosing and timing of antibiotic prophylaxis is of great relevance. A problem is that the penicillin concentrations needed for adequate prophylaxis are not known. From a theoretical point of view, it could be argued that the protective serum penicillin concentrations need to be maintained at levels equal or above the minimal inhibitory concentration (MIC) of the causative micro-organism. It is noteworthy that the majority of the patients in this study received benzathine penicillin 1.2 MU every four weeks as the first prophylactic regimen. With this schedule extremely low penicillin concentrations may be present at the end of the dosing interval.[13] From the literature and also the cases presented here, it is suggested that three-weekly schedules are more effective for preventing erysipelas. In some cases, even two-weekly schedules may be necessary. Another approach to provide protective plasma penicillin levels is increasing the dosage.[14] Doubling the dose prolongs the protective plasma penicillin levels by only one half-life, which in this case may be around seven days.

In addition, the deposition of benzathine penicillin after an injection in the buttocks has been questioned: the majority of injections have been reported to be intralipomatous rather than intramuscular.[15] Finally, the clinician should address the issue of compliance with the prophylactic treatment. If oral prophylaxis is being prescribed, patient information is a crucial issue. The importance of prophylactic treatment to prevent further damage of the lymph vessels and serious infections should be stressed.

Importantly, in half of the cases no valid explanation could be obtained. Thus, the reasons for failure of prophylaxis in the cases remain unclear. The insight that prophylaxis does not allow the prevention of all episodes of erysipelas may lead to more systematic investigations of this topic.

**Table 3.** *Recurrent erysipelas despite antibiotic prophylaxis*

1. Check compliance
2. Reconsider diagnosis (*Staphylococcus aureus, Campylobacter species*)
3. Consider shortening the dosing interval (benzathine penicillin) or raising the dose of oral prophylaxis
4. Change regimen, e.g., to clindamycin

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Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

# Glucose dysregulation in nondiabetic patients with ST-elevation myocardial infarction: acute and chronic glucose dysregulation in STEMI

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## ABSTRACT

**Background: Admission hyperglycaemia is associated with an increased risk of mortality after myocardial infarction. Whether long-term glucose dysregulation (assessed by HbA1c) is more important than acute hyperglycaemia is unknown. We evaluated the prognostic value of admission glucose and HbA1c levels in nondiabetic patients with ST-segment elevation acute myocardial infarction (STEMI).**

**Methods: In 504 unselected, consecutive patients with STEMI, glucose and HbA1c levels were measured on admission. Glucose was categorised as <11.1 mmol/l (n=422) and ≥11.1 mmol/l (n=82). HbA1c levels were categorised as <6.0% (n=416) and ≥6.0% (n=88). Mean follow-up was 1.6±0.6 years.**

**Results: Patients with hyperglycaemia on admission were comparable with those with normoglycaemia. However, patients with HbA1c ≥6.0%, as compared with those with HbA1c <6%, were older, were more often on β-blockers and more frequently had multivessel disease. Thirty-day mortality in the subsequent glucose categories (<11.1 mmol/l and ≥11.1 mmol/l) was 4% and 19% (p<0.001) and in the subsequent HbA1c categories (<6% and ≥6%) was 5% and 12% (p=0.03). After multivariable analyses, admission glucose (OR 4.91, 95% CI 2.03 to 11.9, p< 0.001) but not HbA1c (OR 1.33, 95% CI 0.48 to 3.71, p=0.58) was significantly associated with 30-day mortality. Among 30-day survivors, neither admission glucose nor HbA1c were predictors of long-term mortality.**

**Conclusion: Elevated admission glucose is an important predictor of 30-day outcome after STEMI, while prior long-term glucose dysregulation is a covariate of other high-risk clinical characteristics. Among 30-day survivors, neither admission blood glucose nor HbA1c were predictors of long-term outcome.**

## KEYWORDS

ST-elevation acute myocardial infarction, admission glucose, HbA1c, outcome

## INTRODUCTION

In patients with acute coronary syndrome (ACS), up to 40% have impaired blood glucose levels on admission.[1] This has been associated with increased mortality, irrespective of diabetic status.[2-7] Recent evidence has shown that chronic glucose dysregulation, assessed by HbA1c levels, is also of prognostic value with regard to future cardiovascular disease and congestive heart failure.[8] A previous study with a small sample size (n=146) suggested, however, that admission blood glucose but not HbA1c predicts short-term mortality after ACS.[9] It is unclear whether glucose dysregulation is associated with poor long-term prognosis among 30-day survivors.

We aimed to investigate the 30-day and long-term prognostic value of both admission glucose and HbA1c levels in patients with STEMI.

## MATERIALS AND METHODS

### Patients

It concerns a single-centre, prospective, follow-up study of unselected patients. During a period of 22 months, from April 2002 till February 2004, admission glucose and HbA1c were measured in 504 STEMI patients, none with previously documented diabetes mellitus. If patients revisited our hospital with one or more reinfarction during

the study period, only the first visit was recorded. Data from the patient's medical records were collected in a dedicated database.

**Laboratory measurements**

HbA1c was measured using a high-performance liquid affinity chromatography (HPLC) (Primus GLC 385). This method has an interassay coefficient of variation of 0.51%. Glucose was measured by a hexokinase method using a Modular PPE module device (Roche analytics).

**Definitions of clinical diagnosis**

STEMI was defined as the presence of chest pain, an electrocardiogram with ST-segment elevation of more than 1 mm (0.1 mV) in two or more contiguous leads and a subsequent rise of CK-MB of more than 6% of the total CK, whenever CK was >200 U/l (men) or >170 U/l (women). Previous CAD was defined as a history of myocardial infarction, coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). Diabetes was defined as the use of insulin or glucose-lowering medication on admission or a diet for diabetes documented in the medical history. Hyperglycaemia was defined as glucose ≥11.1 mmol/l based on nonfasting cut-off values for hyperglycaemia from the guidelines of the American Diabetic Association.[10] An HbA1c ≥6.0% was considered an elevated HbA1c.[11] Follow-up information with regard to mortality status was obtained in August 2005. All outpatients' reports were reviewed and general practitioners were contacted by phone. In order to distinguish the short-term and long-term effects, admission glucose and HbA1c, long-term outcome was only assessed among 30-day survivors.

**Statistical analysis**

Statistical analysis was performed using SPSS 12.0. Differences between group means were tested by two-tailed Student's t-test. A $\chi^2$ statistic was calculated to test differences between proportions, with calculation of relative risks and exact 95% confidence intervals. Fisher's exact test was used when the expected value of cells was <5. Statistical significance was defined as a p value <0.05. Admission glucose was included as a categorical variable (<11.1 mmol/l and ≥11.1 mmol/l). HbA1c levels were included as a categorical variable (<6.0% and ≥6.0%). Cox proportional hazards regression models were used to estimate hazard ratios of clinical variables with regard to mortality.

## RESULTS

During the study period, 587 patients with STEMI were admitted to our hospital, 504 (86%) of whom without previously diagnosed diabetes. Mean age was 63 ± 13 years and 72% were male. A total of 474 (94%) underwent immediate coronary angiography, and percutaneous intervention was performed in 428 (85%) of the patients. There were 82 patients (16%) with hyperglycaemia and 88 patients (17%) with HbA1c ≥6.0%. Of the 82 patients with hyperglycaemia, 29 (35%) also had elevated HbA1c, compared with 53 patients (14%) with normoglycaemia (p<0.001). Baseline characteristics of patient groups based on glucose and HbA1c categories are shown in *tables 1* and *2*, respectively.

Patients with hyperglycaemia were comparable with those with admission glucose <11.1 mmol/l, but less often had sinus rhythm and had higher HbA1c levels (*table 1*). Patients with HbA1c ≥6% were significantly older, had a higher prevalence of previous cerebrovascular disease, were more often on β-blockers and more often had multivessel disease.

**Outcome**

On discharge eight patients were treated with glucose-lowering medication. Follow-up was complete in 496 (98%) patients, with a mean duration of 1.6 ± 0.6 years.

**Thirty-day mortality**

At 30 days, 32 patients (7%) had died. The patients who died during follow-up were older, more often had a history of stroke, were less often smokers and less often had a positive family history. Of the patients with a glucose <11.1 mmol/l, 17 patients (4%) died compared with 15 patients (19%) with hyperglycaemia (p<0.001).

Mortality curves of the two patient groups according to admission glucose are shown in *figure 1*. Patients with an HbA1c <6.0% had a mortality of 22 (5%) compared with 10 (12%) in patients with an HbA1c of ≥6.0 (p=0.03). Mortality curves of the patient groups according to HbA1c level are shown in *figure 2*.

**Figure 1.** *Mortality curves according to admission glucose*

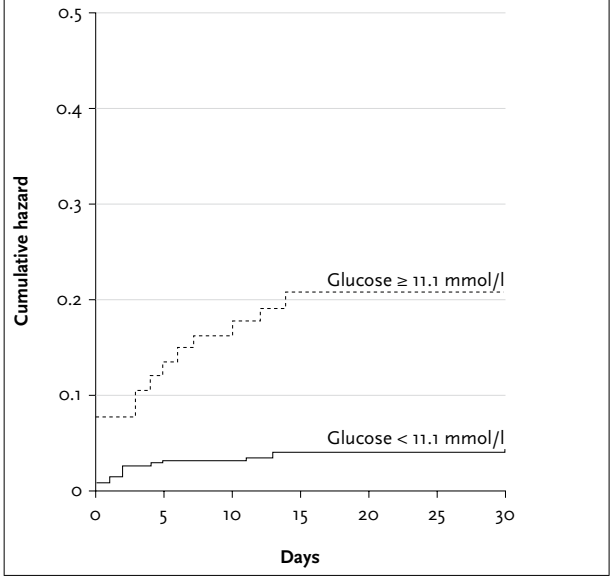


**Table 1.** *Baseline, angiography and outcome according to admission glucose*

| Variable | N | Glucose <11.1 | N | Glucose ≥11.1 | P value |
|---|---|---|---|---|---|
| Age | 422 | 63 ± 13 | 82 | 64 ± 12 | 0.64 |
| Male | 422 | 308 (73%) | 82 | 54 (66%) | 0.19 |
| SBP | 360 | 129 ± 24 | 63 | 126 ± 30 | 0.36 |
| DBP | 360 | 79 ± 16 | 63 | 76 ± 20 | 0.32 |
| **History of** | | | | | |
| • MI | 419 | 56 (13%) | 81 | 8 (10%) | 0.39 |
| • PCI | 418 | 34 (8%) | 81 | 6 (7%) | 0.83 |
| • CABG | 418 | 19 (5%) | 81 | 1 (1%) | 0.22 |
| • CVA | 419 | 11 (3%) | 81 | 1 (1%) | 0.70 |
| Hypertension | 353 | 99 (28%) | 63 | 25 (40%) | 0.06 |
| Hyperlipidaemia | 357 | 82 (23%) | 64 | 16 (25%) | 0.72 |
| Family CAD | 353 | 142 (40%) | 63 | 27 (43%) | 0.70 |
| Smoke | 353 | 187 (53%) | 63 | 26 (41%) | 0.09 |
| Anterior infarct location | 412 | 185 (45%) | 80 | 39 (49%) | 0.53 |
| CAG | 422 | 406 (96%) | 82 | 75 (92%) | 0.06 |
| • 1-VD | 396 | 231 (58%) | 72 | 44 (61%) | 0.81 |
| • ≥2-VD | 396 | 165 (42%) | 72 | 28 (39%) | 0.81 |
| TIMI flow pre-PCI 0 | 380 | 225 (59%) | 69 | 37 (54%) | 0.15 |
| TIMI flow post-PCI 3 | 371 | 342 (92%) | 67 | 59 (88%) | 0.26 |
| Glucose | 422 | 7.9 ± 1.4 | 82 | 14 ± 3.0 | <0.001 |
| HbA1c | 422 | 5.6 ± 0.4 | 82 | 6.1 ± 1.1 | <0.001 |
| Mortality | | | | | |
| • 30-day | 415 | 17(4%) | 81 | 15(19%) | <0.001 |
| • Long-term | 398 | 17 (4%) | 66 | 3 (5%) | 0.92 |

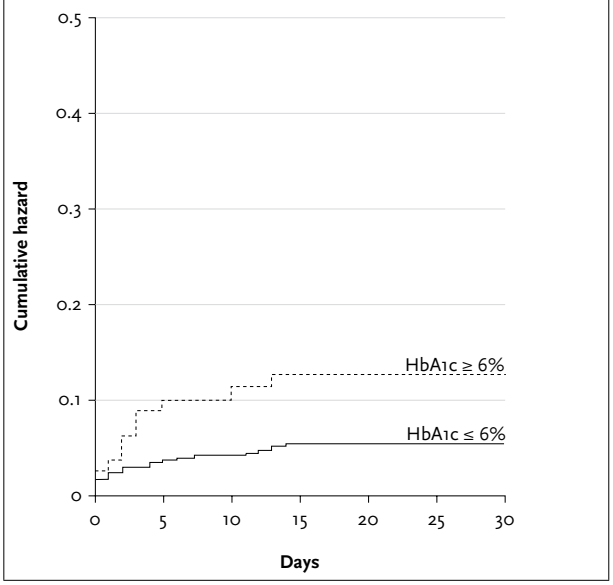
**SBP = systolic blood pressure; DBP = diastolic blood pressure; MI = myocardial infarction; PCI = percutaneous coronary interventions; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; CAD = coronary artery disease; CAG = coronary angiography; VD = vessel disease; TIMI = Thrombolysis In Myocardial Infarction.**

**Table 2.** *Baseline, angiography and outcome according to HbA1c*

| Variable | N | HbA1c <6% | N | HbA1c ≥6 | P value |
|---|---|---|---|---|---|
| Age | 416 | 62 ± 14 | 88 | 68 ± 11 | <0.001 |
| Male | 416 | 296 (71%) | 88 | 66 (75%) | 0.46 |
| SBP | 348 | 127 ± 24 | 75 | 133 ± 28 | 0.059 |
| DBP | 348 | 78 ± 17 | 75 | 80 ± 8 | 0.35 |
| **History of** | | | | | |
| • MI | 412 | 51 (12%) | 88 | 13 (15%) | 0.54 |
| • PCI | 411 | 31 (8%) | 88 | 9 (10%) | 0.40 |
| • CABG | 411 | 18 (4%) | 88 | 2 (2%) | 0.55 |
| • CVA | 412 | 7 (2%) | 88 | 5 (6%) | 0.027 |
| Hypertension | 348 | 99 (28%) | 68 | 35 (37) | 0.17 |
| Hyperlipidaemia | 353 | 80 (23%) | 68 | 18 (27%) | 0.50 |
| Family CAD | 348 | 142 (41%) | 68 | 27 (40%) | 0.87 |
| Smoking | 348 | 175 (51%) | 68 | 37 (54%) | 0.056 |
| Anterior infarct location | 408 | 188 (45%) | 84 | 41 (49%) | 0.58 |
| CAG | 416 | 400(96%) | 88 | 81(92%) | 0.09 |
| • 1-VD | 391 | 241 (62%) | 77 | 34 (44%) | 0.028 |
| • ≥ 2-VD | 391 | 150 (38%) | 77 | 43 (56%) | 0.028 |
| TIMI flow pre-PCI 0 | 379 | 227 (60%) | 69 | 35 (51%) | 0.053 |
| TIMI flow post-PCI 3 | 371 | 341 (92%) | 67 | 60 (90%) | 0.52 |
| Glucose | 416 | 8.6 ± 2.6 | 88 | 10.4 ± 3.6 | <0.001 |
| HbA1c | 416 | 5.5 ± 0.2 | 88 | 6.6 ± 0.9 | <0.001 |
| Mortality | | | | | |
| • 30-day | 408 | 22 (5%) | 86 | 10 (12%) | 0.03 |
| • Long-term | 388 | 15 (4%) | 76 | 5 (7%) | 0.23 |

**SBP = systolic blood pressure; DBP = diastolic blood pressure; MI = myocardial infarction; PCI = percutaneous coronary interventions; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; CAD = coronary artery disease; CAG = coronary angiography; VD = vessel disease; TIMI = Thrombolysis In Myocardial Infarction.**

**Figure 2.** *Mortality curves according to HbA1c*




**Long-term outcome among 30-day survivors**

Long-term mortality in the subsequent glucose categories (<11.1 mmol/l and ≥11.1 mmol) was 4% and 5% (p<0.92). In patients with an HbA1c of <6.0% long-term mortality was 4% compared with 7% in patients with an HbA1c ≥6.0% (p=0.23).

**Multivariate analysis**

To investigate whether the association between elevated glucose levels, HbA1c levels and 30-day outcome were independent of the differences in the baseline characteristics, multivariate analysis was performed. Included variables were age, gender, multivessel disease and HbA1c. Because there was a significant association between HbA1c and glucose, they were separately included in the multivariate analysis. Independent predictors of 30-day mortality were increased age (HR 1.04 per year, 95% CI 1.01 to 1.07, p=0.013) and elevated admission glucose (OR 4.91, 95% CI 2.03 to 11.9, p<0.001). An elevated HbA1c level was not significantly associated with a higher mortality (OR 1.33, 95% CI 0.48 to 3.71, p=0.58).

## DISCUSSION

This study evaluated the prognostic value of admission glucose and HbA1c in patients with STEMI. Elevated glucose levels on admission were a strong and independent predictor of 30-day mortality. Elevated HbA1c was also associated with a worse prognosis but this was not an independent predictor of mortality. Neither admission glucose nor HbA1c were predictors of long-term mortality.

**Prognostic value of HbA1c**

HbA1c is an easy marker of long-term glucose regulation, also unmasking minor glycometabolic disease, such as impaired glucose tolerance, impaired fasting glucose or metabolic syndrome.[12-14] Previous studies have shown that an elevated HbA1c is associated with increased cardiovascular risk in patients with and without diabetes.[15,16] However, other studies reported conflicting results with regard to chronic glycometabolic states and outcome in patients with acute myocardial infarction.[5,9,17-19] Malmberg *et al*.[5] found an association between elevated HbA1c and mortality after myocardial infarction, relative risk (95% CI) 1.07 (1.01-1.21); however, Timmer *et al*. and Cao *et al*. did not confirm this, [1.63 (0.99-2.79] and 1.08 (0.31-3.23)], respectively.[18,19]

In our study, patients with an elevated HbA1c were older, more often had a history of CVA, were more often on a β-blocker on admission and more often had multivessel disease. However, HbA1c ≥6.0% was not a predictor of mortality. This is consistent with a previous small sample size study.[9]

**Prognostic value of admission glucose**

A number of reports have shown the association between elevated admission glucose and poor outcome in patients with myocardial infarction or unstable angina.[2,8] This adverse association may be independent of other clinical prognostic factors, also in the setting of reperfusion therapy and even after correction for HbA1c levels.[6,9,18,20,21] *Table 3* shows the individual and pooled unadjusted relative risk of hyperglycaemia for mortality in several studies. All these studies show that hyperglycaemia on admission is associated with a worse outcome after myocardial infarction.

Several studies have reported the long-term effects of hyperglycaemia.[18-20] However, most effects of hyperglycaemia may occur in the acute phase of myocardial infarction and these studies did not analyse whether the early effects dominate the entire benefit or whether subsequent follow-up also contributes to their demonstrated results. Elevated glucose is not only a symptom of glucose dysregulation, but also of stress and a more high-risk patient population. It has been shown that higher admission glucose is associated with a higher Killip class, a larger infarct size and a lower ventricular function.[18] Thrombotic properties of platelets are increased in a hyperglycaemic environment and this can result in additional cardiovascular complications.[22] Furthermore, elevated glucose levels are accompanied by increased levels of free fatty acids (FFA).[23] These FFA may increase infarct size, compromise myocardial performance during acute coronary syndromes and reduce endothelium-derived vasodilatation in myocardial tissue limiting myocardial reperfusion.[24-26] In addition, hyperglycaemic-induced endothelial dysfunction, hypercoagulability, platelet dysfunction, and vascular

**Table 3.** *Relative risk of in-hospital and long-term mortality after myocardial infarction in patients with admission hyperglycaemia*

| Study | Publication Year | Number of patients | Follow-up | Relative risk (95% confidence interval) |
|---|---|---|---|---|
| Foo[2] | 2003 | 2127 | In-hospital | 2.63 (1.67-4.13) |
| O'Sullivan[3] | 1991 | 714 | In-hospital | 3.20 (1.40-6.65) |
| Sewdarsen[4] | 1989 | 277 | In-hospital | 4.94 (2.15 -11.64) |
| Lynch[8] | 1994 | 420 | In-hospital | 4.33 (4.25-8.54) |
| Bolk[20] | 2001 | 336 | ≥1 year | 2.92 (1.89-4.281) |
| Stranders[21] | 2004 | 846 | ≥1 year | 1.64 (1.28-2.10) |
| Timmer[18] | 2005 | 356 | ≥1 year | 1.94 (1.08-3.40) |
| **Pooled relative risk** | | | | **1.41 (121-1.66)** |

smooth muscle dysfunction may also contribute to the worse outcome in STEMI patients with hyperglycaemia on admission.[27-31]

In the current study we found no relation between admission glucose and long-term outcome among 30-day survivors. A possible explanation is that glucose levels drop after the acute phase of myocardial infarction, which is shown to be associated with an improved outcome.[32] This drop in glucose levels may at last partially be due to the drop in stress hormones after the acute phase of myocardial infarction.[33] Oswald *et al*. showed that stress hormones are the main determinants of plasma glucose in nondiabetic patients with acute myocardial infarction.[34] Others have reported the proportional release of stress hormones to the severity of myocardial infarction.[35]

In our study, there were no major differences in baseline characteristics according to admission glucose. However, elevated glucose levels on admission, but not chronic glucose dysregulation, were a strong and independent predictor of 30-day term mortality. These findings are similar to those reported in diabetes.[19]

## CONCLUSION

In patients with STEMI, elevated admission blood glucose is an important independent predictor of 30-day outcome, while elevated HbA1c reflects a more high-risk patient population. Among 30-day survivors neither admission blood glucose nor HbA1c predicts worse outcome.

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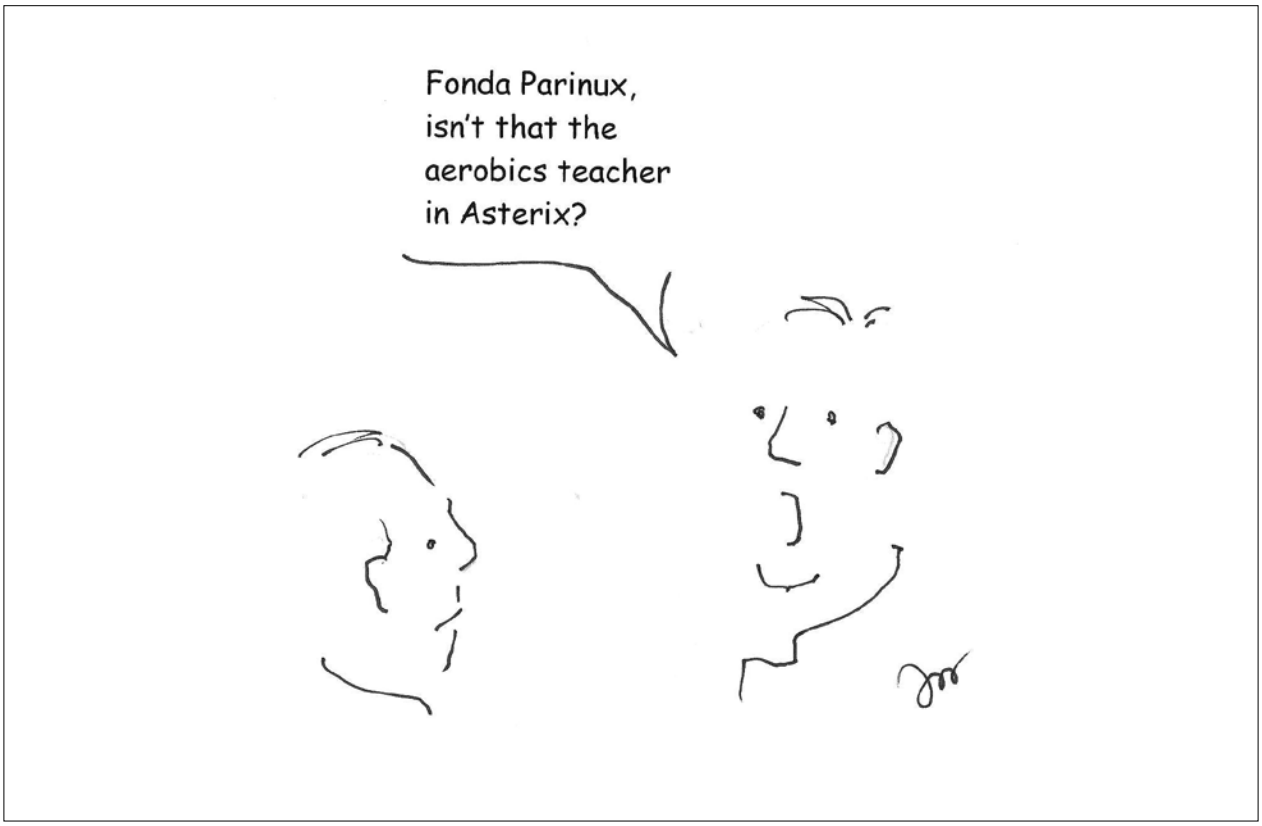


Rasoul, et al. Acute and chronic glucose dysregulation in STEMI.

Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

# Low-dose fondaparinux in suspected heparin-induced thrombocytopenia in the critically ill

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## ABSTRACT

**Background: In critically ill patients, heparin-induced thrombocytopenia (HIT) is estimated to account for approximately 1 to 10% of all causes of thrombocytopenia. HIT exerts a strong procoagulant state. In case of suspected HIT, it is an important clinical decision to stop heparin and start treatment with alternative nonheparin anticoagulation, awaiting the results of laboratory testing for the final diagnosis of HIT (bridging therapy). Fondaparinux acts by factor Xa inhibition and expresses no cross-reactivity with HIT antibodies. Excretion of fondaparinux is mainly renal. We describe our early experience with fixed low-dose fondaparinux bridging therapy and monitoring of anticoagulant activity for safety reasons.**

**Methods: This retrospective cohort study was conducted in a closed format general intensive care unit in a teaching hospital. Consecutive critically ill patients suspected of HIT were treated with fondaparinux after discontinuation of unfractionated heparin or nadroparin. Anti-Xa levels were determined afterwards.**

**Results: Seven patients were treated with fondaparinux 2.5 mg/day for 1.8 to 6.5 days. Anti-Xa levels varied from 0.1 to 0.6 U/ml. A negative correlation was found between creatinine clearance and mean and maximum anti-Xa levels. No thromboembolic complications occurred. Bleeding complications were only minor during fondaparinux treatment. Transfusion requirements did not differ significantly between treatment episodes with fondaparinux or with heparin anticoagulants.**

**Conclusion: In this small sample of critically ill patients suspected of HIT, bridging therapy with fixed low-dose fondaparinux resulted in prophylactic and therapeutic anti-Xa levels. Monitoring of anticoagulant activity is advised in patients with renal insufficiency.**

## KEYWORDS

Critically ill, fondaparinux sodium, heparin-induced thrombocytopenia, pentasaccharide

## INTRODUCTION

In critically ill patients, a decrease in the platelet count is frequently observed. Heparin-induced thrombocytopenia (HIT) is estimated to account for approximately 1 to 10% of all causes of thrombocytopenia.[1] When HIT is suspected an important clinical process of diagnostic and therapeutic strategies starts. Diagnostic laboratory testing needs to be performed to support the diagnosis. Due to the strong procoagulant character of HIT, it may be necessary to stop heparin-like drugs promptly and to start treatment with alternative nonheparin anticoagulation.[2] We call the pre-emptive treatment of suspected HIT, awaiting the test results for the final diagnosis of HIT, bridging therapy. The diagnosis of HIT is based upon the combination of clinical criteria and laboratory test results according to the diagnostic classification systems as developed by the International Society on Thrombosis and Haemostasis (ISTH).[3,4] Continuation of the alternative nonheparin anticoagulation depends on the final diagnosis of HIT.

For treatment of HIT, danaparoid, lepirudin and argatroban are to date the most widely used nonheparin anticoagulants.[5-8] All three drugs have their advantages and disadvantages (*table 1*). In 5 to 10% of cases, Danaparoid, with an anti-Xa:anti-IIa ratio of 28:1, exerts cross-reactivity with antibodies against the heparin/platelet factor 4 (PF4) complex, known as HIT antibodies. Lepirudin can induce antilepirudin antibodies, which may lead to a strong increase of lepirudin activity and anaphylaxis at re-exposure. Excretion of danaparoid and

lepirudin is mainly renal, which may lead to accumulation of anticoagulant activity in case of renal impairment. Argatroban has a short half-life and is metabolised hepatically. In critically ill patients with the multiple organ dysfunction syndrome, the dose has to be adjusted to prevent anticoagulant accumulation due to an apparent degree of hepatic dysfunction.[9] Argatroban is not available in the Netherlands.* Neutralising agents are lacking for all three drugs. Each of these drugs can lead to an increased risk of bleeding, especially in critically ill patients who are already prone to bleeding complications due to thrombocytopenia, other coagulopathies, recent surgery and the necessity of frequent invasive procedures. In this complex situation a balance should be found between the prevention of HIT-induced thromboembolic complications and nonheparin anticoagulant-induced bleeding complications.

In search of a more favourable nonheparin anticoagulant for the treatment of HIT, fondaparinux has emerged as a suitable alternative with possibly a more favourable benefit/harm profile (*table 1*). Fondaparinux, a newly developed synthetic pentasaccharide, inhibits thrombin generation by antithrombin-mediated factor Xa inhibition.[10] Some characteristics of fondaparinux are not different to the other alternative anticoagulants. Excretion is also mainly renal in an unmetabolised form and renal failure can lead to accumulation of anticoagulant activity.[11] However, other characteristics of fondaparinux seem to be advantageous compared with the other drugs. *In vitro*, fondaparinux exerts very low cross-reactivity with HIT antibodies.[12] *In vivo*, anti-fondaparinux/PF4 antibodies can be generated but clinical HIT does not develop.[13] In healthy volunteers, recombinant human factor VIIa emerged as a possible antidote for fondaparinux.[14] Fondaparinux is less costly. Finally, documented clinical experience with prophylactic and therapeutic use of fondaparinux for HIT is emerging.[15-20]

Based upon the possibly favourable characteristics we decided to use fondaparinux for the treatment of critically ill patients with suspected HIT awaiting the definite diagnostic classification. Arbitrarily we chose a fixed prophylactic dose of 2.5 mg/day anticipating a possible accumulation of anticoagulant activity in critically ill patients with a certain degree of kidney dysfunction. The

* All four drugs (danaparoid, fondaparinux, lepirudin and argatroban) are available for treatment of (suspected) HIT in the Netherlands.

**Table 1.** *Alternative nonheparin anticoagulant strategies in patients with heparin-induced thrombocytopenia (HIT)*

| *Drug* | Mechanism of anticoagulation | Monitoring | Pro | Con | Clearance | T½ | Dose adjustment |
|---|---|---|---|---|---|---|---|
| **Danaparoid** Heparinoid from pig-intestinal mucosa | Anti-Xa/anti-IIa 28 : 1 | Anti-Xa[a] | | • 5-10% cross-reactivity to anti-H/PF4<br>• Accumulation in ARF<br>• Not an antagonist | Mainly renal | *Normal:* 25 h<br>*Anuria:* increased | In renal failure |
| **Fondaparinux** Synthetic pentasaccharide | Anti-Xa antithrombin-mediated | Anti-Xa[b] | • Very low cross- reactivity to anti-H/PF4<br>• rFVIIa is potential partial antagonist | • Accumulation in ARF | Renal | *Normal:* 15-20 h<br>*Anuria:* increased | In renal failure |
| **Lepirudin** (Recombinant-hirudin) direct thrombin inhibitor | Anti-IIa direct irreversible | ECT<br>APTT is unreliable[c] | • No cross-reactivity to anti-H/PF4 | • Accumulation in ARF<br>• Antihirudin antibodies increase the anticoagulant effect<br>• Increased bleeding<br>• Anaphylaxis at re-exposure<br>• Not an antagonist | Renal | *Normal:* 60-100 min<br>*Anuria:* 1.5-15h | In renal failure |
| **Argatroban** Synthetic direct thrombin inhibitor | Anti-IIa direct reversible | APTT | • No cross-reactivity to anti-H/PF4 | • Limited availability outside USA<br>• Not an antagonist | • Hepatic<br>• Faecal excretion (16%)<br>• Renal (20%) | 39-51 min | In hepatic failure |

**Anti-H/PF4 = antiheparin/platelet factor 4 antibodies; ECT = ecarin clotting time; rFVIIa = recombinant factor VIIa. [a]Anti-Xa is not a reliable predictor of bleeding; [b]Unknown whether anti-Xa is a reliable predictor of bleeding; [c]Dose-dependent prolongation of APTT in the low-dose range, at higher doses APTT increase is relatively smaller; a higher degree of anticoagulation is therefore easily missed.**

anticoagulant activity of fondaparinux was measured by anti-Xa levels. In this article, we describe our early clinical experience with low-dose fondaparinux bridging therapy, with a focus on monitoring of the anticoagulant activity for safety reasons.

## MATERIALS AND METHODS

### Study design

This assessment was performed as a retrospective cohort study. On 28 November 2002, the Institutional Drug Committee of our hospital approved the use of fondaparinux sodium (Arixtra, the Netherlands; 2.5 mg/0.5 ml) for the treatment of suspected HIT in the critically ill. This indication concerns off-lable use. Fondaparinux is licensed for venous thromboprophylaxis in orthopaedic surgery. To monitor the safety of this novel therapy we determined anticoagulant activities in relationship to calculated endogenous creatinine clearances in the first series of patients for six months. The protocol for the start of fondaparinux treatment was not submitted to the Institutional Medical Ethics Committee. No informed consent was asked of the patients or their legal representatives.

For patients with suspected HIT, a strict diagnostic and therapeutic strategy was followed during the observation period. We used the ISTH classification system to estimate the pretest probability of HIT.[4] If the pretest probability was intermediate or high, unfractionated heparin (UFH) or nadroparin was stopped, a blood sample for HIT antibody testing was drawn and, awaiting the test results, fondaparinux 2.5 mg/day was administered as a once-daily subcutaneous injection at 06.00 hours or as a continuous intravenous infusion without loading dose at the discretion of the treating intensivist. The ISTH diagnostic classification system was used for the final diagnosis of HIT.[3] If HIT was classified as unlikely or possible, fondaparinux was stopped and UFH or nadroparin restarted. If HIT was classified as probable or definite, fondaparinux was continued.

Blood samples were drawn for monitoring the anticoagulant activity of fondaparinux by measurement of anti-Xa levels. Anti-Xa levels were measured before the start of anticoagulation with fondaparinux and every treatment day at 08.00 and 18.00 hours. The endogenous creatinine clearance was calculated from the serum creatinine level in the 06.00 hour routine blood sample and a six-hour urine sample collected between 06.00 and 12.00 hours according to the formula: creatinine clearance (ml/min) = [urine creatinine (mmol/l) x urine volume (ml)/serum creatinine (μmol/l) x urine collection time (min)].

Thromboembolic complications, bleeding complications and the amount of transfusion products administered were documented during the three episodes of anticoagulation, which we distinguished in the natural course of suspicion of HIT: 1) UFH or nadroparin before start of fondaparinux; 2) fondaparinux bridging therapy; and 3) UFH or nadroparin after fondaparinux bridging therapy. An intensive care information system (MetaVision, IMD Soft, Tel Aviv, Israel) was used for prospective data collection.

### Patients and setting

Consecutive patients with suspicion of HIT were treated with fondaparinux in an 18-bed tertiary referral closed format general ICU in a university-affiliated teaching hospital. A team of intensivists takes responsibility for the intensive treatment including antithrombotic treatment, a restrictive transfusion strategy and high volume continuous venovenous haemofiltration.[21] All patients and their legal representatives were informed that clinical and biochemical data concerning disease and treatment were being collected in an electronic database to be available for evaluation of treatment.

### Anticoagulant management

During the observation period of fondaparinux bridging therapy, the anticoagulant management was standardised in our department. Unfractionated heparin sodium (UFH) (manufactured at the Department of Clinical Pharmacy of our hospital: 5000 IU/ml) was used for continuous intravenous administration in a fixed dose (10,000 IU/day) not targeted at a prolongation of the aPTT for heart valve prosthesis thromboprophylaxis. Nadroparin calcium (Fraxiparine) was used for subcutaneous administration for venous thromboprophylaxis: 2850 IU anti-Xa/0.3 ml once daily for a body weight of <100 kg or 3800 IU anti-Xa/0.4 ml once daily for a body weight of >100 kg. Nadroparin was used for anticoagulation of the extracorporeal circuit of CVVH by an intravenous bolus of 2850 IU anti-Xa followed by continuous intravenous administration of 380 IU anti-Xa/h (9120 IU anti-Xa/day). Nadroparin was used for treatment of disseminated intravascular coagulation by continuous intravenous administration of a fixed dose of 3800 IU anti-Xa/day. Coagulation parameters were measured for safety monitoring, but not for targeting of therapy. Trisodium citrate was used for regional anticoagulation of the extracorporeal circuit of CVVH in patients with an increased risk of bleeding.[22]

### Heparin-induced thrombocytopenia, thrombosis and haemorrhage

We defined thrombocytopenia as a platelet count <100 x $10^9$/l measured at least twice and lasting for more than 24 hours with exclusion of pseudothrombocytopenia induced by the EDTA phenomenon. A HIT plot depicting the relationship between use of heparin and nonheparin anticoagulants and platelet count against time was made for all patients.

The diagnostic criteria for HIT, as developed by Warkentin and Chong on behalf of the Subcommittee on Platelet Immunology of the Scientific and Standardisation Committee of the ISTH, were used to support our clinical suspicion of HIT and for diagnostic classification.[3,4]

The four-item scoring system (the 4 T's) according to Warkentin was used for the estimation of pretest probability of HIT and consists of: 1) Thrombocytopenia; 2) Timing of onset of thrombocytopenia; 3) Thrombosis (or other sequelae of HIT); and 4) Other cause for thrombocytopenia apparent. Each item can score 0, 1, or 2 points; a total score of 6 to 8 points is classified as a high pretest probability for HIT, 4 to 5 points as an intermediate pretest probability for HIT, and 0 to 3 points as a low pretest probability for HIT.[4] The scoring system was recently validated in the intensive care setting.[23]

The diagnostic classification system for HIT according to Chong consists of clinical criteria and laboratory tests. The clinical criteria are: thrombocytopenia between 5 to 10 days after starting heparin treatment (3 points), thrombocytopenia between 1 to 4 days or >11 days (1 point), exclusion of other causes of thrombocytopenia (2 points), resolution of thrombocytopenia after cessation of heparin (1 point), reoccurrence of thrombocytopenia after rechallenge with heparin (1 point), and thrombosis (1 point). The laboratory tests are: immunoassay positive (2 points), functional assays: two-point system (i.e. measurement of aggregation in the presence of two heparin concentrations) positive (3 points), non-two-point system positive (2 points). If more than one diagnostic test is used, the test with the maximum score is taken for calculation of the total score. A total score of 0 to 2 points classifies HIT as unlikely, 3 to 4 points as possible, 5 to 6 points as probable, and ≥7 points as definite.[3]

**Laboratory testing**

Testing of HIT was performed in all patients by the direct antibody assay (Asserachrom HPIA Heparin/PF4 antibody ELISA, Stago, Asnière, France) to confirm the presence of antibodies against the heparin-platelet factor 4 complex. To detect possible accumulation of anticoagulant activity, anti-Xa levels (IU/ml) were determined by a chromogenic factor Xa inhibition assay (Coamatic Heparin, Chromogenics, Milan, Italy) calibrated for fondaparinux. Samples for measurement of anti-Xa levels were collected before the start of anticoagulation with fondaparinux and on every treatment day at 08.00 and 18.00 hours. All anti-Xa levels were determined after the observation period of fondaparinux bridging therapy. The prophylactic range was considered to be reflected by anti-Xa levels of 0.2 to 0.4 IU/ml and the therapeutic range by anti-Xa levels of 0.5 to 0.8 IU/ml.

The detection of thromboembolic complications (TEC) was based on regular clinical practice; when symptomatic venous or arterial TEC was suspected, TEC had to be proven by standard diagnostic imaging techniques such as duplex scanning and spiral CT scanning or by pathological anatomical examination. Remarkably early and/or frequent clotting of extracorporeal circuits and haemofilters, defined as two or more circuit survival times of <12 hours in the presence of a normal functioning central venous access catheter, was regarded as a manifestation of a procoagulant state.

Bleeding complications were classified as clinically important major and clinically important minor bleeds according to Landefeld's Bleeding Severity Index.[24] Occult minor bleeding was not analysed separately because this clinical situation often does not represent clinically important bleed. Occult bleeding usually reflects a decrease in the haemoglobin level below a certain trigger level for transfusion upon which erythrocyte concentrates are administered.

Our strategy of transfusion of blood products is restrictive.[25,26] For erythrocyte concentrate, the transfusion trigger was determined at a haemoglobin level of 4.0 mmol/l for patients <40 years with good cardiopulmonary function, at 4.5 mmol/l for patients 40 to 60 years, at 5.0 mmol/l for patients >60 years and at 5.5 mmol/l for patients >60 years with critical coronary atherosclerosis or severe pulmonary disease. A transfusion trigger of 5.5. mmol/l was used in case of overt bleeding for all patients. For platelet concentrate, the transfusion trigger was set at $<10 \times 10^9$/l without overt bleeding and at $<50 \times 10^9$/l in case of a planned percutaneous or surgical intervention. In case of overt bleeding a platelet count of $>50 \times 10^9$/l was targeted.

**Statistical analysis**

Descriptive statistics were used. Variables with a normal distribution were expressed as mean and standard deviation and variables with a nonparametric distribution were expressed as median and range. For comparison between variables, Fisher's exact test, repeated measures analysis of variance (ANOVA) and linear regression and correlation were used when appropriate. The level of significance was 0.05. The statistical software packages Epi Info version 5.00 and Primer Biostatistics version 3.0 were used.[27,28]

## RESULTS

From March to August 2003, we treated seven critically ill patients suspected of HIT with fondaparinux. The baseline characteristics are shown in *table 2*. According to the diagnostic classification system, six patients were classified as having an intermediate pretest probability and one patient as having a high pretest probability of HIT with scores between 4 and 7 points. The samples for HIT-antibody testing were taken between day 2 and day 7 after the start of UFH or nadroparin. HIT

**Table 2.** *Patient characteristics and dose-effect relationship of fondaparinux treatment*

| Patient | Sex | Age (years) | APACHE II score (points) | Diagnosis on ICU admission | Calculated endogenous creatinine clearance (ml/min) | Platelet count nadir (x10$^9$/l) at start of fondaparinux | Fondaparinux (mg/day; route) | Anti-Xa minimum (IU/ml) | Anti-Xa maximum (IU/ml) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 66 | 40 | Cardiac tamponade due to uraemic hemorrhagic pericarditis | 0* | 27 | 2.5 sc | 0.2 | 0.6 |
| 2 | M | 79 | 14 | Re-CABG + MVP | 45 | 56 | 2.5 iv | 0.1 | 0.5 |
| 3 | F | 59 | 21 | Pneumosepsis (*Streptococcus pneumoniae*) complicated by MODS | 36 | 23 | 2.5 sc | 0.3 | 0.6 |
| 4 | M | 50 | 22 | Fasciitis necroticans (Group A Streptococcus) complicated by MODS | 0* | 16 | 1.25 iv | 0§ | 0§ |
| 5 | M | 62 | 16 | CABG + AVR complicated by postoperative cardiopulmonary arrest | 104 | 26 | 2.5 iv | 0.1 | 0.2 |
| 6 | F | 73 | 16 | CABG complicated by perioperative myocardial infarction | 81 | 117 | 2.5 sc | 0.3 | 0.5 |
| 7 | F | 80 | 14 | CABG + AVR complicated by MODS | 14 | 31 | 2.5 iv | 0.6 | 0.6 |

*** Treatment with high volume continuous venovenous haemofiltration (HV-CVVH) was performed with a haemofiltration rate of 4000 ml/h resulting in a creatinine clearance of 67 ml/min; §Undetectable low anti-Xa activities. APACHE = acute physiology and chronic health evaluation; ICU = intensive care unit; CABG = coronary artery bypass grafting; MVP = mitral valve annuloplasty; MODS = multiple organ dysfunction syndrome; AVR = aortic valve replacement; anti-Xa = anti-factor Xa.**

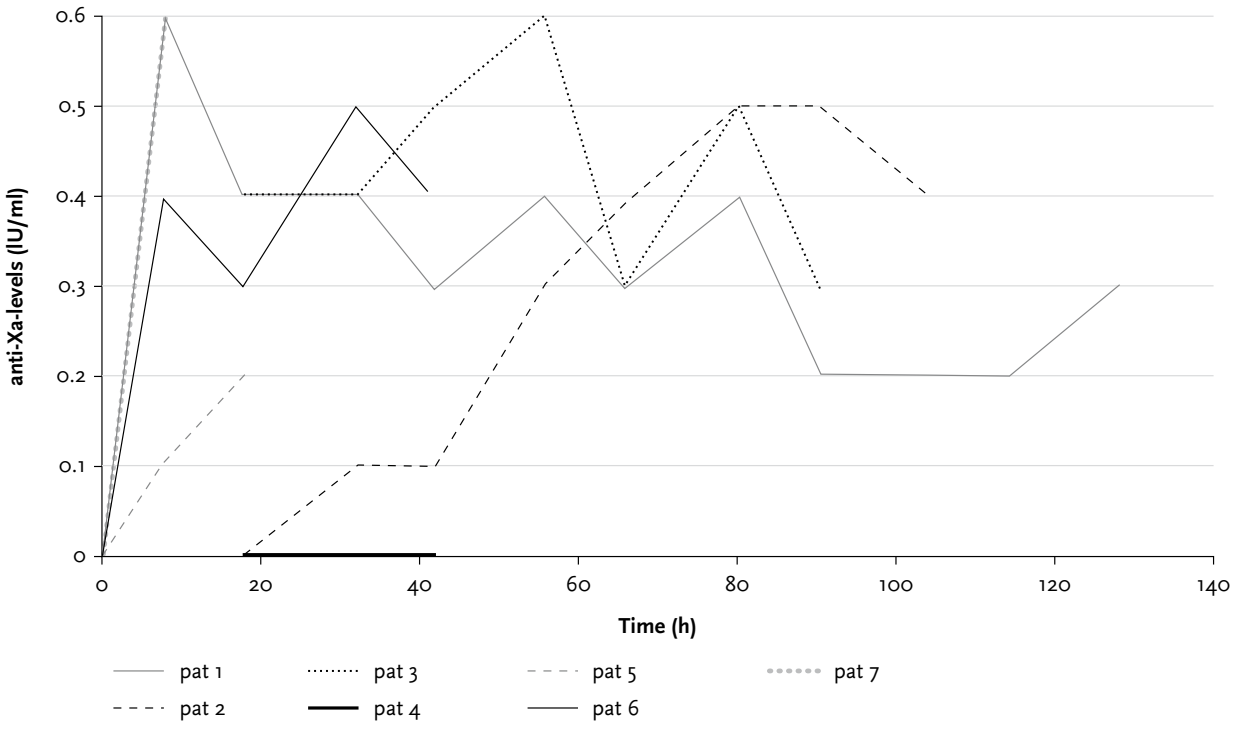
antibodies appeared to be absent in all patients. Five patients were classified as being unlikely of having HIT and two patients as having possible HIT. Thus, none of the patients needed continuation of treatment for proven HIT. Fondaparinux was stopped and replaced again by UFH or nadroparin.

The platelet count recovered in five patients and did not recover in two patients, both of whom died. One patient died in the ICU due to refractory septic shock with multiple organ failure. The other patient died of postanoxic encephalopathy after readmission to the ICU because of a cardiopulmonary arrest due to late postoperative right haematothorax during UFH therapy following re-CABG and mitral valve annuloplasty. The maximal platelet count in the ICU during UFH or nadroparin therapy before fondaparinux bridging therapy was 146 ± 151 x 10$^9$/l (mean ± standard deviation), the platelet count decreased to a nadir of 42 ± 35 x 10$^9$/l in 2 to 5 days, and recovered during fondaparinux bridging therapy followed by UFH or nadroparin to 151 ± 91 x 10$^9$/l in 2 to 9 days (repeated measures ANOVA: p=0.078).

The duration of treatment with fondaparinux was 1.8 to 6.5 days. In one patient treated with a lower dose of fondaparinux of 1.25 mg/day, ordered by the responsible intensivist because of earlier postoperative bleeding complications, anti-Xa levels were undetectable. In the other six patients receiving 2.5 mg/day, anti-Xa levels varied from 0.1 to 0.6 IU/ml. Anti-Xa activities showed an initial peak followed by a decrease suggesting that accumulation of anticoagulant activity did not occur (*figure 1*). We found negative correlations between creatinine clearance and mean anti-Xa-levels (r=-0.86, p=0.028) and between creatinine clearance and maximum anti-Xa-levels (r=-0.77, p=0.072). No TEC occurred. In two patients overt minor bleeding occurred with anti-Xa levels of 0.4 IU/ml in both. A total of 17 units of erythrocyte concentrate, two units of plasma and two units of platelet concentrate were administered in 21 fondaparinux treatment days.

The duration of treatment with UFH and nadroparin per patient varied from 2.0 to 26.9 days with in total 56.8 treatment days. No TEC occurred. In four patients,

**Figure 1.** *Anticoagulant activity during short-term low-dose fondaparinux*




**Vertical axis (Y-axis): anti-Xa levels (IU/ml); horizontal axis (X-axis): time (h); t=0 blood sample drawn before start of fondaparinux treatment, all other blood samples drawn at 08.00 and 18.00 hours during treatment with fondaparinux).**

five episodes of major bleeding occurred during the treatment episode before fondaparinux bridging therapy. In two patients, two episodes of major bleeding occurred during the treatment episode after fondaparinux bridging therapy. A total of 61 units of erythrocyte concentrate, 36 units of plasma and 11 units of platelet concentrate were administered in the treatment episode before fondaparinux bridging therapy. A total of ten units of erythrocyte concentrate, one unit of plasma and no units of platelet concentrate were administered in the treatment episode after fondaparinux bridging therapy.

There was a significant difference in number and severity of bleeding complications between the episode of anticoagulation with UFH or nadroparin before the start of fondaparinux bridging therapy and the episode of anticoagulation with fondaparinux (5 major and 0 minor bleeds *vs* 0 major and 2 minor bleeds: Fisher's exact test p=0.048). No significant difference was found between the episode of anticoagulation with fondaparinux and the episode of anticoagulation with UFH or nadroparin after fondaparinux bridging therapy. Transfusion requirements during the three different episodes of anticoagulation did not differ significantly for erythrocyte concentrates, fresh frozen plasma and platelet concentrates (repeated measures ANOVA: p=0.16, p=0.24 and p=0.16, respectively).

## DISCUSSION

Heparin-induced thrombocytopenia is a rare disease and is characterised by the development of thrombocytopenia during treatment with heparin coagulants. The low platelet count is the result of immune-mediated platelet activation and aggregation caused by antibodies directed at the heparin-platelet factor 4 complex. The HIT antibodies are also directed against the heparan sulphate-platelet factor 4 complex in the endothelial glycocalyx resulting in the release of subendothelial tissue factor, which strongly activates the coagulation cascade. So HIT exerts a strong procoagulant state with a high risk of life-threatening venous and arterial thromboembolism. When HIT is seriously suspected, all heparin anticoagulants should be stopped and treatment with nonheparin anticoagulants should be started.

In this small cohort of critically ill patients with thrombocytopenia suspected of HIT, awaiting the laboratory test results to make a final diagnosis of HIT, short-term bridging therapy with fixed low-dose fondaparinux (2.5 mg/day) resulted in anticoagulant activities in the prophylactic and therapeutic range as measured by anti-Xa levels. Although impairment of endogenous creatinine clearance was associated with higher mean and maximum anti-Xa levels, no accumulation of anticoagulant activity was

detected. Dose reduction of the initial treatment to 1.25 mg/day resulted in undetectable anti-Xa levels in one patient. No TEC occurred during treatment with fondaparinux and treatment with UFH or nadroparin before and after fondaparinux bridging therapy. Despite low platelet counts, overt bleeding was only minor during fondaparinux treatment. We found a significant difference in the number and severity of bleeding complications during treatment with UFH or nadroparin before the start of fondaparinux bridging therapy, but this may well reflect surgery-related bleeding complications. Transfusion requirements did not differ substantially between the different anticoagulation episodes.

Our observation has limitations. Firstly, the small sample of patients limits firm conclusions on the clinical efficacy and safety of bridging therapy with fondaparinux. Large prospective investigations have to elucidate the clinical efficacy and safety of short-term fixed low-dose fondaparinux bridging therapy. Secondly, all patients tested negative for the presence of HIT antibodies and thus HIT was an unlikely cause of the development of thrombocytopenia. The blood samples for HIT antibody testing may have been drawn too early to detect the development of HIT antibodies and repeat testing was not performed. Clearly, other explanations for the low platelet count were present as well, such as loss of platelets due to massive haemorrhage and consumption of platelets due to disseminated intravascular coagulation and treatment with extracorporeal and intravascular devices.[29-31] Sustained treatment with fondaparinux in critically ill patients with proven HIT deserves to be investigated and its anticoagulant activities and clinical efficacy and safety need to be determined. Thirdly, the optimal target for therapeutic anti-Xa levels is unknown. Ideally, target anti-Xa levels should reflect levels of anticoagulation for adequate prevention or treatment of TEC due to HIT at the lower level balanced by a safe treatment with nonheparin alternative anticoagulants without increased bleeding risk at the higher level. Anti-Xa levels between 0.30 and 0.50 IU/ml may be adequate therapeutic target values.

In conclusion, fixed low-dose fondaparinux bridging therapy in critically ill patients suspected of HIT, awaiting definite diagnostic classification, can lead to therapeutic anticoagulant activity. To reduce the risk of bleeding, we ideally advocate determination of anti-Xa levels to detect possible accumulation of anticoagulant activity, especially in patients with renal insufficiency. In daily clinical practice in the ICU, suspicion of HIT occurs regularly leading to the need to make important diagnostic and therapeutic decisions. A possible role for bridging therapy with low-dose fondaparinux in this complex clinical context remains to be elucidated in future investigations.

## PRESENTATION

The content of this article was presented at the 17th Annual Congress of the European Society of Intensive Care Medicine, 10 to 13 October 2004, Berlin, Germany and was published as an abstract in Intensive Care Medicine (Koole MA, Wester JPJ, Bosman RJ, et al. Efficacy and safety of fondaparinux sodium in the critically ill. Intensive Care Med 2004; 30(Suppl1): S88,P332).

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CASE REPORT

# Embolisation of hydatid cysts in the pulmonary artery presenting with haemoptysis

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## ABSTRACT

**A 49-year-old female patient who had undergone surgery for hepatic echinococcosis five years previously was admitted with haemoptysis. MRI angiography showed total occlusion of the left inferior pulmonary artery. Echocardiography showed no pulmonary hypertension. The patient underwent pneumonectomy and cysts in the left pulmonary artery were observed. Pulmonary artery involvement should be considered in patients who have undergone hepatic cyst surgery if haemoptysis is the first presenting symptom, especially in endemic regions for hydatidosis.**

## KEYWORDS

Hydatid disease, pneumonectomy, pulmonary arteries, pulmonary embolism

## INTRODUCTION

Hydatid disease, resulting from the larval stage of *Echinococcus granulosus* in the intermediate host, develops in the liver in 60% of cases and in the lungs in 25%. The heart is the most common site in the cardiovascular system (0.02 to 2%). Most common cardiac localisations are the left ventricle wall (60%), followed by the right ventricle (10%), pericardium (7%), atrium (6%) and interventricular septum (4%).[1] Pericardial complications have only been reported in 2.1% of pulmonary hydatid cysts.[2] Hydatid cysts may seldom develop within pulmonary arteries after ruptured cardiac or hepatic cysts. We report a patient with multiple hydatid cysts within the pulmonary arteries that necessitated left pneumonectomy. We believe that there are no previous reports of similar patients treated by lung resection in the literature.

## CASE REPORT

We present a 49-year-old female patient with haemoptysis. Her past history revealed surgery for a hepatic hydatid cyst five years previously, which was performed elsewhere. Physical examination was unremarkable except for rales on the left lung. Chest X-ray revealed left hilar enlargement, and a right paracardiac pulmonary nodule. Chest CT disclosed a cystic mass lesion lying within and obliterating the left main pulmonary artery, widespread tubular dilatation and peribronchial thickening in the left lower lobe bronchi and two small nodules in the right lower lobe. Chest MRI revealed septated cystic lesions in the left main pulmonary artery and MRI angiography showed an amputed left inferior pulmonary artery (*figure 1*). Ventilation-perfusion lung scan confirmed a perfusion defect in the left lower lobe. Echocardiography was normal. The patient underwent left pneumonectomy for irreversible pulmonary arterial wall and parenchymal destruction under total circulatory arrest. Numerous intact or ruptured hydatid cysts were observed on dissecting the pulmonary artery (*figure 2*). The intimal destruction was prominent in the dilated and thinned pulmonary artery wall. Albendazole treatment was given to the patient for the remaining small cysts on the right side. The patient was free of symptoms after eight months of follow-up.

## DISCUSSION

The establishment of hydatid cysts within pulmonary arteries is usually the result of pulmonary embolisation, the source of which is either a cardiac or rarely a hepatic cyst. Cardiac cysts, especially those localised on the right side, are identified as a clinical entity because of the severe preoperative and intraoperative complications.[3] The rupture of right-sided cardiac cysts is responsible for the pulmonary artery localisation of hydatid cysts.[4] The majority of

**Figure 1: A.** *Chest MRI scan showing septated cystic lesions (white arrow) in the left main pulmonary artery.* **B.** *MRI angiography showing total occlusion of the left inferior pulmonary artery.*

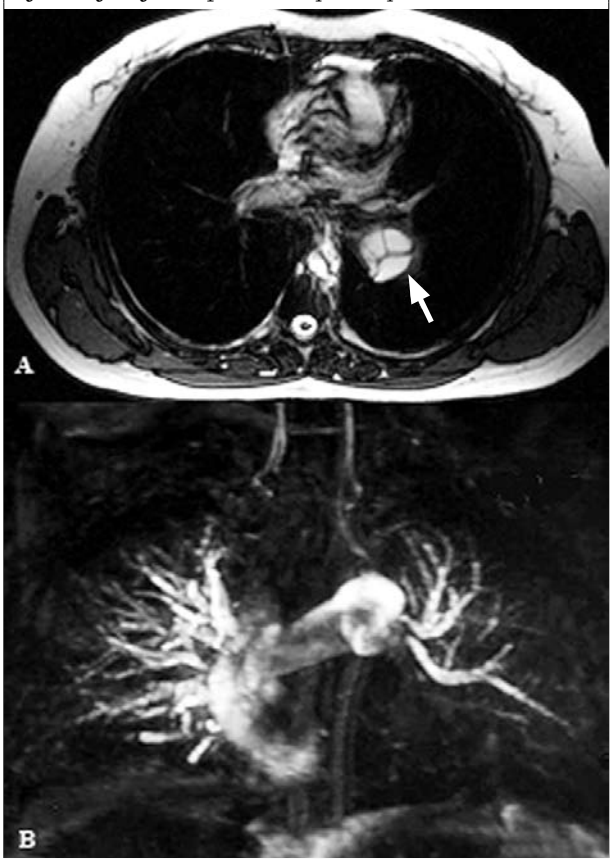
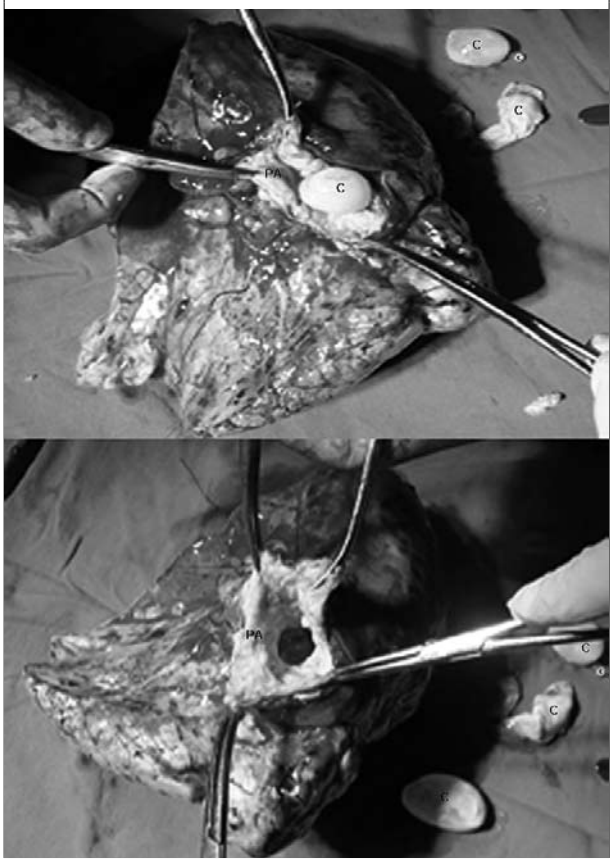



**Figure 2:** *Numerous intact or ruptured hydatid cysts (C) within the pulmonary artery (PA) after pulmonary artery dissection in resected specimen.*




pulmonary hydatid cysts are secondary cysts that arise from pulmonary embolisation of ruptured hepatic cysts near the hepatic vein or the neighbouring inferior vena cava. In these cases, the rupture site is very small and even contrast cavography fails to visualise the site. If the rupture is extensive, the embolism may be massive and thus fatal. Such intraoperative rupture examples have been reported in the literature.[5] Wherever the primary focus, hydatid cyst embolism into the pulmonary artery is rarely encountered. In our patient, it is obvious that the primary origin is the liver. Hydatid embolism is clinically classified into three groups: 1) acute fatal cases, 2) subacute pulmonary hypertensive cases that result in death within a year after diagnosis, and 3) chronic pulmonary hypertensive cases.[6] Our case was totally different from those previously described in that no pulmonary hypertension was determined, although the left lower lobe parenchyma was affected and the main pulmonary artery showed fusiform dilatation due to intimal degeneration. The hydatid obstruction was entirely caused by the cysts or daughter vesicles without accompaniment of any clotting or local thrombosis.

Morbidity is due to cyst rupture with or without anaphylaxis, cyst infection, obstruction caused by progressive growth of the cyst and/or the dysfunction of involved organ. Sudden deaths have been reported among asymptomatic cases and even during hydatid surgery.[5] Such patients may be asymptomatic for a long time since the cyst grows slowly within pulmonary artery and thus pulmonary perfusion is maintained via the bronchial arteries. Both spiral CT and MRI angiography clearly disclose cystic occlusion of the pulmonary artery and its branches as happened in our case.[4-7] Surgical intervention is the primary treatment. Embolectomy and/or enucleation are often the preferred surgical options. Off-pump surgery is mandatory except for distal localisations in the pulmonary artery and its branches.[1-7] The degree of the degenerative changes in the arterial wall, proximal or distal localisations of the pulmonary artery occlusion and irreversible parenchymal changes are the factors influencing selection of the operative procedure. We were obliged to perform pneumonectomy in this patient since the hydatid emboli adherent to the artery had caused downward aneurysmatic dilatation beginning from the proximal part of left main pulmonary artery as

a result of intimal degeneration and leading to chronic pulmonary destruction. By-pass surgery was preferred to prevent hydatid dissemination to the contralateral lung. As the disease occurred after hepatic surgery, it is clear that during surgery to remove hepatic hydatid cysts located deep or within the neighbourhood of hepatic venous structures, the following measures should be taken to avoid a situation such as in our case: 1) inferior vena cava should be clamped; 2) no hepatic traction should be performed and when needed cavo-caval by-pass may be carried out; 3) interventional procedures (by gastroenterologists or radiologists) should be avoided, and 4) surgery should be performed in centres where extracorporeal surgery is possible.[5] Such patients should be treated with albendazole due to the disseminated hydatidosis.[7]

In conclusion, although it is rare, pulmonary artery involvement must be taken into consideration in patients who have undergone hepatic cyst surgery if haemoptysis is the first presenting symptom, especially in endemic regions for hydatidosis.

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CASE REPORT

# Intact germinal layer of liver hydatid cysts removed after administration of albendazole

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## ABSTRACT

**Background: Hydatid disease is a common health problem especially in Mediterranean and sheep-farming countries, caused by infection with the metacestode stage of the tapeworm *Echinococcus*. The liver is the most frequent primary site of *Echinococcus granulosus* infection in humans. Surgery remains the main treatment modality for cystic hepatic hydatid disease, with complete resection of the germinal layer being of major importance for recurrence. Perioperative administration of albendazole has been reported to improve surgical outcome but the results are controversial. We report here our observations on the usefulness of preoperative chemotherapy in surgical outcome in terms of morbidity and recurrence.**

**Methods: Five patients with complex liver hydatid cysts received 28 days of albendazole prior to partial cystectomy. Radiological examinations with computed tomography and ultrasound and surgical outcome were used to assess the efficacy of the regimen.**

**Results: Three patients underwent a complete removal of the germinal layer of the cyst and there were no cases of biliary fistula in these patients. There were no relapses in any of the patients at 12 months' follow-up.**

**Conclusions: Preoperative use of medical therapy consisting of albendazole facilitates complete resection of the germinal layer by detaching it from the laminar layer, thus reducing not only the recurrence rates but also the postoperative complications, especially bilious fistulas.**

## KEYWORDS

Liver hydatidosis, albendazole, biliary fistula

## INTRODUCTION

Echinococcal cystic disease is caused by infection with the tapeworm *Echinococcus granulosus*. In the liver, the most frequent primary site, an active cyst wall consisting of an innermost single cell germinal layer (endocyst) and a thicker gelatinous laminar acellular layer (ectocyst) is formed. An outermost reactive fibrous layer of liver parenchyma, called the pericyst, surrounds the active cyst. The germinal layer produces the hydatid fluid and small secondary cysts known as brood capsules. Protoscolices are produced within the brood capsules over time. The detached brood capsules and protoscolices form the hydatid sand, with potential infectious features. Fragmentation of the germinal layer and brood capsules results to the daughter cysts.[1,2]

Surgery is the mainstay of treatment for cystic hepatic disease. Surgical options include the radical operations of hepatectomy and pericystectomy and the more conservative ones such as partial cystectomy.

The ideal surgical procedure should effectively deal with the parasite and the residual cavity with the minimal morbidity and mortality.[3] There is a continuing debate over the appropriate surgical procedure for the treatment of hepatic echinococcal disease, and the role of antiparasitic chemotherapy as an adjunct to surgery has not been clarified either.

We report on the surgical outcome of five patients with complex echinococcal cysts of the liver who received albendazole preoperatively, followed by computed tomography evaluation of the cyst status prior to surgery. Furthermore, based on our findings, we advocate that preoperative administration of antiparasitic chemotherapy facilitates the surgical treatment and possibly reduces postoperative complications, particularly biliary fistulas.

## MATERIAL AND METHODS

From 2003 to 2005 five patients, three men and two women, presented with liver hydatid disease. All five cases had either complex or relapsing hydatid cysts. The diagnosis was based on radiological imaging and clinical history, while serological tests were also performed.

Informed consent was acquired from all patients. Afterwards, albendazole was administered for a specific period of 28 days, at a dose of 10 mg/kg/day, orally, in two doses a day. Evaluation of the medical treatment was performed by radiological investigation with abdominal CT scan prior to surgical intervention. Complete blood count analysis and liver function tests were assessed weekly.

The surgical procedure performed in all these patients was partial cystectomy. After isolation of the cyst with gauzes irrigated with 25% NaCl solution, the cyst was punctured with a trocar suction device. The cyst was then filled with 25% NaCl solution and reaspirated. The contents of the cyst were removed with forceps, suction or a spoon and afterwards the germinal layer was removed with forceps. The cyst cavity was again filled with the scolicidal solution. Finally the cyst cavity was inspected for bile leaks that are oversewn. We did not perform any obliteration of the cyst cavity and two drains were inserted before abdominal closure. A latex drain was positioned inside the cyst cavity and a Jackson-Pratt drain was placed in the proximity of the lesion.

The cyst contents were sent for pathological evaluation, which verified the diagnosis. However, no assessment of the germinal layer or scolices viability was performed.

Radiological examinations evaluated the status of the germinal membrane, with the detachment of the membrane as the sign of good response to medical therapy. Other objective evidence of cyst response to chemotherapy, such as solidification or calcification, disappearance of the cyst, egg shell-like calcification of cyst wall, improved volumetric reduction, splitting or floating signs were also recorded.

Finally, complications in the 30 days after surgery were recorded and follow-up examination was performed at 12 months postoperatively.

## RESULTS

The mean age of our patients was 68 years, with a range from 47 to 78 years (*table 1*). Clinical findings included upper abdominal pain or palpable mass and hepatomegaly. Fever and loss of appetite were accompanying symptoms. The cysts averaged 8.3 cm in diameter, ranging from 7 to 12 cm (*table 1*). No patients discontinued treatment due to drug side effects such as abdominal pain, nausea, vomiting, and increased hepatic transaminases.

The cysts were located in the right lobe in two patients and in the left lobe in one patient. Both liver lobes were affected in two of the patients. Three cases had a single cyst while multiple cysts were documented in the others (*table 1*).

After completion of the medical treatment, computed tomography showed partial detachment of the germinal layer in three of our patients (*figure 1*). Other radiological evidence implying cyst response to chemotherapy was not observed. These findings are to be expected since calcifications are usually seen after three months of successful treatment and changes in size are evident with even more prolonged regimens.[4]

There was no radiological evidence of response to medical treatment in the other two patients.

During surgery complete removal of an intact germinal layer was performed in three patients (*figure 2*) while in the remaining two patients the germinal layer was partially removed by repeated traction with forceps and forceful evacuation with a spoon.

There were no biliary fistula recorded in the patients with the intact removal of the germinal layer, while in one patient with partial removal of the germinal layer a low output biliary fistula (>50 ml bile per day) was evident on the fourth postoperative day. Resolution of the bile leak was

**Table 1.** *Summary of observations*

| No. | Age | Cyst size | Location segments | Number of cysts | Preoperative, postchemotherapy CT findings | Intraoperative observations | Complications | Recurrence 12 months |
|---|---|---|---|---|---|---|---|---|
| 1. | 47 | 7x5<br>4x3 | IV, V, VIII | 2 | Partial detachment of the germinal layer | Complete removal of the germinal layer | Infection | No |
| 2. | 76 | 12x8 | IV, V, VIII | 1 | Partial detachment of the germinal layer | Complete removal of the germinal layer | Atelectasis | No |
| 3. | 65 | 8.3x6<br>3.5x3<br>4,5x3 | VII, VIII | 3 | No | Partial removal of the germinal layer | No | No |
| 4. | 78 | 7.8x5 | III | 1 | Partial detachment of the germinal layer | Complete removal of the germinal layer | No | No |
| 5. | 68 | 8.6x4,2 | V,VIII | 1 | No | Partial removal of the germinal layer | Biliary fistula | No |

**Figure 1.** *Abdominal computed tomography demonstrates partial detachment of the germinal layer of a liver hydatid cyst in a patient after 28 days of preoperative administration of albendazole*

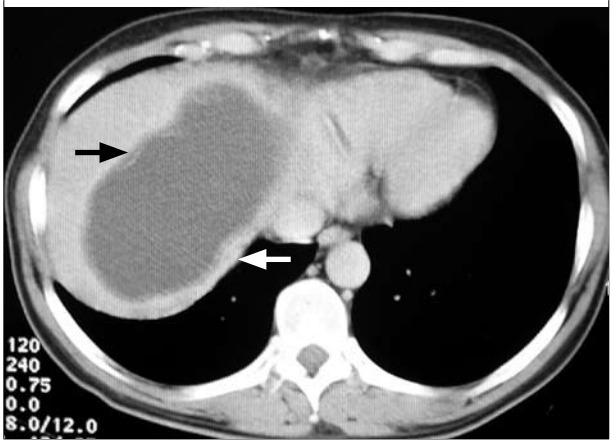
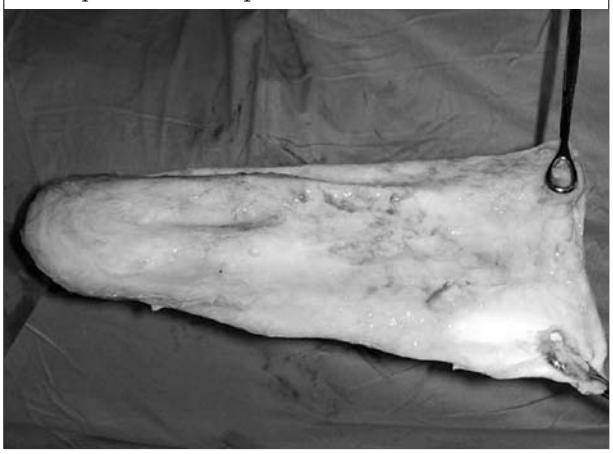



**Figure 2.** *Intact removal of the germinal layer of the liver cyst in the same patient*



accomplished after the insertion of a nasobiliary catheter on the 13th postoperative day.

Infection of the residual cyst complicated the progress of a patient with intact removal of the germinal layer which was successfully treated by removal of the drain and antibiotics. We attributed this complication to the presence of a long-standing foreign body (drain) inside the cyst cavity, since repeated ultrasound examinations failed to show any fluid collections and the infection resolved with removal of the drain.

There were no relapses at 12 months of follow-up.

## DISCUSSION

Chemotherapy consists of the benzimidazoles, mebendazole and albendazole. Benzimidazoles inhibit the assembly of tubulin into microtubules, thus impairing glucose absorption through the wall of the hydatid parasite. This causes glycogen depletion and degeneration of the endoplasmic reticulum and mitochondria of the germinal layer of the metacestode, and results in an increase in lysosomes and subsequent cellular death.[5,6] However, recurrence rates after medical treatment alone can be as high as 80%, rendering this option nonviable as sole therapy.[7,8] Thus, it should be used only as a supplementary therapy, in combination with a drainage procedure, either surgery or the PAIR procedure.

With regards to cystic liver disease, chemotherapy is indicated for patients unfit for surgery, when there is difficulty in reaching the lesion, if patients refuse to undergo surgery, advanced age, pregnancy, severe comorbidity, multiple cysts difficult to access, dead cysts either partially or totally calcified, very small cysts, and in some highly endemic regions where waiting lists are long and there is a lack of adequate medical facilities or experienced staff.[9,10]

Medical therapy is also combined with surgery to preoperatively decrease the size of the cysts and reduce postoperative recurrences.[11,12]

Albendazole is more effective than mebendazole, because its pharmacokinetic profile leads to higher serum and cyst fluid concentrations.[13] It has been also used pre- and postoperatively to avoid relapses in case of both multiple and large cysts.[4-14] The success of the treatment is based upon the capacity of the drug to operate on the germinal layer and the protoscolices of the hydatid cyst interior at adequate concentrations for sufficient periods. Albendazole sulphoxide penetrates the cyst membrane and reaches the hydatid fluid, being calculated at 13 to 22% of the serum concentration.[13] Thus, parasite structures, protoscolices, and germinal layer are reached by albendazole's active form.[15,16] However, efficacy seems to be correlated more with the duration of therapy than with the serum or cyst levels achieved.[6]

Although the majority of the reports state that preoperative administration of albendazole reduces the recurrence of the cystic echinococcal disease,[11,12,17-19] in the report by Mentes *et al.* albendazole pretreatment failed to show any advantage.[20] Furthermore, reports addressing cyst and protoscolice viability provided conflicting data. Firstly, Moris *et al.* reported that 10 mg/kg/day for a month resulted in sterilisation of 93.75% of the cysts studied.[21] Additional reports support these findings.[11,12,22] When viability is assessed by radiological appearance, albendazole therapy leads to an improvement in the appearance of the cyst in approximately 75 to 85% of patients.[23-27] On the other hand, Manterola *et al.* reported only a 40% success rate for the preoperative regimen in sterilising the cyst.[28,29] He has also reported that there was no association between the concentration of albendazole in the hydatid fluid and the viability of the scolices.[29]

The optimal duration of the drug is also controversial. Preoperative treatment with albendazole, ranging from one to three months in duration, has been clearly shown to reduce recurrence when cyst spillage, partial cyst removal or biliary rupture has occurred.[11,17] Although in the majority of reports albendazole is administered for a month or longer,[11,18,30] successful results have been documented with shorter periods in association with the PAIR procedure.[31,32]

So, to achieve improved results, the combined preoperative chemotherapy of albendazole and praziquantel seems promising.[33] Cobo *et al.* used the combination regimen in 26 patients and compared the results with albendazole monotherapy.[34] They found that the combined treatment resulted in significantly higher sterilisation rates and higher albendazole sulphoxide levels in the serum and the cyst fluid than monotherapy. Moreover, the combination regiment did not show higher morbidity than monotherapy.

Albendazole has low toxicity and no apparent cumulative effect, thus is considered safe and effective. In systemic administration, the side effects are minimal, dose-dependent and reversible.[4,18] Haematological toxicities and hepatic dysfunction are the most frequent and serious side effects. Gastrointestinal symptoms (nausea, abdominal pain), alopecia and rash may develop. None of the patients in our series discontinued treatment due to drug side effects, but in more prolonged regimens close monitoring of haematological parameters and hepatic function is essential.[29]

Surgery is the mainstay of treatment, with unroofing (partial cystectomy) and external drainage of the cyst the most frequently performed technique. Apart from partial cystectomy, total pericystectomy and hepatic resections are commonly performed surgical procedures. The goals of surgery in hydatid disease are to inactivate the cestode parasites, evacuate the cyst cavity, remove the germinal layer, and obliterate the residual cavity.[35] An overall recurrence rate of 4.5% at a median of 4.5 years, regardless the surgical technique followed, has been reported.[36] Disadvantages of cyst drainage include spillage into the peritoneal cavity, causing a high rate of recurrence, bleeding and damage to bile ducts in close proximity to the cyst wall, as the cyst's contents are manually removed. These complications constitute potential risks, especially in case of complex hydatid liver cysts, such as those >10 cm in diameter, especially if associated with multiple daughter cysts, superficially located single cysts at high risk of rupture and complicated cysts such as those accompanied by infection, compression or obstruction. Completing resection of the whole germinal layer without any spillage is obviously of major importance to reduce the recurrence rate.

We advocate that preoperative use of albendazole facilitates complete resection of the germinal layer by detaching it from the outer cover of the ectocyst. In three out of five patients, ultrasound and abdominal CT scan conducted after completion of the medical therapy, just before surgical intervention, clearly showed detachment of the germinal from the laminar layer. Moreover, we advocate that albendazole also acts by lessening tension and detaching the germinal layer for easier cyst removal.[12,16] Thus, during unroofing and drainage of the cysts, complete resection of the germinal layer as a whole was achieved without any spillage or partial excision. Furthermore, complete and easy removal of the germinal layer helps to prevent rupture of the small biliary ducts in close proximity to the pericyst and thus postoperative biliary leakage. No external biliary fistulas were observed in these three cases where complete excision of the germinal layer was accomplished. Thus, we suggest that further studies should be conducted to ascertain whether preoperative administration of albendazole or combined with praziquantel, reduces morbidity, especially the postoperative rate of persistent postoperative biliary fistula and recurrences.

If established, this fact could be explained by the detachment of the germinal from the laminar layer of the cyst due to albendazole action that facilitates its excision without rupture of minor biliary ducts adjoining the pericyst.

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CASE REPORT

# Ruptured hydatid cyst following minimal trauma and few signs on presentation

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## ABSTRACT

**Hydatid disease is a parasitic infection caused by *Echinococcus granulosus* characterised by cyst formation in any organ, although the liver is the most commonly involved. Hydatid cysts can rupture either spontaneously or following trauma. Surgical treatment can be life-saving. This paper reports the atypical presentation of a young girl admitted to the emergency department. She presented with pain on her palms due to falling down a few steps. Because of the rebound tenderness on the right upper quadrant of her abdomen on physical examination, bedside ultrasonography was performed to identify the underlying cause, and promptly revealed a 62 x 72 mm lobular cyst on the right lobe of the liver with free fluid in the subcapsular area. Shortly afterwards, urticaria developed. Fluid resuscitation, methylprednisolone and diphenylhydramine were administered intravenously. Afterwards she was taken to the operation room for unroofing, drainage and capitonage. In conclusion, primary care and emergency physicians should perform a complete physical examination on all admitted patients with vague symptoms and a high index of suspicion for a ruptured hydatid cyst, even following trivial trauma, especially in endemic regions.**

## KEYWORDS

Bedside ultrasonography, hydatid cyst, rupture, presentation

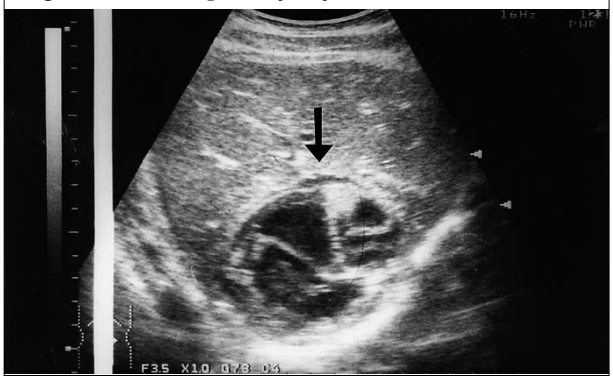
## INTRODUCTION

Hydatid cyst is an infection of *Echinococci* and still represents a serious problem in endemic regions, especially in the Middle East, Mediterranean countries and Australia. It is a parasitic infestation caused by the larval stage of *Echinococcus granulosus* and develops by passing eggs from the excreta of infected dogs. The cyst enlarges slowly and is generally asymptomatic until it reaches a certain size, shows a space-occupying effect or ruptures. Rupture of cyst can occur spontaneously or during surgery as well as due to trauma. Rupture by minor trauma is very rare and can produce anaphylactic reactions and fatal anaphylaxis. We describe a patient who after minimal trauma presented to the emergency department with scant physical signs.

## CASE

A 18-year-old girl was admitted to the emergency department after falling down only a few steps from the stairs of the library, 10 to 15 minutes previously. She only complained of pain on the palms of her hands and stated that she had vomited once. On presentation, her Glasgow Coma Scale score was 15, blood pressure 110/80 mmHg, pulse rate 108 beats/min and temperature was 37 °C. Her physical examination was normal except for mild rebound tenderness on the right upper quadrant of her abdomen. White blood cell count was 18,100/mm$^3$, eosinophilia was absent and the other laboratory tests were within normal limits. The bedside ultrasonography revealed a 62 x 72 mm lobular cyst on the right lobe of the liver and free fluid in

**Figure 1.** *Extracapsular free fluid*



the subcapsular area (*figure 1*). Approximately 10 minutes after presentation, general urticaria developed and it was progressive. Fluid resuscitation, methylprednisolone and diphenylhydramine were administered intravenously. Meanwhile, adrenaline was prepared to administer in case she needed it. She vomited again when she was being examined for abdominal sensitivity and rebound tenderness, and the area of urticaria increased. The patient turned out to have a rupture of a hydatid cyst and she was immediately taken to the operating room by the general surgeons. Unroofing, drainage and capitonage of the cyst were performed during the operation. She was started on 10 mg/kg/day of albendazole for six months and discharged after one week without any complications or sequelae.

## DISCUSSION

Hydatid cysts result from infection by the parasite *E. granulosus,* and dogs are the definitive host. It is commonly located in the liver; however, it can be found in lungs or in any organ.[1] As the cyst of the echinococcus enlarges slowly and is generally asymptomatic, hydatid cysts undergo progressive enlargement and may eventually rupture[1-15] or spread into the bloodstream without rupture.[2]

Generally, in patients admitted with complications as anaphylaxis[1,3-7] due to rupture, the findings clearly indicate the organ involved; sudden death often occurs.[2,8,9] However, there are no reports of ruptured hydatid cyst with an unclear presentation.

Rupture of hydatid cyst is very rare and can occur spontaneously or iatrogenically,[3,4] following serious injuries[1-15] or even minor trauma as in our paper. Falls are reported to be the most common mechanism of trauma.[10] Also, rupture of hydatid cysts attributed to sporting activities and blunt trauma have been reported.[10,11] Cysts may rupture into the peritoneal or pleural cavity, into the pericardium, the bile ducts, the gastrointestinal tract or even into blood vessels.[1,2,9-11,14,15] Although computed tomography has a sensitivity of 100% in demonstrating cyst rupture, ultrasound is more practical and inexpensive.[1,10,13] There is generally not much time before surgery as anaphylaxis is the most frequent cause of death in cases of hydatid cyst rupture.[1]

The present patient fell down only a few steps and on arrival to the emergency room was only complaining of her aching hands. If a complete physical examination had not been performed, the vague abdominal sign of an uncertain, localised, positive rebound tenderness would not have been noted until her condition deteriorated due to the ruptured cyst. The ruptured hydatid cyst was identified by ultrasound. In this way, the patient could be treated very rapidly.

In conclusion, therefore, important prerequisites for the management of ruptured hydatid cysts are a high index of suspicion on routine complete physical examination and confirmation by ultrasound as early as possible, especially in endemic areas.

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PHOTO QUIZ

# Abdominal pain in a veterinarian with cysts in the liver

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A 44-year-old male veterinarian from the Kyrgyz Republic has been living in the Czech Republic for the last 18 months. He has a history of vomiting, nausea and epigastric pain which always lasted approximately one hour. The vomiting and epigastric pain worsened, and would persist for several hours, so he was hospitalised in May 2005. Physical examination revealed stable vital signs; the abdomen was soft with mild epigastric tenderness. Liver function tests showed elevated serum values: total bilirubin 32 mmol/l (range 0-20), alanine transaminase 3.65 μkat/l (range 0-0.8), aspartate transaminase 6.23 μkat/l (range 0-0.65), alkaline phosphatase 2.67 μkat/l (range 0-2.13), and γ-glutamyl transpeptidase 7.44 μkat/l (range 0-1.1). Other laboratory investigations were C-reactive protein 4 mg/l (range 0-8), white blood cells 6.3 x $10^6$/l (range 4.0-10.0), eosinophils 0.16 (range 0.00-0.05) and S-IgE total >2000 IU/ml (range 1.0-200.0).
Surgical examination ruled out any acute abdominal event.
CT scanning of the abdomen was performed (*figures 1* and *2*) which showed multiple multilocular septic cystoid lesions with large calcifications in the right liver lobe and lobus quadratus, cholecystolithiasis and one cyst in the core of the left kidney.

## WHAT IS YOUR DIAGNOSIS?

Is it possible to judge the diagnosis from the characteristics of the lesions?

**Figure 1.** *CT scan of the abdomen demonstrates multilocular cysts and large calcifications in the right liver lobe*

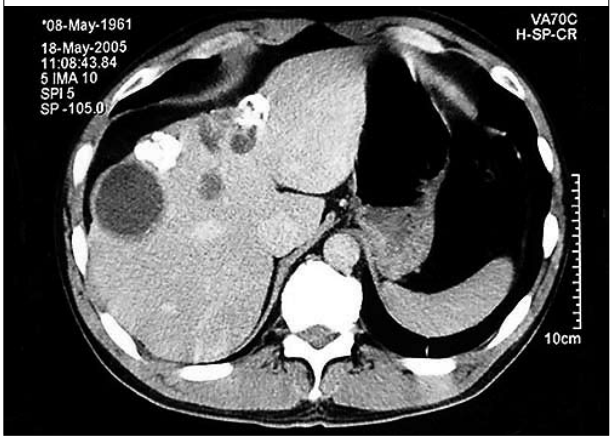
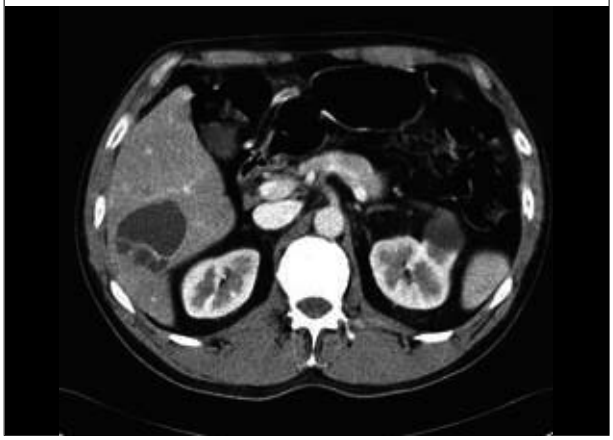



**Figure 2.** *CT scan demonstrates cystoid multiseptic lesion in the right liver lobe*



ANSWER TO PHOTO QUIZ (ON PAGE 119)

ABDOMINAL PAIN IN A VETERINARIAN WITH CYSTS IN THE LIVER

## DIAGNOSIS

The diagnosis is hydatid disease, with hypereosinophilia due to toxocariasis.

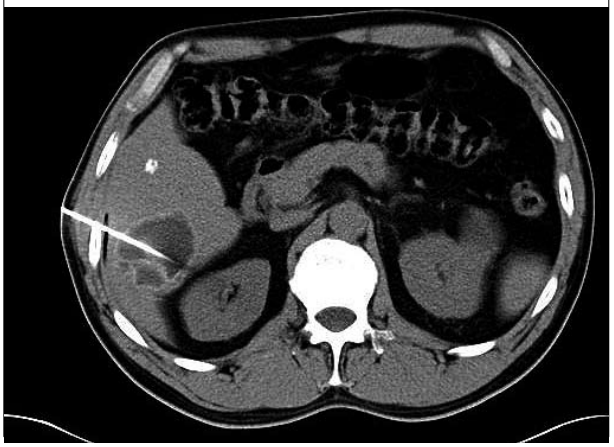
Hydatid disease (also known as cystic echinococcosis) is caused by the larval stage of the small tapeworm *Echinococcus granulosus*, whose primary host is the dog (particularly sheepdogs), and whose cysts mainly affect sheep. Humans are infected by the eggs that migrate from the gut to parenchymal organs, usually the liver and occasionally the lung, where they develop into cysts containing several tapeworm scolices. *E. multilocularis* tapeworm affects foxes (but can exist in dogs), and cysts are found in small rodents on which the foxes prey. This disease (alveolococcosis) is very aggressive, tumour-like and induces much more serious liver damage than cystic echinococcosis.[1,2]

Serological examinations were performed with the following results: positive values on hydatid disease (using ELISA and confirmation with haemaglutination reaction), positive values on toxocariasis and cysticercosis (ELISA in both). The patient was treated with albendazole at a dose of 400 mg twice daily for four weeks, and this was repeated three times, with two-weekly intervals between the courses. Liver and renal function were checked during the treatment. We saw a rapid normalisation of the elevated values of aminotransferases after starting the therapy, but alkaline phosphatase and γ-glutamyl transpeptidase were still moderately elevated. High values of eosinophilia (ranging between 0.21 and 0.25) persisted after the albendazole treatment and repeatedly positive serological examinations for toxocariasis made it possible to determine the concomitant diagnosis of toxocariasis. Toxocariasis is the most common cause of asymptomatic eosinophilia.[2] Eosinophilia is not usually seen in patients with hydatid disease,[1] moreover the therapy with albendazole is simultaneously efficacious in the treatment of toxocariasis. We interpret the positive titres for cysticercosis as a cross-reaction with hydatid disease, because both diseases are invasive cestode infections. We performed aspiration of the hydatid cyst in the liver after the first month of therapy (*figure 3*). The hydatid cyst did not contain fluid, so we could not instil ethanol into it, but we could also avoid major surgery. It might be important to mention that ethanol infusion is contraindicated in liver cysts if there is any possibility of a connection to the biliary tree.[3]

The CT findings (*figures 1* and *2*) are consistent with hydatid disease. Hydatid cysts at CT scanning are sharply limited and round; density is close to water (10-20 Hu) with masses in the cyst; the wall is thin. The cyst may be multilocular with internal septa representing the daughter cysts; calcifications can be present in the wall. Benign cysts are sharply, softly contoured, round or oval, with density close to that of water (10-20 Hu), with a thin wall, without internal septa, nonenhancement after administration of contrast medium intravenously. In polycystic liver disease there are multiple cysts of a low density (10-20 Hu); cysts are of different sizes, mostly up to 2 cm.

Pyogenic abscess: sharply limited, homogenous area with a density usually higher than in a benign cyst but lower than in a solid tumour (30-40 Hu), nonenhancement after administration of a contrast medium intravenously but a ring of tissue can be saturated on the periphery of the cavity more than in healthy tissue. A similar picture may be found also in solid, necrotic tumours.

**Figure 3.** *Aspiration of hydatid cyst in the liver*



Amoebic abscess: sharply limited, homogenous area with a density usually higher than a benign cyst but lower than a solid tumour (30-40 Hu). Saturation is not visible, even after administration of the contrast substance intravenously; however, the ring on the periphery of the cavity can be saturated. This saturation can be higher than the density of surrounding healthy tissue. A similar finding can occur in necrotic tumours.
Mycotic abscess: multiple, small, round lesions of low density, some lesions can have centrally increased density. The characteristic 'honeycomb' appearance on computed tomography scans was described recently in patients with *Burkholderia pseudomallei* liver abscesses.[4]

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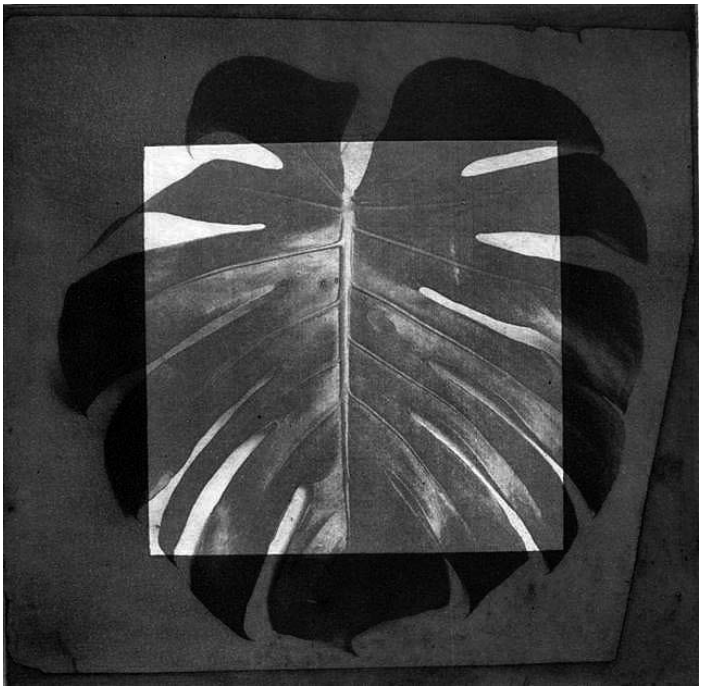
ABOUT THE COVER

# Monstera Deliciosa

**Caroline Koenders**



The technique used for this month's cover is called photopolymer intaglio. The artists creates an image on transparent material, referred to as the positive. This positive is then placed together with a photopolymer plate in an exposure unit to ultraviolet light for a special amount of time. After developing, it can be treated and printed the same way as an etching.
The image of this print is based on a photo taken of a leave from the plant Monstera Deliciosa. It is a recent work from a serial of botanical prints. This theme, like stones, shells and seeds, inspires the artist to work on for several years now. More work can be seen on her website: www.caroline.koenders.exto.nl.
A very limited edition (8) or the original print (size 50 x 65 cm) is available at the price of € 200 at Galerie Unita, Rijksstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands, e-mail: galerie-unita@planet.nl or on our website: www.galerie-unita.com.

## MONTHLY NJM ONLINE HITLIST

The table lists online hits for all articles published in the December issue of the Netherlands Journal of Medicine, 2006. This is based on analysis of our user log file on 6 February 2007.

| Article | Hits |
|---|---|
| EDITORIALS | |
| Thalidomide, treat with caution! | 132 |
| The Netherlands Journal of Medicine's hitlist: which 2004 paper was best cited? | 136 |
| REVIEWS | |
| SWAB guidelines for antimicrobial therapy of acute infectious diarrhoea | 167 |
| From Trousseau to angiogenesis: the link between the haemostatic system and cancer | 140 |
| ORIGINAL ARTICLES | |
| Application of guidelines on preoperative antibiotic prophylaxis in León, Nicaragua | 197 |
| The safety of electroconvulsive therapy in patients with asthma | 123 |
| CASE REPORTS | |
| Successful treatment of myelodysplastic syndrome-induced pyoderma gangrenosum | 140 |
| Thalidomide as treatment for digestive tract angiodysplasias | 156 |
| PHOTO QUIZ | |
| Right subclavian vein cannulation? | 135 |
| NOTE | |
| The blue rubber bleb nevus syndrome co-existing with celiac disease | 179 |
| **Total** | **1505** |

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

**Manuscripts**
Manuscripts submitted to the Journal should report original research not previously published or being considered for publication elsewhere. Submission of a manuscript to this Journal gives the publisher the right to publish the paper if it is accepted. Manuscripts may be edited to improve clarity and expression.

**Language**
The language of the Journal is English. English idiom and spelling is used in accordance with the Oxford dictionary. Thus: Centre and not Center, Tumour and not Tumor, Haematology and not Hematology.

**Submission**
All submissions to the *Netherlands Journal of Medicine* should be submitted online through Manuscript Central at http://mc.manuscriptcentral.com/nethjmed. Authors should create an account and follow the instructions. If you are unable to submit through Manuscript Central contact the editorial office at g.derksen@aig.umcn.nl, tel.: +31 (0)24-361 04 59 or fax: +31 (0) 24-354 17 34.

**Preparation of manuscripts**
Type all pages with double spacing and wide margins on one side of the paper. To facilitate the reviewing process, number the lines in the margin and the pages.
*Subheadings* should not exceed 55 characters, including spaces.
*Abbreviations*: Measurements should be abbreviated according to SI units. All other abbreviations or acronyms should be defined on the first appearance in the text. Use a capital letter for generic names of substances and materials.
A *Covering letter* should accompany the manuscript, identifying the corresponding person (with the address, telephone number, fax number and e-mail address). Conflicts of interest, commercial affiliations, consultations, stock or equity interests should be specified. In the letter one to three sentences should be dedicated to what this study adds. The letter should make it clear that the final manuscript has been seen and approved by all authors. All authors should sign the letter. The letter should either be submitted through http://mc.manuscriptcentral.com/nethjmed or faxed to the editorial office (+31 (0)24-354 17 34).

Divide the manuscript into the following sections: Title page, Abstract, Keywords, Introduction, Materials and methods, Results, Discussion, Acknowledgements, References, Tables and Figures with Legends.

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

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

*Keywords*: Include three to five keywords.

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

The *Materials and methods* should be sufficiently detailed so that readers and reviewers can understand precisely what has been done without studying the references directly. The description may be abbreviated when well-accepted techniques are used.

The *Results* should be presented precisely, without discussion.

The *Discussion* should directly relate to the study being reported. Do not include a general review of the topic, but discuss the pertinent literature.

*Acknowledgement*: All funding sources should be credited here. Also a statement of conflicts of interest should be mentioned.

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

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

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

Please note that all authors should be listed when six or less; when seven or more, list only the first three and add et al. Do not include references to personal communications, unpublished data or manuscripts either 'in preparation' or 'submitted for publication'. If essential, such material may be incorporated into the appropriate place in the text. Recheck references in the text against the reference list after your manuscript has been revised.
The use of bibliographic software programmes that are designed to generate reference lists such as Reference Manager© or Endnote© is highly encouraged. Authors can use the predefined output 'Vancouver' style from these programmes.

*Tables* should be typed with double spacing each on a separate page, numbered consecutively with Arabic numerals, and should contain only horizontal lines. Provide a short descriptive heading above each table with footnotes and/or explanation underneath.

*Figures* must be suitable for high-quality reproduction (>300 DPI). Submit line drawings made in Word or other computer programmes but not in a PowerPoint file. Colour figures are occasionally possible and will be charged to the authors.
*Legends for figures* should be typed, with double spacing, on a separate page.

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

**Mini reviews**
Mini reviews are concise notes that bring the reader up to date with the recent developments in the field under discussion. The review article should mention any previous important reviews in the field and contain a comprehensive discussion starting with the general background of the field. It should then go on to discuss the salient features of recent developments. The authors should avoid presenting material which has already been published in a previous review. The manuscript should be divided as follows: title page, abstract and main text. The text may be subdivided further according to the areas to be discussed. The text should not exceed 2500 words.

**Letters to the editor (correspondence)**
Letters to the editor will be considered by the editorial board. Letters should be no more than 400 words. Please use SI units for measurements and provide the references conform the Vancouver style (N Engl J Med 1991;324:424-8). No more than one figure is allowed. For letters referring to articles previously published in the Journal, the referred article should be quoted in the list of references.

**Photo quiz**
A photo quiz should not exceed 500 words and include no more than two figures and four references conform the Vancouver style. Abbreviations of measurements should be quoted in SI units.

**Book reviews**
The editorial board will consider articles reviewing books.

**Reviewing process**
After external and editorial review of the manuscript the authors will be informed about acceptance, rejection or revision. We require revision as stated in our letter.

**Proofs**
Proofs will be sent to the authors to be carefully checked for printer's errors. Changes or additions to the edited manuscript cannot be allowed at this stage. Corrected proofs should be returned to the editorial office within two days of receipt.

**Offprints**
These are not available. The first author receives a sample copy of the Journal with the published article.