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# The Journal of Medicine

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EDITORIAL

# Thalidomide, treat with caution!

**R.J. Powell**

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Thalidomide's unique properties are now being recognised and unravelled. Various new clinical applications are being reported and two case reports in this journal are a testament to this.[1,2]

In 1953, thalidomide was synthesised and designed into a drug by researchers at Chemie Grunenthal in West Germany. It was a novel therapeutic agent that failed to control epileptic fits as anticipated from animal studies. However, it caused such drowsiness that it was subsequently marketed as a sedative. Its promotion ironically emphasised its safety as overdoses in animal tests failed to cause fatalities. However, in 1960 the recognition of thalidomide's neuropathic potential, and a year later its devastating teratogenic effects, led to its product license being revoked in many countries around the world. However, its unique effects in erythema nodosum leprosum, a vasculitis that occurs during the treatment of leprosy with antilepromatous therapy, facilitated its continued availability, albeit on a very limited basis. Countries around the world have struggled to manage and monitor the usage of thalidomide and specifically the USA has felt it necessary to license thalidomide and now has very strict controls and monitoring in an attempt to prevent indiscriminate use (STEPS programme).[3] The UK guideline for the clinical use and dispensing of thalidomide[4] antedated the USA guideline and offered a more balanced approach to contraceptive measures; however, as the main thalidomide producer is based in America, the STEPS programme prevails.

On this background, the renaissance of this novel and powerful immunomodulatory agent has appropriately been in clinical areas where other drugs have failed. Since the 1980s, increasing numbers of articles reporting the usefulness of thalidomide have appeared, but thalidomide's success in the treatment of severe intractable orogenital ulceration and subsequently its value in the management of the oropharyngeal ulceration seen in HIV/AIDS is particularly notable. More recently thalidomide's place in the treatment of refractory multiple myeloma has been confirmed with polymorphisms of the TNF-alpha gene promoter predicting outcome, that is high producers of TNF-α are more likely to respond.[5,6]

Chronic graft-versus-host disease (GvHD), following allogeneic bone marrow transplantation, occurs in approximately 40% of patients. Refractory GvHD is a therapeutic challenge but initial reports of benefit from the introduction of thalidomide must now be tempered by a recent randomised controlled trial that failed to show any clear benefit from adding this agent to conventional immunosuppressive treatment.[7,8] Other promising indications for thalidomide are in wasting conditions, cancer cachexia, Crohn's disease, and certain dermatological/rheumatological disorders including cutaneous lupus and scleroderma.

Thalidomide's immunomodulatory actions are intriguing and incompletely understood. Many of thalidomide's actions were initially ascribed to its ability to inhibit TNF-α production particularly by monocytes, and more recently to its enhancement of IL-4 and IL-5 production promoting a shift from a Th1 to Th2 cytokine pattern. However, thalidomide can also act as a T cell costimulant: when added to cultures of T cells activated through the T cell receptor, there is an enhanced Th1 response with enhanced production of both IL-12 and interferon-γ with an increase in cell proliferation.

Further research has revealed evidence of antiangiogenic effects induced by inhibiting angiogenesis, which is induced by vascular endothelial derived growth factor and basic fibroblast growth factor. This latter effect appears to be independent of TNF-α suppression. These antiangiogenic affects are probably the mechanism underlying thalidomide's benefit in the two case reports related to thalidomide in this journal.

Koca *et al*. describe the successful treatment of myelodysplastic syndrome-induced pyoderma gangrenosum with thalidomide in combination with interferon-α2a

allowing discontinuation of corticosteroid therapy.[1] The dramatic before and after clinical pictures are compelling evidence of benefit in this single case report. The authors fail to mention the steps taken to ensure that conception did not occur in this 40-year-old lady whilst taking thalidomide and no mention is made of the monitoring of sensory nerve action potentials for evidence of thalidomide-induced axonal neuropathy. The authors do not give any details on how the 200 mg daily dose of thalidomide was reduced but nevertheless electrophysiological studies remain paramount.

Heidt *et al*. in this journal used thalidomide in the treatment of angiodysplasia of the bowel in an 80-year old-male with co-existing von Willebrand's disease and a past history of poliomyelitis.[2] Commendable attempts were made to keep the dose of thalidomide to a minimum and neurophysiological monitoring was undertaken.

There is a paramount need to develop thalidomide derivatives avoiding the teratogenic and neuropathic side effects. Many such compounds have been produced and those entering trials fall into two groups. The immunomodulatory analogues strongly inhibit TNF-α, IL-1β, IL-6, and IL-12 whilst augmenting production of IL-10 and are potent costimulators of T lymphocytes. The other group have more selective inhibitory effects on cytokines, predominantly TNF-α, with minimal effects on T cell activation.

Thalidomide continues to intrigue and mystify. As thalidomide's mode of action is unravelled and as new analogues become available, thalidomide's true place in the therapeutic armamentarium will be assured. Till then use thalidomide with caution!

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EDITORIAL

# The Netherlands Journal of Medicine's hitlist: which 2004 paper was best cited?

**J.P.H. Drenth**

Associate Editor, the Netherlands Journal of Medicine, Department of Medicine, Division of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, the Netherlands, tel.: +31 (0)24-361 47 60, fax: +31 (0)24-354 01 03, e-mail: JoostPHDrenth@CS.com

As editors of the Netherlands Journal of Medicine, we are very interested in the type of articles that appeal most to the scientific community in general and to the readers of the Journal in particular.[1] One way of obtaining this information is to go directly to our readership and ask them what they expect from the Journal and what they want from the Journal. Over the last few years we have twice sent out a questionnaire and the results were instrumental in bringing changes to the Journal. We have been resuscitating the 'letter to the editor' section and we challenge you as readers of the Journal to send us your comments. We strive for lively, readable articles that can help you to cope with the myriad of clinical questions you are faced with every day. Thus, we see it as our mission to make the Journal a source for up-to-date relevant clinical information. On the other hand, medical science is an ever-evolving profession and novel insights are gained each day. The question is how you really can tell which articles in the Journal will have an impact on helping to shape the research agenda. One parameter used is the number of times an article appears in the reference lists of other papers, in other words gets cited. We face the reality that in our scientific world most papers never get to be cited. Is that a problem? You could argue that articles that provide useful clinical information do not need to be cited, but in fact that is not true. Papers that receive the most attention have more effect because these papers stay in the limelight. We wanted to know how we are doing and in line with our efforts of last year, we have made a list of articles published in 2004 that were most cited thereafter. In 2004 we published 81 citable articles; 64 (79%) received at least one citation and only 17 papers were not cited at all. The articles that were cited received an average of 1.9 (standard deviation 1.3) cites since the moment they were published. We will focus on the papers that fall within the top-15. As can be expected, the majority of papers are reviews, with the list containing ten of them. As has been noted before, reviews tend to be cited more than other papers. Much to our delight we also find three original articles, one case report and one editorial among the most-cited papers.

The article that was cited most (7 times) was authored by Dr Hazenberg from the University Medical Centre Groningen.[2] He and his colleagues wrote a fine primer on the diagnostic and therapeutic aspects of amyloidosis. It provides the reader with a systemic stepwise approach on how to classify patients with amyloidosis. As such, it is a well-written paper with an excellent educational value. The case report that attracted the most citations was written by Dr Rodenburg *et al*. and deals with a family with inherited hypercholesterolaemia.[3] This paper is a nice example of translational research as it provides molecular evidence of the diagnosis and describes the treatment of this intriguing disorder.

As outlined earlier, the Journal has adopted an open-access model[4] and we have implemented a software programme that allows us to follow the number of online hits that a published article receives. From January 2007 we will publish a monthly review of the number of online hits for the papers that have recently been published. *Table 1* also contains data on the number of times these articles were downloaded. Contrary to earlier data we could not find a correlation between the number of online hits and citations. This is most probably due to the small sample and the small range in the number of citations. Furthermore, we only implemented the tracking software in November 2005 so downloads before that date were not counted. We would like to salute the authors who made it to the list and we encourage prospective authors to write enticing papers for the Journal that hopefully make it to this list.

*Table 1* lists the most cited articles published in 2004.

**Table 1.** *Most cited articles published in the Netherlands Journal of Medicine in 2004*

| # | Hits | Cites | Author | Title | Type | Hospital |
|---|---|---|---|---|---|---|
| 1 | 327 | 7 | Hazenberg BP[2] | Diagnostic and therapeutic approach of systemic amyloidosis | Review | Academic Medical Centre, Groningen |
| 2 | 263 | 5 | Riksen NP[5] | Ischaemic preconditioning: from molecular characterisation to clinical application--part I. | Review | Radboud University Nijmegen Medical Centre, Nijmegen |
| 3 | 390 | 4 | Kemper HCG[6] | The prevention and treatment of overweight and obesity. Summary of the advisory report by the Health Council of the Netherlands | Review | VU University Medical Centre, Amsterdam |
| 4 | 342 | 4 | Melles DC[7] | Prevention of infections in hyposplenic and asplenic patients: an update | Review | Erasmus Medical Centre, Rotterdam |
| 5 | 275 | 4 | Lowe SH[8] | Antiretroviral therapy in previously untreated adults infected with the human immunodeficiency virus type I: established and potential determinants of virological outcome | Review | Academic Medical Centre, Amsterdam |
| 6 | 228 | 4 | Spoelstra MA[9] | No effect of folic acid on markers of endothelial dysfunction or inflammation in patients with type 2 diabetes mellitus and mild hyperhomocysteinaemia | Original | VU University Medical Centre, Amsterdam |
| 7 | 436 | 3 | Schnog JB[10] | Sickle cell disease: a general overview | Review | St Elisabeth Hospital, Curacao |
| 8 | 431 | 3 | Rodenburg J[3] | A boy with autosomal recessive hypercholesterolaemia | Case | Academic Medical Centre, Amsterdam |
| 9 | 317 | 3 | Timmers HJLM[11] | Baroreflex failure: a neglected type of secondary hypertension | Review | Radboud University Nijmegen Medical Centre, Nijmegen |
| 10 | 343 | 3 | Huussen J[12] | The (fixed) urinary sediment, a simple and useful diagnostic tool in patients with haematuria. | Review | Radboud University Nijmegen Medical Centre, Nijmegen |
| 11 | 260 | 3 | Janssen MJR[13] | The influence of pretreatment on cure rates of *Helicobacter pylori* eradication | Original | Radboud University Nijmegen Medical Centre, Nijmegen |
| 12 | 253 | 3 | Lipsky BA[14] | Pneumococcal polysaccharide vaccines do not protect the elderly from pneumococcal infections. | Editorial | Washington School of Medicine, Seattle |
| 13 | 249 | 3 | Assendelft WJJ[15] | Pneumococcal vaccination for the elderly in the Netherlands? Assessment of the quality and content of available comparative studies | Review | Academic Medical Centre, Amsterdam |
| 14 | 249 | 3 | Vanoostrom AJ[16] | Increased expression of activation markers on monocytes and neutrophils in type 2 diabetes | Original | Academic Medical Centre, Utrecht |
| 15 | 246 | 3 | Kamphuisen PW[17] | Thrombophilia screening: a matter of debate | Review | Radboud University Nijmegen Medical Centre, Nijmegen |

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REVIEW

# SWAB guidelines for antimicrobial therapy of acute infectious diarrhoea

**J.C. Bos[1,4], C. Schultsz[3,5], C.M.J. Vandenbroucke-Grauls[2,3], P. Speelman[1], J.M. Prins[1*]**

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## ABSTRACT

**The Dutch Working Party on Antibiotic Policy (SWAB: Stichting Werkgroep Antibioticabeleid) develops evidence-based guidelines for the use of antibiotics in hospitalised adults. In this article we discuss the guideline on antibiotic treatment of acute infectious diarrhoea (AID). AID can be subdivided into community-acquired diarrhoea, traveller's diarrhoea and hospital-acquired (nosocomial) diarrhoea. For the first two categories, the need for antibiotic treatment is generally restricted to individuals with severe illness, dysentery and/or a predisposition to complications. Infection with *Campylobacter* species is the most common cause of bacterial AID in the Netherlands. In human *Campylobacter* isolates in the Netherlands, but also in other parts of the world, high rates of primary fluoroquinolone resistance are prevalent. If antibiotic treatment in community-acquired AID and AID in travellers on return to the Netherlands is indicated, it is therefore advised to use oral azithromycin for three days as empirical treatment. If intravenous treatment is necessary, the combination of ciprofloxacin and erythromycin for five to seven days may be used. As soon as the identity of the causative organism is known, antimicrobial treatment should be tailored accordingly.**

## KEYWORDS

Acute infectious diarrhoea, antimicrobial therapy, *Campylobacter,* guideline, resistance

## INTRODUCTION

The Dutch Working Party on Antibiotic Policy (SWAB: Stichting Werkgroep Antibioticabeleid) initiates and coordinates activities aimed at optimisation of antibiotic policy in the Netherlands. Through the development of evidence-based guidelines for the use of antibiotics in hospitalised adults, it offers local antibiotic and formulary committees a tool for the development of their own local antibiotic policies.

We present here the SWAB guideline for acute infectious diarrhoea. Apart from meta-analyses and guidelines collected via the Cochrane Library (www.update-software.com/ebmg) and the National Guideline Clearinghouse (www.guideline.gov), relevant literature from the Embase and Medline electronic databases was used. In our guideline, a degree of evidential value was assigned to each of the recommendations according to the handbook of the Dutch Institute for Healthcare Improvement (CBO) (www.cbo.nl/product/richtlijnen/handleiding_ebro). The complete guideline is available at www.swab.nl. In this report, we will mainly focus on empirical treatment strategies. The most important conclusions from the literature review with their level of evidence are summarised in *table 1*. For a schematic overview of antimicrobial recommendations for individual causative agents we refer to *table 2*.

**Table 1.** *Summary of conclusions of the literature review, with level of evidence*

| Conclusion, reference | Level of evidence[#] |
|---|---|
| *Campylobacter* | |
| Early treatment with erythromycin for 5 days can reduce the duration of both symptoms and faecal excretion[58-61] | 1 |
| Early treatment with azithromycin 500 mg OD for 3 days appears to be effective as well[47] | 3 |
| *Shiga toxin-producing E. coli (STEC)* | |
| There is no favourable effect of antibiotics on symptoms of STEC-related AID[24] | 3 |
| A clear association between the use of antibiotics for STEC-related AID and HUS is absent[25] | 1 |
| STEC-related AID should not be treated with antibiotics | 4 |
| The use of antiperistaltics such as loperamide should be avoided[26,27] | 3 |
| *Toxigenic Clostridium difficile* | |
| Interruption of the offending antimicrobial is an important part of the treatment of CDAD, as it may lead to spontaneous recovery in 15-23% of cases[30,31] | 3 |
| Oral metronidazole (250 mg Q6h or 500 mg TD) and oral vancomycin (125 mg Q6h) for 10 days are equally effective for the treatment of CDAD[28,30,63] | 1 |
| Metronidazole is considered to be the treatment of choice, because it is effective and cheap and unlike vancomycin, its use is not associated with the emergence of 'vancomycin-resistant enterococci' | 4 |
| Treating silent *C. difficile* carriage is not useful[64] | 3 |
| *Recurrent toxigenic Clostridium difficile infection* | |
| A relapse is almost never the result of resistance to the initial drug, and a first relapse can be treated with the same antibiotic[31] | 3 |
| If relapses continue to occur after the first relapse, CDAD can be treated with a vancomycin taper or pulse regimen for 3-4 weeks[35,36] | 3 |
| *Empirical treatment of community-acquired AID* | |
| Antibiotic treatment with a fluoroquinolone has a favourable effect on duration and severity of symptoms if started within 5 days after the onset of disease[42-44] | 1 |
| *Campylobacter* spp. are the most frequently found causative agents of bacterial AID in the Netherlands. Resistance rates for fluoroquinolones amongst endemic *Campylobacter* strains are as high as 30.9% for *C. jejuni* and 39.2% for *C. coli*. For erythromycin, the resistance rates are 3.9 and 6.3%, respectively | NA |
| Azithromycin for 3-5 days is effective for the treatment of AID caused by *S. typhi*, and *Campylobacter* and *Shigella* spp.[47,48,50,51,65] | 2 |
| *Empirical treatment of AID in travellers* | |
| Antibiotics can limit the duration of symptoms[52] | 1 |
| A single dose of a fluoroquinolone and fluoroquinolone regimens with longer duration are equally effective[53,54,57,66] | 1 |
| A single dose of azithromycin (1000 mg) and a single dose of a fluoroquinolone appear to be equally effective[55] | 3 |
| The combination of an antibiotic and loperamide is more effective in terms of duration of symptoms than an antibiotic alone[54,56,57,67,68] | 1 |
| Loperamide is contraindicated in case of severe illness and dysentery | 4 |

**[#]Level of evidence according to the CBO manual: level 1: conclusion or recommendation is supported by at least two independent randomised studies of good quality or by a meta-analysis; level 2: supported by at least two randomised trials of moderate quality or insufficient size or another comparative study (not randomised, cohort studies, patient control studies); level 3: not supported by research of the above-mentioned levels; level 4: based on the opinion of members of the guideline committee. STEC = Shiga toxin-producing *E. coli*; HUS = haemolytic uraemic syndrome; CDAD = *Clostridium difficile*-associated disease; NA = not applicable, OD = once daily; TD = thrice daily; Q6h = every six hours.**

## DEFINING ACUTE INFECTIOUS DIARRHOEA

In the Netherlands, about 4.5 million cases of gastroenteritis are diagnosed every year, but a general practitioner is only consulted in one out of 20 cases.[1] An even smaller group of patients with diarrhoea will eventually be admitted to a hospital.[2] Children under the age of 5 are most frequently affected, but mortality is low.

A worldwide accepted definition of acute infectious inflammation of the gastrointestinal tract (acute infectious gastroenteritis) is not available and therefore the illness may be best characterised by its clinical symptoms such as diarrhoea, with or without blood and/or mucus, nausea, vomiting and fever, in combination with the detection of a viral, bacterial or parasitic pathogen. The World Health Organisation (WHO) defines diarrhoea as the evacuation of a minimum of three loose stools in 24 hours. Diarrhoea is qualified as 'acute' when symptoms are new and have not been present for more than 14 days. Dysentery is a diarrhoeal illness that involves the evacuation of bloody stools.

This guideline is restricted to acute infectious inflammation of the gastrointestinal tract manifesting primarily as diarrhoea, a condition that will be referred to as 'acute infectious diarrhoea' (AID). Therefore, *Helicobacter pylori* infections are not included. For the same reason, acute diarrhoea caused by ingestion of microbial toxins (food poisoning) and systemic infections accompanied by diarrhoea, such as legionellosis, listeriosis, viral hepatitis and other viral infections, fall outside the scope of this guideline. AID can be subdivided into community-acquired AID, AID in travellers and hospital-acquired (nosocomial) AID.

**Table 2.** *Pathogen-directed therapy in acute infectious diarrhoea*

| Pathogen | Antibiotic* | Comments |
|---|---|---|
| **Bacteria** | | |
| *Campylobacter* spp. | 1. Azithromycin, 500 mg OD orally, 3 days<br>2. Erythromycin, 500 mg BD iv, 5 days | No antibiotics unless high or persistent fever, dysentery or immunocompromised host |
| *Salmonella* spp. (non-typhi) | 1. Ciprofloxacin, 500/400 mg BD orally/iv, 7 days<br>2. TMP-SMZ, 960 mg BD orally/iv, 7 days | No antibiotics unless high or persistent fever or dysentery. Immunocompromised host or prosthetic material in situ: treat for 14 days<br>Long-term carrier state possible |
| *Shigella* spp. | 1. Ciprofloxacin, 1000 mg single dose orally<br>2. Azithromycin, 250 mg OD orally, 5 days (first day 500 mg)<br>3. TMP-SMZ, 960 mg BD orally, 3 days | No antibiotics unless high or persistent fever or dysentery. Immunocompromised host: oral/iv ciprofloxacin 500/400 mg BD or TMP-SMZ 960 mg BD for 7-10 days |
| *Yersinia* spp. | 1. TMP-SMZ, 960 mg BD orally/iv, 5 days<br>2. Ciprofloxacin, 500 mg /400 mg BD orally /iv, 5 days | No antibiotics unless complicated infection or immunocompromised host |
| E*scherichia coli* spp. | | |
| STEC 0157 | None | Avoid the use of antiperistaltics such as loperamide |
| ETEC | 1. TMP-SMZ, 960 mg BD orally, 5 days<br>2. Ciprofloxacin, 500/400 mg BD orally /iv, 3 days or single dose 1000 mg orally | No antibiotics unless severe illness |
| EPEC, EIEC, EAEC | See ETEC | Clinically indistinguishable from ETEC |
| *Vibrio cholerae* O1 or O139 | Doxycyclin, 300 mg single dose orally or TMP-SMZ, 960 mg BD orally, 3 days or ciprofloxacin, 1000 mg single dose orally | |
| Toxigenic *Clostridium difficile* | 1. Metronidazole, 500 mg TD orally, 10 days<br>2. Vancomycin, 125 mg Q6h orally, 10 days | Interrupt offending antimicrobial regimen and isolate patient |
| Ribotype 027 | Vancomycin, 250-500 mg Q6h orally, 10 days | First relapse: repeat same treatment<br>Multiple relapses: tapered dosing regimen with vancomycin orally: after treatment: first week 125 mg Q6h, second week 125 mg BD, third week 125 mg OD, followed by 250-500 mg twice weekly for 1-2 weeks |
| **Parasites** | | |
| *Giardia lamblia* | 1. Tinidazole, 2 g single dose orally<br>2. Metronidazole, 2 g OD orally, 3 days | Tinidazole is (temporarily?) not available in the Netherlands<br>Silent carrier state occurs relatively frequently and does not require treatment |
| *Entamoeba histolytica* | Metronidazole, 750 mg TD orally, 5-10 days or tinidazole, 2 g OD orally, 3 days | |
| *Entamoeba histolytica* carrier state | 1. Paromomycin, 500 mg TD orally, 10 days<br>2. Clioquinol | Paromomycin is not registered in the Netherlands<br>Effectiveness and dose unclear |
| *Entamoeba dispar* | None | Apathogenic |
| *Cryptosporidium* spp. | None | Any antibiotic regimen is disputed. Consider antibiotic treatment if immunocompromised or HIV+ with CD4 count < 150/mm$^3$: paromomycin 500 mg TD orally, 7 days |
| *Cyclospora* spp. | TMP-SMZ, 960 mg BD orally, 7 days | Immunocompromised host: TMP-SMZ 960 mg BD orally 10 days, followed by secondary prophylaxis: 960 mg OD, 3 times/week |
| *Isospora* spp. | None | Immunocompromised host: TMP-SMZ 960 mg BD orally 10 days, followed by secondary prophylaxis: 960 mg OD, 3 times/week |

**STEC = Shiga toxin-producing *E. coli*; ETEC = Enterotoxic *Escherichia coli*; EPEC = Enteropathogenic *E. coli*; EIEC = Enteroinvasive *E. coli*; EAEC = Enteroaggregative *E. coli*; HAART = highly active antiretroviral therapy; TMP-SMZ = trimethoprim-sulphamethoxazole (co-trimoxazole); OD = once daily; BD = twice daily; TD = thrice daily; Q6h = every six hours. *Taking into account the susceptibility of the cultured micro-organism.**

## EPIDEMIOLOGY

AID is commonly associated with a bacterial or viral infection, whereas chronic diarrhoea is more likely to be associated with parasitic disease.[3] In the Netherlands, approximately 300,000 people suffer from AID due to infection with *Campylobacter* species (spp.) every year and this is the most prominent bacterial cause of AID in our country.[4] In contrast to children below the age of 5, adults with community-acquired AID who seek medical help from a general practitioner are more likely to suffer from bacterial (mainly *Campylobacter* spp.) or parasitic disease

(*Giardia lamblia*) than from viral disease. Noroviruses, formerly known as 'Norwalk-like' viruses, are the most common viral causative agents in adult community-acquired AID (*table 3*).

**Table 3.** *Epidemiology of acute infectious diarrhoea in Dutch general practices*[3]

| Pathogen | Prevalence |
|---|---|
| *Campylobacter* | 10.4/0.5 |
| *Salmonella* | 3.9/0.2 |
| *Shigella* | 0.1/0.0 |
| *Yersinia* | 0.7/1.1 |
| STEC O157 | 0.5/0.6 |
| Viruses | 16.5/4.8 |
| Parasites (incl. *G. lamblia*) | 8.6/4.4 |

**Percentage of patients/percentage healthy controls from all ages who tested positive for specified causative agent.**

AID is the most frequent disease in travellers outside Europe: about 10 to 60% of them develop a more or less severe form of diarrhoea. The causative agents of traveller's AID are a subset of the agents responsible for AID in local communities, as there tend to be differences in exposure and immunity between travellers and residents. Enterotoxigenic *Escherichia coli* (ETEC) is the most important pathogen in traveller's AID, although enteroaggregative *E. coli* (EAEC) is believed to play an important causative role as well. In addition, *Campylobacter* spp. are 'emerging pathogens', as they are responsible for 15 to 25% of AID cases in travellers to Asia.[5,6] In travellers who have returned to the Netherlands with severe AID, the distribution of causative agents is likely to be different and it is reasonable to suppose that in this situation ETEC plays a far less important role, as ETEC-related disease tends to be mild and short lived.

Shiga toxin-producing *E. coli* (STEC) is the most important cause of haemorrhagic colitis and of kidney failure in children worldwide.[7] Cattle is the main reservoir for STEC and transmission occurs through consumption/ingestion of contaminated beef, water or (raw) milk. Although an estimated 1250 cases of STEC-related AID occur in the Netherlands every year, in 2003 only 40 cases were reported and 20 cases, mainly involving children, were complicated by the haemolytic uraemic syndrome (HUS). In patients with HUS, the O157:H7 strain is the predominant serotype.[8]

In the Western world, toxigenic *Clostridium difficile* infection is the main cause of nosocomial AID.[9] Hospital rooms can remain contaminated for a long period of time, as spores can survive outside the host for months. The disease is often transmitted via contaminated hands of healthcare workers. Although it is still generally accepted that a patient colonised with a toxigenic strain is not likely to develop *C. difficile*-associated disease (CDAD) until he or she is treated with antibiotics, recent publications on severe CDAD in healthy persons thought to be at low-risk suggest that CDAD epidemiology might be changing.[10-12] Although clindamycin, amoxicillin and cephalosporins are most commonly implicated – partially reflecting the extensive use of some of these drugs – almost all classes of antibiotics have been associated with CDAD. If AID develops after a stay of at least three days in a hospital, it is advised to avoid/interrupt the use of antibiotics and to carry out a proper diagnostic strategy for CDAD. This should include screening of a stool specimen for *C. difficile* toxins, since testing schemes that rely solely on *C. difficile* cultures yield a significant number of false-positive results (*figure 1*).[11]

## TREATMENT OF IMPORTANT INDIVIDUAL PATHOGENS

In this section we will only discuss the most important pathogens briefly. Please refer to the complete guideline and *table 2* for detailed information.

### *Campylobacter*

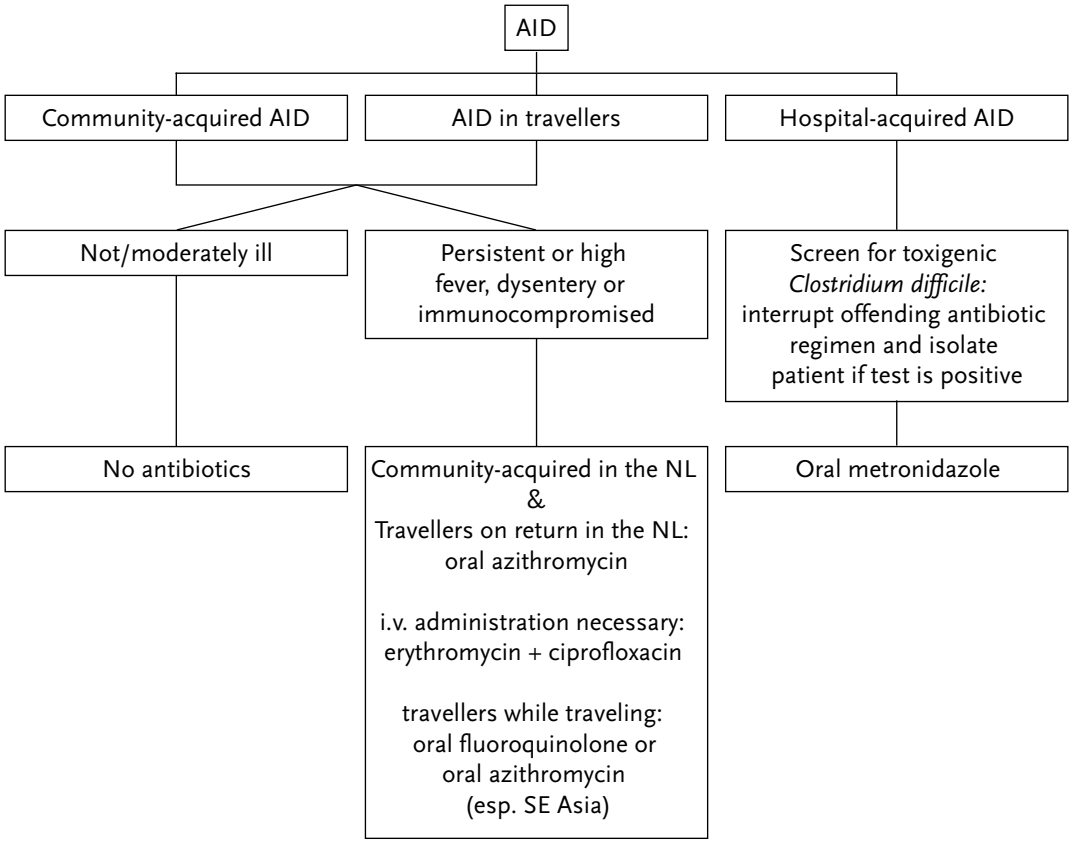
Infections with fluoroquinolone-resistant *Campylobacter* strains have become increasingly prevalent, coinciding with the introduction of fluoroquinolones in veterinary medicine.[13] Resistance data from 2002 and 2003, based on data from 16 regional laboratories in the Netherlands, reported high fluoroquinolone resistance rates amongst endemic *Campylobacter* isolates, ranging from 30.9% for *C. jejuni* to 39.2% for *C. coli*. For erythromycin, the resistance prevalence was 3.9 and 6.3%, respectively.[14]

Analogous to the Dutch situation, many countries across Europe and the Americas, but especially in Southeast Asia, struggle with increasing fluoroquinolone resistance among *Campylobacter* spp, although regional differences are common. In a recent Thai study, a prevalence as high as 50 to 85% was found.[15] In this part of the world, not only *Campylobacter*, but also the other common causative agents of dysentery, such as *Shigella* spp. and nontyphoidal *Salmonella*, are becoming increasingly resistant to most agents commonly in use. The same study shows evidence of the emergence, although limited (6%), of combined resistance to fluoroquinolones and azithromycin among *Salmonella* and *Campylobacter* spp. Fluoroquinolone resistance rates of *Campylobacter* spp. isolated from travellers returning to the Netherlands are as high as 52.5% for *C. jejuni* and 59.1% for *C. coli*. The corresponding prevalence of erythromycin resistance is 2.7 and 10.5%, respectively.[14]

### *Salmonella*

AID caused by nontyphoidal *Salmonella* spp., the second most frequently found bacterial pathogens in the Netherlands, is usually mild, although more severe

**Figure 1.** *Flowchart showing empirical antimicrobial treatment for acute infectious diarrhoea (AID)*




systemic illness with metastatic infection may occur, especially in the elderly and immunocompromised.[16,17] Antibiotic treatment is not recommended, as the use of antibiotics has not proven to be effective in uncomplicated disease and may even have a negative effect on relapse risk and carrier state.[18-20] It is, however, recommended to start antibiotic treatment in case of severe illness or when the patient is immunocompromised, although scientific evidence is lacking. In this case, it is advised to use a potent bactericidal drug with intracellular activity, such as ciprofloxacin.[21] In 2003, fluoroquinolone resistance in human *Salmonella* spp. isolates in the Netherlands was reported to be almost nonexistent, although the prevalence of multiresistance against amoxicillin, doxycycline, TMP (-SMZ) and chloramphenicol was as high as 45%, depending on the serotype.[22,23]

**Shiga toxin-producing *E. coli***

In Shiga toxin-producing *E. coli* (STEC)-related AID, antimicrobial therapy does not seem to affect the duration of diarrhoeal disease.[24] There are data that suggest a relationship between the use of antibiotics and HUS. In a prospective study in 2000, investigators found evidence for an increased risk for HUS when using antibiotics for STEC-related AID, but this conclusion could not be confirmed in a meta-analysis.[25] It is nevertheless advised to treat STEC-related AID strictly symptomatically. The use of loperamide should be avoided, as it may increase the risk of systemic disease.[26,27]

**Toxigenic *C. difficile* and CDAD**

The use of antibiotics is clearly associated with CDAD and discontinuation of the offending regimen may lead to recovery in 15 to 23% of cases. Antibiotic treatment is indicated for individuals with longstanding symptoms and for patients with an underlying disease. Hospitalised patients should be treated irrespective of the severity of the disease to prevent transmission. Oral metronidazole is considered to be the regimen of choice because it is effective, cheap and it does not carry a risk of colonisation and infection with vancomycin-resistant enterococci (VRE).[28,29] Oral vancomycin is regarded as equally effective, although some authors suggest that treatment with metronidazole may be more likely to fail.[30-32] A recent outbreak of a virulent strain of *C. difficile*, ribotype 027, in the Netherlands has led to controversy about the preferred first-line treatment.[33]

When taken orally for diarrhoea, metronidazole reaches bactericidal concentrations in faeces as a result of decreased absorption and active secretion by the infected intestinal epithelium. Consequently, the luminal concentration may

decrease to an undetectable level when the diarrhoea resolves.[34] Although bactericidal faecal levels can be reached when metronidazole is given intravenously, the efficacy of the drug has only been established for oral administration.

**Recurrent toxigenic *C. difficile* infection**

Relapses of CDAD are common, occurring in 20 to 30% of patients initially treated successfully. Once a first relapse has occurred, the chance of getting multiple relapses increases to 45 to 65%.[29,35] Recurrent CDAD is hardly ever attributable to drug resistance and a first relapse can therefore be successfully treated with renewed administration of the same drug.[31] There is some evidence that multiple relapses are best treated with vancomycin in a 'tapered or pulsed dosing regimen': in a prospective study in 2002 including 163 patients with relapsing CDAD, tapered and pulsed dosing regimens with vancomycin and metronidazole were compared.[36] Patients treated with vancomycin had a better outcome compared with those treated with metronidazole, but the study was neither randomised nor controlled. The use of tapered or pulsed regimens is based on the idea that after discontinuation of therapy, spores may develop into vegetative stages, which can be killed by renewed exposure to vancomycin. Starting from the second relapse, we recommend a tapered dosing regimen with vancomycin for 19 to 25 days (*tables 1* and *2*).

*Saccharomyces boulardii*, a non-pathogenic yeast that can be isolated from lychees, has also been used for the treatment of (recurrent) CDAD. Animal studies have shown that prophylactic administration of *S. boulardii* can have a protective effect on the development of CDAD. In addition, the outcome of two prospective human trials supports the idea that adding *S. boulardii* to a standard antibiotic regimen can prevent recurrent CDAD, although the beneficial effect in the first study was limited to the subgroup of patients using the highest dose of vancomycin and the antibiotic regimens in the second study had not been standardised.[37,38] Not unimportantly, a few cases of disseminated *Saccharomyces cerevisiae* infections have been described since the introduction of *S. cerevisiae* as a probiotic drug.[39]

An adequate immune response to *C. difficile* toxins can protect against CDAD and relapses. Even though small studies suggest that the administration of intravenous and especially oral immunoglobulins against toxin A has a therapeutic effect on relapsing CDAD, it is still too early to recommend immunoglobulins as standard treatment.[40,41]

## EMPIRICAL TREATMENT

**Community-acquired AID**

In patients with community-acquired AID presenting in general practice or at an outpatient clinic, a favourable effect has been noted on duration and severity of symptoms when antibiotic treatment with a fluoroquinolone is initiated within five days after the onset of the disease. The effect is independent of culture results. Most studies were performed with a five-day therapeutic regimen and therefore, at present, this should be regarded as the standard duration of therapy in the absence of appropriate diagnostic results.[42-44]

The favourable effect of fluoroquinolones must, however, be weighed against the aforementioned increase in *Campylobacter* resistance, which raises the concern that initial empirical treatment with ciprofloxacin is becoming increasingly inadequate. Whereas erythromycin can not be used for treating causative agents of AID other than *Campylobacter*, azithromycin can. Compared with erythromycin, the $MIC_{90}$ of azithromycin for intestinal pathogens is at least eight times lower.[45,46] In addition, a number of studies have demonstrated the effectiveness of azithromycin for the treatment of AID caused by *Shigella, Campylobacter* and nontyphoidal *Salmonella* spp.[47,48] As *Salmonella* spp. have the ability to survive in macrophages, it is of major importance that *in vitro* and animal studies have shown that azithromycin achieves high intracellular concentrations and a bactericidal response for S*almonella* spp.[49] Furthermore, comparative human studies have shown that azithromycin is effective for the treatment of *Salmonella typhi* infections.[50,51] As a result of its pharmacokinetic profile this drug can be administered once daily.

Community-acquired AID in healthy adults, often of viral origin, is usually mild and short-lived, and empirical antibiotic treatment should therefore be restricted to individuals with high or long-standing fever, patients with dysentery and immunocompromised patients (*figure 1*). For these patient groups, we recommend a regimen of 500 mg azithromycin, once daily for three days. If intravenous treatment is necessary, a combination of ciprofloxacin and erythromycin, for five to seven days, may be used. As there is no clear evidence for a causative relationship between the use of antibiotics and HUS during STEC-related AID, there seems to be no reason to deny empirical antimicrobial treatment to an otherwise qualifying AID patient.

**Traveller's diarrhoea**

Multiple studies have demonstrated that antibiotics can limit the duration of symptoms in traveller's AID and recently this was confirmed in a Cochrane systematic review.[52] For years, TMP-SMZ has been the drug of empirical choice, but despite its low costs, its applicability is now greatly reduced due to worldwide resistance. Since the 1980s, fluoroquinolones have offered a new opportunity in antibiotic intervention and a three- to five-day course of ciprofloxacin can lead to a significant decrease in the duration of symptoms in adults, from three to five days to less than two days. A single-dose treatment is as effective as longer treatment courses.[53,54] In a study that involved American travellers to Mexico with AID, a single dose of azithromycin 1000 mg appeared to be

as effective as a fluoroquinolone. Mild to moderate AID in healthy adult travellers does not require antibiotic treatment (*figure 1*).[55] Moderate AID or AID in immunodeficient travellers can be treated with fluoroquinolones, possibly in combination with loperamide. The favourable effect of this combination on duration of symptoms has proven to exceed the effect of an antibiotic alone.[56,57] In case of severe illness and/or dysentery, the use of loperamide is considered to be contraindicated. Depending on local epidemiology and resistance patterns, ciprofloxacin should be replaced by a single dose of azithromycin. At present, this seems to be mainly the case in Southeast Asia.

Because of the selection of pathogens mentioned earlier, patients with severe AID on return to the Netherlands should be treated according to the recommendations for community-acquired AID, with either azithromycin orally or a combination of erythromycin and ciprofloxacin intravenously.

## NOTES

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REVIEW

# From Trousseau to angiogenesis: the link between the haemostatic system and cancer

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## INTRODUCTION

Thrombosis is one of the major complications of cancer. In 10 to 15% of the patients with clinically overt cancer, spontaneous venous thrombosis, thromboembolism after cancer surgery, thromboembolism during chemotherapy and thrombosis of central venous access lines occur as clinical manifestations of thrombosis.[1] The relationship between cancer and thrombosis is also obvious by the clinical observation that thrombosis may be a presenting symptom of cancer. Of all noncancer patients presenting with an idiopathic thromboembolism, 10 to 20% develop cancer in the next three years.[2] It was Armand Trousseau in the 19th century who first noted the 'alteration of the blood' in cancer patients.[3]

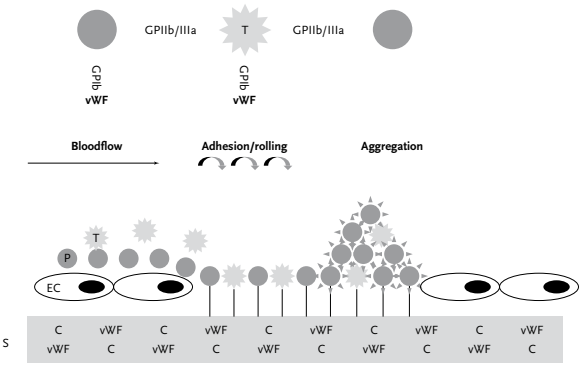
Moreover, there is now considerable evidence that the blood coagulation system is not only involved in cancer-associated thrombosis, but also plays an important role in the biology of malignant tumours. Cancer cells interact with the coagulation system for their growth, for angiogenesis and for the dissemination through the body. Many components of the coagulation system are involved in tumour neovascularisation, and fibrin present in the matrix around tumour cells facilitates tumour cell growth.[4] The interference of tumour cells with the coagulation system leads to an increased activation of several coagulation pathways. And it is this hypercoagulability state that is the major determinant of the increased risk for the above-mentioned thromboembolic complications in cancer patients.

## ACTIVATION OF THE PRIMARY HAEMOSTATIC SYSTEM

In normal primary haemostasis a vascular lesion is closed by the formation of a platelet plug. First, the platelets adhere transiently to subendothelial von Willebrand factor (vWF) through the GPIb receptor. This adherence significantly slows the movement of the platelets. Secondly, the slowly moving platelets start to roll across the subendothelium and adhere to vWF and collagen through the GPIb and platelet collagen receptors. Finally, these interactions lead to platelet activation and aggregation through the GPIIb/IIIa receptors on platelets, thereby stably adhering to the damaged vessel wall (*figure 1*). Hence, vWF plays an essential role by promoting the adhesion of platelets to the subendothelium.

In cancer patients both platelets and vWF are believed to be involved in cancer growth and dissemination.[5] It has been shown that platelets release vascular endothelial growth

**Figure 1.** *Involvement of tumour cells in the primary haemostatic system*




**S = subendothelium; EC = endothelial cell; P = platelet; C = collagen; vWF = von Willebrand factor; GP = glycoprotein; T = tumour cell. Circulating platelets and tumour cells adhere to the subendothelial vWF and collagen, leading to rolling, adhesion and aggregation through the GPIb and GPIIb/IIIa receptors on platelets as well as tumour cells.**

factor (VEGF), the important regulator of tumour-induced angiogenesis.[5,6] Moreover, VEGF-stimulated endothelial cells promote adhesion and activation of platelets.[7] Previous animal studies show that thrombocytopenia inhibits and platelet transfusion stimulates tumour metastasis in animals.[8] Tumour cell adhesion to platelets might be essential for dissemination. Blocking tumour-binding receptors on platelets inhibits metastasis *in vitro* and *in vivo*.[9] Platelets adhering to tumour cells prolong tumour cell survival in mice by protecting them from lysis by natural killer cells.[10] It is suggested that by binding to activated platelets, tumour cells are able to adhere better to the endothelium (*figure 1*). Moreover, they secrete cytokines increasing the permeability of the vessel wall, thereby enabling dissemination in the surrounding tissue.[9,11]

Elevated vWF levels have been reported in various cancers in humans, including breast cancer and colorectal cancer.[12-15] In the latter it has been shown that vWF levels are associated with tumour stage and metastases.[15] Experimental models *in vitro* and *in vivo* suggest that vWF facilitates binding of platelets to tumour cells thereby hiding the tumour cells from the immune system and enabling the attachment of tumour cells to the endothelium.[9] It has been demonstrated that tumour cells express the GPIb and the GPIIb/IIIa receptor.[16] These receptors can bind the tumour cell to vWF and to platelets (*figure 1*). Patients with disseminated cancer also have a significant increase in unusually large vWF multimers which facilitates further binding to tumour cells. This presence of unusually large vWF multimers is the result of a local acquired deficiency of vWF cleaving protease (ADAMTS 13).[17]

In conclusion, there is cumulating evidence for an important role of platelets and vWF in tumour growth and dissemination.

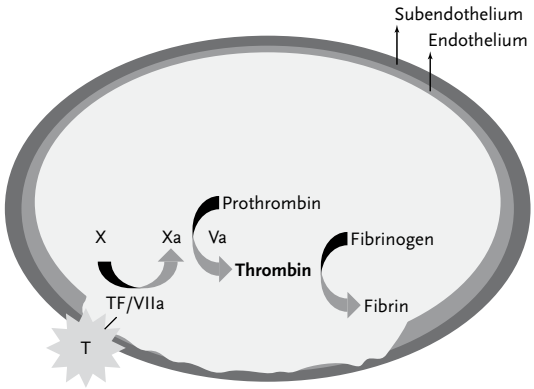
## ACTIVATION OF THE SECONDARY HAEMOSTATIC SYSTEM

In normal secondary haemostasis a fibrin clot is formed at the site of a vascular lesion by activation of a coagulation pathway starting with the exposition of subendothelial tissue factor (TF) eventually leading to the conversion of fibrinogen to fibrin. This TF has also been thought to play a pivotal role in cancer-induced hypercoagulability.

TF is the key initiator of the coagulation cascade.[18] In the first or initiation phase TF activates coagulation factor VII to factor VIIa. The formed TF/factor VIIa complex directly activates coagulation factor X to Xa. Together with factor Va, factor Xa is responsible for the conversion of prothrombin to thrombin (i.e. factor II to IIa). Thrombin induces clot formation by inducing the conversion of fibrinogen to fibrin (*figure 2a*).

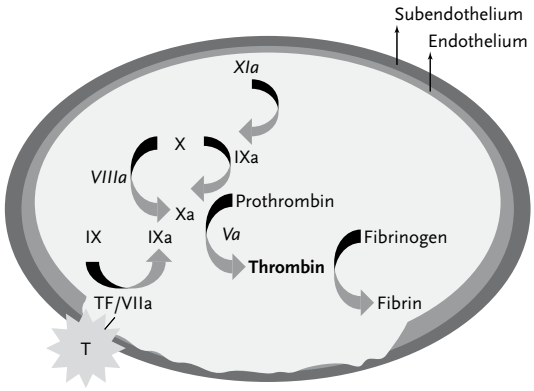
In addition to directly activating factor X, in the next or propagation phase, the TF/factor VIIa complex also indirectly activates factor X to Xa by activating coagulation factor IX to IXa which, together with factor VIIIa, also activates factor X to Xa. Again this leads to the conversion of prothrombin to thrombin and fibrinogen to fibrin (*figure 2b*). Thrombin induces clot formation not only by inducing the conversion of fibrinogen to fibrin but also by directly activating platelets and by stimulating its own formation by activating clotting factors V, VIII and XI (*figure 2b*). Negatively charged phospholipids (e.g. the platelet membrane) and calcium are essential in the whole process of fibrin formation.

**Figure 2a.** *The initiation phase of the secondary haemostatic system and the activation by tissue factor (TF) on the tumour cell (T)*




**The TF/VIIa complex activates factor X to Xa, which, together with factor Va, activates factor II (prothrombin) to factor IIa (thrombin). Finally, thrombin catalyses the conversion of fibrinogen to fibrin.**

**Figure 2b.** *The propagation phase of the secondary haemostatic system and the activation by tissue factor (TF) on the tumour cell (T)*




**The TF/VIIa complex also activates factor IX to IXa, which, together with factor VIIIa, activates factor X to Xa. Consequently, this leads to the conversion of prothrombin to thrombin and fibrinogen to fibrin. Thrombin stimulates its own formation by directly activating the clotting factors V, VIII and XI.**

TF is normally only localised in extravascular tissues not directly in contact with the blood stream. In case of a vascular lesion the subendothelial TF will be exposed to the blood resulting in platelet activation, fibrin formation and closing of the lesion. In cancer patients, however, TF is expressed aberrantly on endothelial cells, monocytes and, most importantly, on tumour cells themselves (*figures 2a* and *2b*). Moreover, cancer cells may produce a cysteine proteinase, known as cancer procoagulant (CP), which directly activates coagulation factor X to Xa.[19]

Endothelial cells do not normally express TF. TF on endothelial cells is induced by cytokines as TNF-α and IL-1β produced by tumour cells.[20] Moreover, these tumour cytokines induce expression of adhesion molecules on endothelial cells, making them capable of attaching other tumour cells.[21] This accumulation of tumour cells leads to increased cytokine production and thereby increased TF expression on the endothelial cells. It is suggested that this is a major contribution to the cancer-induced hypercoagulability.

Monocytes do not normally express TF. They do express TF when they are activated by stimulating agents such as bacterial endotoxins, inflammatory cytokines and complement factors. TF on monocytes has been demonstrated in cancer patients mainly in *in vitro* studies. Isolated monocytes obtained from cancer patients expressed more tissue factor than monocytes from healthy controls.[22-26] No studies have been performed with direct *in vivo* measuring of the TF expression on monocytes. However, TF expression on monocytes is still thought to have a major role in cancer-induced hypercoagulability.[27]

TF expression on tumour cells has been shown in many cancers, including breast cancer, lung cancer, colorectal cancer and pancreatic cancer. Elevated levels of tissue factor on tumour cells have been correlated with increased angiogenesis, increased vascular density, unfavourable prognosis and advanced disease.[28-31] TF on tumour cells is considered another important factor in the cancer-induced hypercoagulability and plays a pivotal role in angiogenesis. In preclinical studies TF-deficient mice died after ten days of embryonic development because of abnormal formation of yolk-sac vessels, suggesting a role for TF in physiological angiogenesis.[32] The same applies to VEGF-deficient mice, suggesting that TF and VEGF regulate similar functions.[33] Expression of TF in tumours upregulates the expression of VEGF, thereby inducing a switch to a more angiogenic phenotype and inducing sprouting of new blood vessels from pre-existing vessels.[34] Tumour cells overexpressing TF grew more rapidly and formed a larger and more vascularised tumour than TF underexpressing tumour cells.[34]

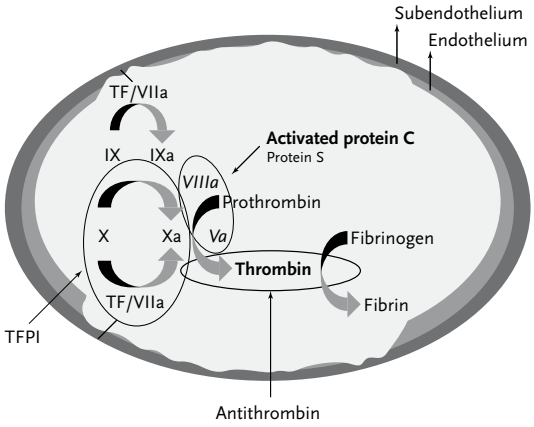
In conclusion, TF plays a central role in the activation of the coagulation system in cancer-related thrombosis and in the enhancement of angiogenesis, tumour growth and tumour metastasis

## CHANGES IN THE ANTICOAGULANT SYSTEMS

In normal haemostasis there is a terminating system to prevent ongoing clotting and to confine the fibrin clot to the site of the vascular lesion. Key players in this system are tissue factor pathway inhibitor (TFPI), antithrombin (AT) and activated protein C. TFPI, which is synthesised in the endothelium, is the natural inhibitor of TF. It binds to the TF/factor VIIa complex and binds directly to factor Xa, thereby terminating the initiation phase of the coagulation cascade.[35] Antithrombin is the (slow) inhibitor of coagulation factors IXa, Xa and thrombin, thereby terminating the propagation phase. Its effect can be greatly accelerated by heparins.[36] Activated protein C (aPC), together with its cofactor protein S, inhibits the activity of coagulation factors VIIIa and Va, contributing to the termination of the propagation phase (*figure 3*). Vitamin K-dependent protein C is activated to aPC on the surface of endothelial cells by thrombin bound to the membrane glycoprotein thrombomodulin. The endothelial protein C receptor (EPCR) further stimulates protein C activation.[37]

Decreased activation of the anticoagulant factors TFPI, antithrombin and the proteins of the protein C pathway could lead to activation of haemostasis in cancer patients. Indeed, decreased levels of antithrombin and protein C have been reported.[38] Moreover, there are strong indications that cancer patients without the factor V Leiden mutation have an acquired aPC resistance.[39-41]

**Figure 3.** *The initiation phase (lower part) and propagation phase (upper part) of the secondary haemostatic system and the termination by tissue factor pathway inhibitor (TFPI), antithrombin and activated protein C in the termination phase*



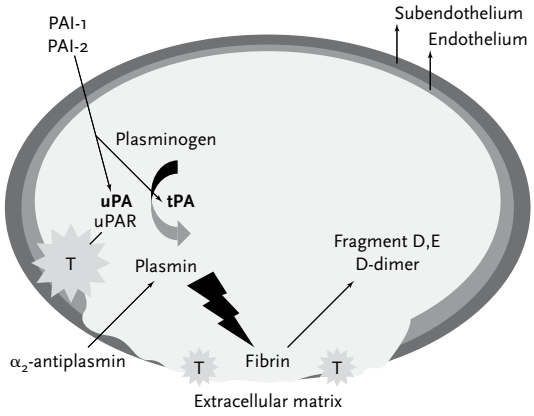

**TFPI is the inhibitor of the TF/VIIa complex and factor Xa, antithrombin is the inhibitor of thrombin and activated protein C, together with its cofactor protein S, inhibits the activity of coagulation factors VIIIa and Va.**

On the contrary, elevated plasma levels of TFPI have been demonstrated in patients with solid tumours.[42,43] TFPI-1 is the main inhibitor of TF, factor VIIa and factor Xa and directly binds cancer cells to the extracellular matrix, thereby promoting cancer cell migration.[44] TFPI-2 has a low inhibitory activity to TF, factor VIIa and factor Xa, but is a potent inhibitor of plasmin. Plasmin is a protease able to degrade the extracellular matrix directly or indirectly by activating matrix metalloproteinases. These matrix metalloproteinases degrade collagen and other matrix proteins, thereby allowing tumour cells and monocytes to invade the extracellular matrix and the surrounding tissues.[45] TFPI-2 inhibits the plasmin-mediated activation of matrix metalloproteinases involved in tumour progression, invasion, and metastasis.[46] Thus, elevated levels of TFPI-1 stimulate and elevated levels of TFPI-2 inhibit growth and dissemination of cancer cells.
In conclusion, there is cumulating evidence of an important role for the anticoagulant proteins in cancer biology.

## ACTIVATION OF THE FIBRINOLYTIC SYSTEMS

The fibrin formed in the initiation and the propagation phase of the secondary haemostatic system is strengthened by thrombin-activated factor XIII, catalysing the formation of cross-links between adjacent fibrin chains to yield the mature clot.[47] The fibrinolytic system is responsible for the lysis of these fibrin clots. In normal fibrinolysis plasminogen is converted to plasmin by activation of tissue plasminogen activator (tPA) or urokinase plasminogen activator (uPA). Plasmin cleaves the fibrin network and releases fibrin degradation products fragment D, fragment E and D-dimer. Plasmin is inactivated by α2-antiplasmin with the formation of plasmin-α2-antiplasmin (PAP) complexes. The activity of tPA and uPA is inhibited by specific inhibitors, plasminogen activator inhibitor (PAI) 1 and 2 (*figure 4*).
It has been demonstrated that the fibrinolytic system, in particular the urokinase-type plasminogen activator system, is involved in the process of tumour cell invasion and metastasis. Urokinase-type plasminogen activator binds to the urokinase-type plasminogen activator receptor (uPAR), which is present on tumour cells and monocytes, thus facilitating the conversion of plasminogen to plasmin. Plasmin is a protease not only able to cleave the fibrin network of a clot but, as mentioned before, also able to degrade the extracellular matrix, thereby allowing tumour cells and monocytes to invade the extracellular matrix and the surrounding tissues (*figure 4*).[45]
Elevated tumour levels of uPA, uPAR and PAI-1 are associated with poor prognosis in various malignancies, including cancers of the lung, stomach, colorectum, bladder, ovary and breast.[48] Several studies have been carried out in patients with breast cancer. Breast cancer patients with high tumour levels of uPA had a significantly shorter disease-free and overall survival and the tumour uPA level was a strong prognostic marker in node-positive as well as node-negative breast cancer patients.[49-55] High tumour levels of uPAR were associated with a shorter disease-free and overall survival, particularly in the subgroup of node-positive postmenopausal women with breast cancer.[56,57] Tumour PAI-1 was a strong independent prognostic factor and an important parameter to predict metastatic potential in both node-negative and node-positive breast cancer patients.[53,58,59] On the contrary, elevated tumour PAI-2 levels have been associated with favourable prognosis.[60,61] It has been demonstrated that the plasma levels of soluble uPAR are significantly increased in stage IV breast cancer patients.[62-64]
Elevated D-dimer levels, indicating the degradation of fibrin by the fibrinolytic system, have been described before in breast cancer patients as well as in various other cancers.[65] Recently it has been demonstrated that in breast cancer patients preoperative plasma D-dimer levels correlate with clinical stage and axillary lymph node status.[66] Moreover, in patients with metastatic breast cancer plasma D-dimer levels correlated with tumour volume, progression rate and survival.[67] Plasma D-dimer levels were significantly elevated in breast cancer patients with metastases compared with patients without metastases and were highly significantly correlated with survival.[64]

**Figure 4.** *Involvement of the fibrinolytic system in the process of tumour cell invasion and metastasis*




**In normal fibrinolysis plasminogen is converted to plasmin by activation of tissue plasminogen activator (tPA) or urokinase plasminogen activator (uPA), cleaving the fibrin network and releasing fibrin degradation products fragment D, fragment E and D-dimer. Plasmin is inactivated by α-2-antiplasmin; tPA and uPA are inhibited by plasminogen activator inhibitor (PAI) 1 and 2. In cancer patients uPA binds to the urokinase-type plasminogen activator receptor (uPAR) on tumour cells, facilitating the conversion of plasminogen to plasmin, thereby cleaving the fibrin network and degrading the extracellular matrix, allowing tumour cells (T) to invade the extracellular matrix and the surrounding tissues.**

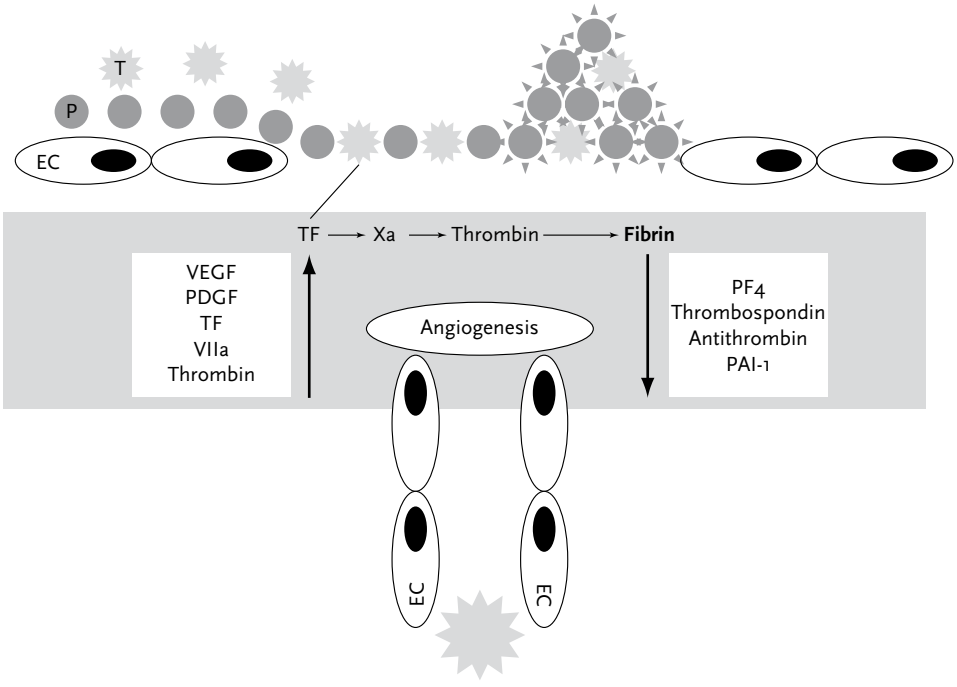
In conclusion, the fibrinolytic system seems to play a significant role in the process of tumour cell invasion and metastasis.

## ANGIOGENESIS

Angiogenesis is the development of new blood vessels from the existing vasculature. It occurs in a highly regulated manner in normal physiological processes as wound healing. Angiogenesis is closely related to the haemostatic system in case of vascular damage. Following injury, the haemostatic system regulates platelet adherence and fibrin formation, thereby stopping the bleeding; the angiogenic system regulates the formation of new blood vessels, a vital step in healing the wound. Once clot stabilisation is achieved, angiogenesis is modulated by proteins and peptide fragments generated from the coagulation and fibrinolytic systems.[68-70] The fibrin clot, formed in the haemostatic process, serves as a matrix for migrating endothelial cells. This process is tightly regulated by a local balance of pro- and antiangiogenic factors. Proangiogenic factors stimulate migration, proliferation and differentiation of endothelial cells whereby new vessels are formed. Proangiogenic factors identified in the haemostatic system include platelet release products, such as VEGF and platelet-derived growth factor, and coagulation proteins as thrombin, TF, factor VII and factor XIII. Antiangiogenic factors characterised from the haemostatic system include other platelet release products, as platelet factor 4 and thrombospondin, and coagulation proteins as antithrombin and PAI-1.[68,69] In close cooperation, the haemostatic and angiogenic systems quickly repair the damaged blood vessel.

In 1971 Folkman first described the pivotal role of angiogenesis in tumour growth.[71] For their growth tumours need oxygen and essential nutrients. When tumours are very small, oxygen and nutrients can diffuse into the tumour cells. In order to grow and metastasise a tumour has to develop an adequate vasculature. By activating the haemostatic system, tumour cells induce the production of proangiogenic factors as thrombin, TF and factor VII, thereby creating the environment for the formation of new blood vessels, comparable with physiological angiogenesis. The fibrin locally formed by activation of the haemostatic system by the tumour cells provides the matrix on which the new (often thin-walled, leaky and poorly organised) blood vessels are being formed by stimulation of the proangiogenic factors (*figure* 5). The newly formed blood vessels allow the

**Figure 5.** *Activating the haemostatic system by tumour cells and platelets leads to the production of proangiogenic factors and antiangiogenic factors thereby creating the environment for the angiogenesis*




**VEGF = vascular endothelial growth factor; PDGF = platelet-derived growth factor; TF = tissue factor; VIIa = activated coagulation factor VII; PF4 = platelet factor 4; PAI-1 = plasminogen activator inhibitor 1; EC = endothelial cell; P = platelet; T = tumor cell. The fibrin locally formed by activation of the haemostatic system by the tumour cells provides the matrix in which the new blood vessels are formed.**

tumour to grow more rapidly and increase the surface area through which the tumour cells can escape and metastasise.[68]

Because coagulation factors are proteases that have many additional functions in (cancer) cell regulation, the idea that coagulation activation in cancer patients is solely linked to angiogenesis is an optimistic short cut. For example, direct cell signalling by coagulation proteases activating protease-activated receptors (PARs) leads to proliferation and invasiveness of cancer cells. This shows that other mechanisms, many yet to be elucidated, might be more important than regulation of angiogenesis.[72,73]

In conclusion, tumour cells activate the haemostatic system as an essential step in the formation of new blood vessels, in order to grow and eventually metastasise.

## ANTICOAGULANTS AND CANCER

Because cancer cells need the coagulation system for their growth, angiogenesis and dissemination through the body, it has been hypothesised that anticoagulants might have an antitumour effect. First coumarin derivates were studied. Although promising results were shown in animal studies, clinical studies in humans are limited and results are conflicting. No differences in survival were observed between warfarin-treated and control groups for advanced non-small-cell lung, colorectal, head and neck and prostate cancer.[74] However, warfarin therapy was associated with a significant prolongation in disease-free and overall survival in patients with small-cell lung cancer.[74] Remarkably, in patients treated with coumarins for six months after a venous thromboembolism significantly fewer (urogenital) cancers were found compared with patients treated for six weeks.[75] However, the incidence of clinically overt cancer was not reduced in patients with idiopathic venous thromboembolism treated with oral anticoagulants for one year compared with three months.[76] More studies have been carried out with low-molecular-weight heparins (LMWH). In studies comparing LMWH and coumarins in the treatment of new patients with a venous thromboembolism three-month mortality data suggested a survival advantage for the patients on LMWH. Subgroup analysis showed that this increased survival was in the cancer patient group.[77,78] Recently it has indeed been shown that LMWH improves survival, although in all studies the effect seems limited to the patient groups with the relatively better prognosis.[79-81] Moreover, adding LMWH to chemotherapy in small-cell lung cancer improved survival compared with chemotherapy alone.[82] It is suggested that apart from the effect of LMWH on coagulation, other mechanisms influenced by heparins are also involved.[83,84] More studies treating cancer patients with LMWH or newer antithombotics, as pentasaccharides and oral thrombin inhibitors, are currently underway.

## FUTURE PERSPECTIVES

Several research groups are continuously investigating the molecular pathophysiology of the activation of the coagulation system by tumour cells. At first this was mainly a topic for haematologists. However, since it has been demonstrated that anticoagulant treatment with LMWH might prolong survival in cancer patients, oncologists have been alerted. The survival advantage shown with LMWH in selected patients seems comparable with the survival advantage demonstrated with the very expensive targeted drugs currently used in oncology.[79-82] New studies in various malignancies will follow soon and will attract more attention from oncologists. When the effect of LMWH has been definitely proven in patients with advanced disease, the next step will be to add LMWH to adjuvant treatment in cancer patients. The main goal of adjuvant treatment in, for example, breast or colorectal cancer is to prevent the development of local recurrence and distant metastases. This is currently achieved with standard chemotherapy. Trials in breast cancer have shown that adding targeted therapy with monoclonal antibodies is improving disease-free survival in certain types of breast cancer.[85,86] By adding this targeted immunotherapy to the standard therapy a substantial reduction in recurrences has been achieved. When it has indeed been proven that LMWH prolongs survival in advanced disease, LMWH treatment in the adjuvant setting added to the standard adjuvant treatment with chemotherapy and targeted therapy might give a further reduction in recurrences and distant metastases in breast cancer patients and other cancers. Further understanding of the pathophysiology of the hypercoagulability in cancer will lead to the development of new tools in conquering the cancer.

## CONCLUSIONS

Almost one and a half century after Armand Trousseau first noted the hypercoagulability in cancer patients, we are beginning to understand that many proteins of the haemostatic and fibrinolytic system play a pivotal role in tumour biology. By activating the haemostatic and fibrinolytic systems, tumour cells are able to grow, form new blood vessels and metastasise. This activation of the coagulation system leads to an increased risk of thromboembolism in cancer patients. More insight in the underlying mechanisms might lead to the discovery of new agents that interfere with vital processes in tumour behaviour. Armand Trousseau could only dream of these developments.

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ORIGINAL ARTICLE

# Application of guidelines on preoperative antibiotic prophylaxis in León, Nicaragua

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## ABSTRACT

**Background: To determine adherence to the guideline for preoperative antibiotic use in Nicaragua.**
**Methods: An observational study in the University Hospital of León, Nicaragua. All surgical patients in the departments of general surgery, orthopaedics, gynaecology and obstetrics, and paediatrics during a four-week period were included. Patients with infections prior to surgery were excluded. Main outcome measures were the proportion of patients that received appropriate preoperative antibiotics based on wound classification, suspected pathogens, administered antibiotics (type and dose), therapy duration and timing according to the local protocol.**
**Results: In the study, 297 patients received a total of 395 antibiotics with 2595 doses for a total of 1087 days. Only 68% of patients received antibiotic prophylaxis for indications mentioned in the protocol. Antibiotics were given without indication or as treatment in 23%. In 9% of the cases no preoperative antibiotic therapy was given (no indication for 6%, but indicated for 3%). Of the 201 patients with an indication for prophylaxis, 25% received more antibiotic therapies than indicated. Antibiotic choice was discordant with the protocol in 69%, dose in 20%, and both the moment of administration and duration in 78%. Overall adherence was achieved in 7% of patients. Complete protocol violations were observed in 12%. The 243 patients in the prophylaxis group received 1707 doses, 83% of which were administered unnecessarily.**
**Conclusion: Protocol violations are frequent in preoperative antibiotic prophylaxis in Nicaragua leading to considerable overprescription. Educational strategies to reinforce protocolised antibiotic use are essential for reducing costs and antibiotic resistance rates.**

## KEYWORDS

Adherence, antibiotic prophylaxis, protocol, surgical site infection

## INTRODUCTION

When appropriate antibiotic prophylaxis is used, the incidence of surgical site infections is between 2 and 5% and the associated mortality is 0.6%.[1,2] Inadequate prophylaxis leads to an increased incidence of surgical site infections of up to 15%.[3-5] Studies have shown inappropriate antibiotic prophylaxis, hyperglycaemia, preoperative condition (ASA score), wound classification and the duration of the operation to be independent risk factors for such infections.[3,6] The aetiology of surgical site infections is dependent on the location of the surgery, the bacterial load in the tissue or blood perioperatively and the integrity of host defenses.[2,4,6] Adequate prevention of such infections is important because they are associated with increased mortality and hospital costs of up to tenfold.[2,4,6-8] Inappropriate use of antibiotics (including overprescription and the unnecessary use of broad-spectrum antibiotics) can also lead to increased bacterial resistance.[9,10] A sound and restrictive policy minimises antibiotic resistance, prevents surgical site infections and is cost-effective.[11-13]

Protocols for antibiotic prophylaxis have been designed worldwide to optimise local administration of antibiotics. Monitoring and intervention can be effective in increasing the adherence to a protocol as has been shown in studies in which the appropriateness of antibiotic prophylaxis was increased from around 50 to 95 to 100% by the stricter implementation of an existing protocol.[14,15]

As baseline data are lacking in Nicaragua, we set out to evaluate the adherence to guidelines for preoperative antibiotic use in León, Nicaragua.

## METHODS

### Preoperative antibiotic guidelines

In Nicaragua, the Ministry of Health published two documents on preoperative antibiotic treatment in the mid-1990s. In 1997, a nationwide project was initiated to promote rational use of medications on the basis of these documents.[16] In 2000, the University of León and the Ministry of Health collaborated on this topic and published a final protocol for the preoperative use of antibiotics.[17] To detect deviations from the protocols in Western countries, the widely accepted Dutch protocol formulated by the SWAB (Dutch Working Party on Antibiotic Policy) was used as a reference.[18] Even though there are some minor differences between Dutch hospitals, the SWAB guidelines are used in this study as the official Dutch national protocol for comparison purposes. The Nicaraguan and Dutch protocols were compared on a number of points: wound classification, most likely pathogens, suggested antibiotics (primary and secondary), and ideal moment of administration.

### Design, setting and study population

We conducted an observational study during a four-week period in 2005 in the University Hospital of León, Nicaragua. All consecutive persons of any age undergoing surgery in the departments of general surgery, orthopaedics, gynaecology and obstetrics, and paediatrics were eligible for inclusion into the study. We excluded patients with current infections or contaminated wounds prior to surgery by review of the patient records. When an infection became apparent during the operation, the initial prophylaxis was switched to treatment. Therefore, only the initial dose given prior to surgery was evaluated.

### Measurements

During the study period, all patient records from the participating departments were checked on a daily basis for new surgical procedures as well as to follow up the patients already included in the study. For our research purposes, a case record form was developed which included information on patient characteristics, surgical procedures and antibiotic treatments for each subject. Wound classification was obtained from the antibiotic ordering form which was sent to the hospital pharmacy for each patient prior to surgery. When the wound classification was not reported, the wound was classified from the operation report according to the Nicaraguan protocol standards for that type of surgical procedure.[16]

Follow-up data were updated daily with regard to additionally administered doses, changes in type of antibiotic medication and administration intervals as well as for signs of postoperative wound infections. If more than one antibiotic was prescribed, they were evaluated separately. Subsequently, a final assessment of all antibiotics per patient was made. Antibiotic therapy given to patients at discharge was not included. All antibiotics administered within 1.5 hours before surgery were recorded as being concordant with the Nicaraguan protocol.[16] When the patient record indicated 'antibiotics given in the operating theatre', such antibiotics were regarded as being given at the start of anaesthesia. The authors did not attend the surgical procedures themselves, thus not influencing the timing and administration of antibiotics by their presence. All other moments of administration in relation to the surgery were treated as protocol violations. All antibiotics prescribed were compared with the Nicaraguan protocol.

## RESULTS

A comparison of the Nicaraguan and Dutch protocols (*table 1*) shows only minor differences between them. The moment of administration is stricter in Nicaragua but the criteria for a second dose during surgery are the same. Moreover, the Nicaraguan protocol does not differentiate between contaminated and dirty wounds. The Nicaraguan and Dutch protocols use the same definition for surgical site infections.

Of the 297 patients, the majority of procedures were carried out in women (80%) and the mean age was 29 years (standard deviation 18 years). Most patients were from the obstetric wards (45%), followed by general surgery (21%), gynaecology (15%), paediatrics (10%) and orthopaedic wards (8%). Comorbidity was present in 12% of these patients, and 2% had a known allergy to antibiotics. Of all surgical wounds, 77% were clean-contaminated, 14% were clean and 9% were contaminated-dirty. The mean duration of the surgical procedure was 56 minutes (standard deviation 39 minutes). Only 1.4% of patients had an infection postoperatively.

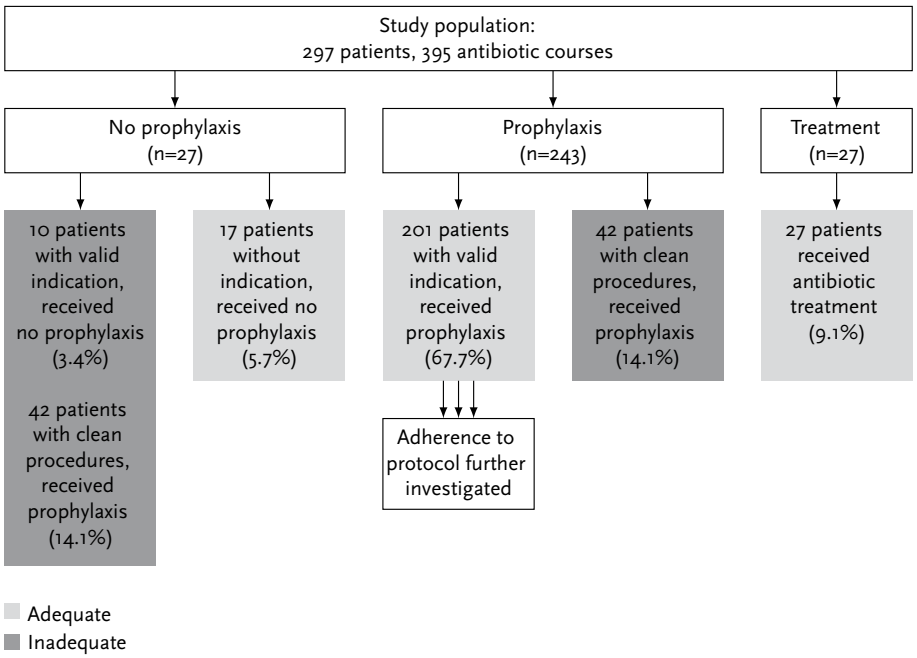
In all, 395 antibiotic therapies were prescribed for these 297 patients (*figure 1*). The majority, 201 patients (68%), received antibiotics for an appropriate prophylaxis indication. However, 69 cases (23%) received antibiotics either without indication since the procedure could be considered a clean one (42 patients, 14.1%) or as antibiotic treatment (27 patients, 9.1%) for a contaminated wound. Contaminated wounds are susceptible to infections due to the presence of bacteria in the wound and therefore require more intensive treatment than prophylaxis alone.

**Table 1.** *Protocol comparison*

| | **Léon, Nicaragua** | **Utrecht, the Netherlands** |
|---|---|---|
| Time of administration | 90-15 minutes before incision | 120-30 minutes before incision |
| Additional dose* | Every 3-4 hours with: operation length >3 x $t^{1}/_{2(antibiotic)}$, blood loss >2 litres, extracorporal circulation | |
| Wound classification | Clean (surgery without trauma or infection, with asepsis, without opening airways, intestinal tract or urogenital system and without implantation of prostheses): no prophylaxis indicated | Clean (elective surgery, closed without drains, no infection found, good asepsis, without opening airways, intestinal tract or urogenital system): no prophylaxis indicated |
| | Clean-contaminated: controlled opening of the airways, intestinal tract, biliary tract or urogenital system. Penetrating abdominal trauma without signs of visceral damage or infection during surgery, cardiothoracic surgery, large vessel surgery | Clean-contaminated: controlled opening of the airways, intestinal tract, biliary tract or urogenital system<br><br>Contaminated: open traumatic wounds, leakage from intestinal tract, open urogenital or biliary tract with infected urine or bile, infection without pus |
| | Contaminated-dirty: therapy required, all surgery that is not clean or clean-contaminated | Dirty-infected: traumatic wounds with necrosis, corpus alienum or (faecal) infection, perforated viscera, acute bacterial infection with pus |
| Surgical site infection | Manifest after a surgical procedure (within 48 hours) and have a direct relation to this procedure | |

*The rules for administering an additional dose are the same in both countries.

**Figure 1.** *Patient flow chart*




No antibiotics were received by 27 patients since they were not indicated in a clean procedure (17 patients, 5.7%) or prophylaxis was indicated but not prescribed (10 patients, 3.4%). All 96 patients who did not receive prophylactic antibiotic treatment were not followed up further.

In total, 201 patients with an indication for prophylaxis received 282 antibiotic therapies. In 51 patients (25.4%) an additional antibiotic therapy was prescribed, contrary to the protocol. Of these 282 prescriptions, antibiotic choice was discordant with the hospital protocol in 68.8%, dose in 19.9%, moment of administration in 77.7% and duration in 78.4%. Overall, 690 violations of any aspect were recorded in the 282 antibiotic therapies. Overall adherence to the protocol was achieved with only 21 (7.4%) antibiotic therapies, 38 (13.5%) were in accordance with the protocol on all but one item, 41 (14.5%) on two items and 149 (52.8%) were only correctly prescribed for one item

(mostly a correct dose). In 33 cases (11.7%) the antibiotics were not in accordance with any of the items mentioned in the protocol. There were no statistically significant differences in protocol adherence between the different surgical wards.

The 201 patients who were given prophylaxis received 211 (of 282) antibiotic therapies perioperatively, 71 courses (25%) were given additionally at a later time. Of all 211 initial therapies 78% of the antibiotics were administered outside the correct dosing interval; 63% were administered after the operation, with a mean delay of 6.9 hours. Fifteen percent of the antibiotics were administered ≥90 minutes before entering the operating theatre, on average 8.8 hours before surgery. Only 22% were administered in the correct dosing interval. Eleven percent of antibiotics were administered between 90 minutes before entry and entering the operating theatre. Another 11% were administered in the operating theatre. For these, it was not possible to establish a more precise moment of administration and it was assumed that they were given prior to incision.

Protocols for prophylaxis propose the preferential use of certain antibiotics over others. An overview of the types of antibiotics used in patients in whom prophylaxis was given for a valid indication is shown in *table 2*. Ampicillin (58.3%) and cefazolin (13.0%) were most often prescribed. Cefazolin and cefoxitin are the antibiotics that are most often administered correctly according to the protocol (*table 3*). Ampicillin and ceftriaxone are not mentioned in the protocol, but they are often prescribed for prophylactic purposes.

The 243 patients in the prophylaxis group (*figure 1*) received a total of 322 antibiotic therapies or 1707 doses for a total of 721 days in the four-week study period. According to the protocol, 1409 of these 1707 doses (83%) were administered unnecessarily for 411 days, as regulations indicated that fewer doses would have been sufficient. There were no patient characteristics, wards or types of antibiotic which could significantly predict overprescription.

**Table 2.** *Administration of antibiotics of the study population (n=201)*‡

| Antibiotic received | % of total | No. of doses | No. of days |
|---|---|---|---|
| Ampicillin | 58.3% | 793 | 272 |
| Cefazolin* | 13.0% | 177 | 93 |
| Gentamicin* | 9.8% | 133 | 90 |
| Penicillin | 5.7% | 77 | 25 |
| Cefoxitin* | 4.7% | 64 | 33 |
| Ciprofloxacin | 2.3% | 31 | 24 |
| Ceftriaxone | 1.3% | 17 | 12 |
| Metronidazole* | 1.2% | 16 | 8 |
| Amoxicillin* | 0.6% | 8 | 6 |
| Others** | 3.2% | 44 | 26 |
| *Total* | *100%* | *1360* | *589* |

‡**Initial, first-choice therapies only;** ***antibiotics mentioned in the prophylactic protocol;** ****dicloxacillin, amikacin, cephalexin, clindamycin, nitrofurantoin, cefadroxil.**

**Table 3.** *Local prophylaxis guideline**

| Type of surgery (clean-contaminated) | Recommended antibiotics |
|---|---|
| Head and neck surgery | 1. Cefazolin<br>2. Clindamycin + gentamicin |
| Stomach/duodenal/biliary surgery | 1. Cefazolin<br>2. Clindamycin + gentamicin |
| Colorectal surgery, appendectomy (nonperforated) | 1. Cefoxitin<br>2. Clindamycin + gentamicin |
| Penetrating abdominal trauma | 1. Cefoxitin ± gentamicin<br>2. Clindamycin + gentamicin |
| Vaginal surgery, caesarean section, abdominal hysterectomies | 1. Cefazolin<br>2. Clindamycin ± metronidazole |
| Cardiovascular surgery | 1. Cefazolin<br>2. Vancomycin |

***In the local guidelines, for each type of surgery, two choices of antibiotic prophylaxis are given.**

## DISCUSSION

When the Dutch and Nicaraguan protocols are compared, there are few differences in the timing of antibiotic prophylaxis and wound classification.[16-18] Furthermore, the expected pathogens for each type of surgery and the primary antibiotics recommended are generally the same (results not shown). However, about half of the antibiotics used (*table 2*) are not mentioned as a suitable prophylactic drug either in the Nicaraguan or Dutch protocols. Of these drugs, ampicillin is used in León by the gynaecologists as standard prophylaxis for caesarean sections. This use is not supported by the local infectious diseases specialist and there are no bacterial resistance or sensitivity data that warrant its use. Therefore, these cases were considered protocol violations. Many of the studied patients underwent a caesarean section and the use of ampicillin thus influences the results significantly.

The study data indicate that protocol violations are frequent in preoperative antibiotic prophylaxis in Nicaragua, which leads to considerable overprescription of antibiotics. It has been established in numerous studies that the use of preoperative prophylaxis reduces

the rate of surgical site infections and it is now accepted as standard care (and recommended by the Centre for Disease Control).[3-5] It was shown that for 68% of patients the appropriate choice to administer antibiotics is made. In addition in 5% of the cases the appropriate decision of not administering prophylaxis was made. However, when the indication was appropriate, antibiotic choice, duration, dose and timing were discordant with hospital guidelines in many patients. Van Kasteren *et al.* conducted a similar study in 13 Dutch hospitals and found antibiotic choice to be discordant with hospital guidelines in 8%, duration in 18%, dose in 11% and timing in 50%.[19] Considering these much lower discordance rates with the protocol, we may conclude that there is still room for improvement in adherence to the protocol in Nicaragua. A more recent study showed that the implementation of the SWAB guidelines improved long-term adherence.[13] This resulted in a decrease in inappropriate antimicrobial use and lowered costs without impairing patient outcome.

Of particular concern is the timing of the prophylaxis in Nicaragua. The majority of antibiotics are administered outside the correct preoperative dosing window. Most antibiotics were administered too early or too late leading to ineffective antibiotic blood levels at the time of surgery. A limitation of this study is the inability to comment on the 9% of antibiotics administered in the operating theatre, because it is unclear if the antibiotic was given before or after the incision. In future studies one could consider a method to record the timing more precisely. In some cases antibiotics were given for periods longer than 24 hours. Studies have shown, however, that effective prophylaxis can be established with short courses of less than 24 hours and that longer administration not only has no benefit but may be detrimental due to an increased incidence of resistance.[2,20] Moreover, during a caesarean section, guidelines advise antibiotic prophylaxis just after cutting the umbilical cord, but in this study, only 14 caesarean sections (11%) were performed correctly as advised. In 21 patients (16%), prophylaxis was given before the caesarean section and in 94 patients (73%) prophylaxis was given on the ward, 0.5 to 24 hours after the caesarean section.

Currently prophylactic antibiotics take up a large part, up to 30% or more, of the prescribed antibiotics in hospitals.[14] Adherence to local guidelines could keep costs to a minimum. Literature suggests various cost-effective strategies to improve protocol adherence. Prado *et al.* show that when the pharmacy is given a central role in the administration of prophylaxis, the appropriateness of the indication increased from 56 to 100%, while the costs decreased by 40%.[15] Moreover, Zwar et al. found that giving feedback on prescription behaviour increased the appropriateness of the prescriptions.[21] Welschen *et al.* conclude that by organising a group education and consensus meeting and monitoring prescriber behaviour, prescription errors decreased by 12% compared with controls.[22] Alerany *et al.* showed that integrating all the above strategies resulted in an increase in the adherence from 51 to 95% in operations requiring prophylaxis.[14] They used an antibiotic prophylaxis chart in the operating theatres, pharmacy-controlled administration and education and prescriber feedback. It can be noted that the main causes of misuse in the article by Alerany *et al.* were timing and choice, which were also problematic in this study.

In León, antibiotics must be ordered from the pharmacy prior to the operation. A specific form must be completed for all procedures, including clean ones. It is the only form on which the wound classification has to be indicated and if not filled in completely, the information might be lost. This form was completed for only 25% of the study subjects. It is important for future prescriptions to stress the value of filling in this form. An effort to consistently classify the wounds might result in a better awareness and understanding of the protocol and, subsequently, the adherence to it.

General population statistics show that an allergy to antibiotics occurs in roughly 5 to 10% of the population.[23] Thus a 2.4% allergy rate in our study population could be an underestimation.
The incidence of surgical site infections or postoperative infections ranges from 2.5 to 10% depending on the type of surgery.[8,24] It was not part of the objective to study the effectiveness of the protocol in terms of prevention of surgical site infections.

## CONCLUSION

Adherence to the preoperative antibiotic therapy protocol is far from optimal and in concordance with the Nicaraguan guidelines leading to more than half of the antibiotic doses administered unnecessarily according to the protocol rules. This is a huge toll on the budget of the hospital and obviously also plays a major role in the formation of antibiotic resistance. Successful prescription of antibiotic prophylaxis is dependent on the national policy on the control of antimicrobials, quality of the local protocols, their implementation, hospital staff education, monitoring, and feedback interventions to increase the adherence.

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ORIGINAL ARTICLE

# The safety of electroconvulsive therapy in patients with asthma

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## ABSTRACT

**Background: Patients with depression and other psychiatric disorders being considered for electroconvulsive therapy (ECT) may also have asthma. Since ECT requires the administration of general anaesthesia, it is assumed that extra care should be taken with asthmatic patients before and during ECT. We sought to investigate the safety of ECT in asthmatic patients.**

**Methods: A retrospective review was conducted of the medical records of all of the patients with currently active and managed asthma who underwent ECT for severe depressive syndromes at Mayo Clinic, Rochester, Minnesota, between 1 January 1998, and 30 June 2006.**

**Results: Thirty-four patients with asthma who also underwent ECT were identified. Of these, 27 (79%) were women. The median age was 45 years (range 23-84 years). All 34 patients were using asthma medications daily at the time of ECT. The 34 patients underwent a total of 459 ECT sessions. Four (12%) patients experienced exacerbation of their asthma on a total of five occasions. Each exacerbation was successfully treated with standard asthma medications, and all four patients completed their courses of ECT.**

**Conclusion: ECT in patients with asthma appears to be safe. Although exacerbation of asthma after ECT was rare in our series, a prospective study would be needed to determine the precise risk of pulmonary complications of ECT in asthmatic patients.**

## KEYWORDS

Asthma, electroconvulsive therapy, pulmonary complications, reactive airways disease

## INTRODUCTION

Electroconvulsive therapy (ECT) is a commonly used psychiatric procedure for patients with severe depression or other syndromes.[1] Asthma is also a common condition; hence, ECT practitioners and clinicians who conduct preprocedure assessments of patients being considered for ECT should expect to encounter and manage some patients with asthma. However, only one case of an asthmatic patient treated with ECT has been reported.[2] ECT involves the administration of general anaesthesia; thus, one might expect more complications (e.g. bronchospasm) among asthmatic patients during and after ECT than in patients without asthma. Although ECT is a procedure with low morbidity and mortality,[3] it is assumed that care (e.g. premedication with bronchodilators or continuous pulse oximetry monitoring) should be taken before and during ECT in patients with asthma. At Mayo Clinic, more than 3000 ECT sessions are conducted every year. Herein, we report our experience treating asthmatic patients with ECT. We also provide a set of recommendations for the preprocedural and intraprocedural management of asthmatic patients undergoing ECT.

## METHODS

The Mayo Foundation Institutional Review Board granted permission to undertake this retrospective records review. A computerised search of the medical records of all patients who underwent ECT at our tertiary care academic medical institution between 1 January 1998 and 30 June 2006 identified any patient whose medical records also contained the term *asthma* (or a synonym such as *reactive airways disease*). Using an algorithm described previously,[4] we further identified among these patients all of those who

had asthma. Patients were identified as having asthma if they met one or more of the following criteria in the year before having ECT: 1) a diagnosis of asthma in the hospital database; 2) the dispensing of two or more asthma-related medications (i.e. filling a prescription for one medication and refilling it within one year or filling prescriptions for two different medications); 3) an asthma-related visit to an emergency department or clinic. Asthma-related medications included β-agonist and corticosteroid inhalers, other inhaled anti-inflammatory drugs, and oral leukotriene inhibitors. Patients excluded from the current study were those who had a distant history of asthma but no symptoms of asthma and no recent (i.e. within one year) asthma-related clinic, emergency department, or hospital visits, and were not currently using asthma medications. Most of the other excluded patients did not have asthma but had another airway disease (e.g. chronic obstructive lung disease) or no airway disease at all. The medical records of the patients with asthma were then carefully reviewed, and relevant data were abstracted on the patients' demographic features, history and physical examination findings, and laboratory test results (e.g. pulmonary function tests (pFTs)). We also recorded any relevant data from the course of ECT, such as number of treatments and complications (e.g. respiratory distress). At our institution, patients for whom ECT is being considered have a preprocedure history taken and undergo a physical examination, blood tests (including a complete blood cell count and measurement of electrolytes), and an electrocardiogram. When indicated, further testing may include chest X-rays, PFTs, and cardiac stress tests. All patients take nothing by mouth after midnight the morning before each ECT session except for any necessary medications, which for asthmatics might include inhalers. The ECT technique at our institution begins with the administration of intravenous glycopyrrolate a few minutes before the treatment as an antisialagogue and to reduce the likelihood of bradyarrhythmia during and shortly after the ECT-induced seizure.[5] General anaesthesia is usually induced with thiopental sodium but occasionally with methohexital sodium, etomidate, propofol, and, rarely, with sevoflurane in certain circumstances.[6] Muscular paralysis is induced with succinylcholine chloride, a depolarising agent. Respiration is maintained using positive pressure ventilation with 100% oxygen and continuous-pulse oximetry. Continuous ECG and frequent blood pressure monitoring are also maintained. Patients are discharged from the postanaesthesia care unit when their vital signs are stable, (airway) maintenance is unassisted, and level of consciousness is commensurate either with going back to their hospital room or to being dismissed home with an adult in attendance. Notably, patients with asthma who undergo ECT at our institution continue their asthma medications as prescribed by their primary clinician throughout the ECT course.

## RESULTS

The computerised search of the medical records of all patients who had ECT between 1 January 1998 and 30 June 2006 identified 102 patients whose medical records also included the word *asthma*. Of these 102 patients, 34 were determined to have currently active and managed asthma. The demographic and clinical features of the 34 patients with asthma who underwent ECT are summarised in *table 1*. For all 34 patients, the indication for ECT was a depressive syndrome. Of the 34 patients, 27 (79%) were women. Their median age was 45 years (range 23-84 years). Nine patients (26%) were smokers. All 34 patients were using asthma medications daily at the time they had ECT. Twenty-eight patients (82%) were using inhaled corticosteroids daily. Thirty-three patients (97%) were using inhaled β-agonists regularly. Overall, the 34 patients underwent 459 ECT sessions. The median number of treatments per patient was eight (range 2-61). The reasons for such a wide range of ECT sessions included the withdrawal of some patients from ECT before completion of the series of treatments and the use of maintenance ECT in some patients because of their history of recurrent, medication-refractory depression. For all 34 patients, ECT was well tolerated and free from intraprocedural complications. Four patients (12%) experienced a total of five postprocedure exacerbations of asthma. Only one of these four patients was a smoker. An upper respiratory tract infection developed in two patients. One patient (patient 2) developed wheezing after the first ECT session. She was treated with antibiotics and an inhaled corticosteroid, and she had to use bronchodilators more often. Although her second ECT session was delayed for three days, she ultimately completed her course of ECT. The other patient (patient 34) developed dyspnoea and wheezing after the third ECT session. She improved after treatment with a nebulised β-agonist bronchodilator. After her fourth ECT session, the dyspnoea recurred. She also developed a cough with clear sputum production. Physical examination revealed clear lung fields, and a chest X-ray was unremarkable. She was treated with antibiotics and inhaled salmeterol xinafoate, and her symptoms promptly improved. She completed her course of ECT without delay or further respiratory problems. In the third patient (patient 23), wheezing developed after an ECT session. It was successfully treated with the regular administration of an inhaled β-agonist. Her symptoms resolved, and she completed the course of ECT without delay. The fourth patient (patient 24), a smoker, underwent several courses of ECT. She experienced one asthma exacerbation during each of two different courses of ECT. Both exacerbations were successfully controlled with the scheduled regular administration of an inhaled β-agonist, and she was able to complete each course of ECT without delay. Notably, when patient 17 was admitted to the inpatient psychiatry unit before undergoing ECT, she was

**Table 1.** *Characteristics of 34 patients with asthma who had electroconvulsive therapy*

| Patient no. | Age (years) | Sex | ECT treatments, no. | Smoking status | Daily asthma medications* |
|---|---|---|---|---|---|
| 1 | 40 | F | 6 | Yes | Fluticasone propionate and salmeterol xinafoate |
| 2 | 55 | F | 5 | No | Fluticasone and albuterol sulphate<br>Oral montelukast sodium |
| 3 | 42 | F | 6 | No | Fluticasone, salmeterol, and albuterol |
| 4 | 23 | F | 9 | Yes | Albuterol |
| 5 | 32 | F | 6 | Yes | Fluticasone, salmeterol, albuterol, and tiotropium bromide |
| 6 | 40 | F | 5 | Yes | Fluticasone and albuterol |
| 7 | 37 | F | 44 | No | Fluticasone and albuterol |
| 8 | 67 | F | 15 | No | Fluticasone and salmeterol<br>Ipratropium bromide and albuterol<br>Oral montelukast and corticosteroids |
| 9 | 39 | M | 8 | No | Salmeterol and albuterol |
| 10 | 58 | F | 7 | No | Fluticasone and albuterol |
| 11 | 57 | F | 4 | No | Triamcinolone acetonide, salmeterol, albuterol, and ipratropium |
| 12 | 42 | F | 19 | No | Fluticasone and albuterol<br>Oral corticosteroids |
| 13 | 25 | F | 2 | No | Budesonide, salmeterol, and albuterol |
| 14 | 48 | M | 28 | Yes | Fluticasone, salmeterol, and albuterol |
| 15 | 33 | F | 16 | No | Salmeterol |
| 16 | 49 | F | 6 | No | Fluticasone and albuterol |
| 17 | 35 | F | 7 | Yes | Albuterol |
| 18 | 28 | M | 32 | No | Albuterol<br>Oral montelukast |
| 19 | 47 | M | 5 | No | Triamcinolone, salmeterol, and albuterol |
| 20 | 45 | F | 25 | Yes | Fluticasone, salmeterol, and albuterol<br>Oral corticosteroids |
| 21 | 32 | F | 7 | No | Flunisolide and albuterol |
| 22 | 53 | F | 11 | No | Triamcinolone and albuterol |
| 23 | 61 | F | 61 | No | Budesonide, salmeterol, and albuterol |
| 24 | 41 | F | 22 | Yes | Triamcinolone, salmeterol, and albuterol |
| 25 | 60 | M | 3 | No | Fluticasone and albuterol |
| 26 | 71 | F | 6 | No | Budesonide, salmeterol, and albuterol<br>Oral montelukast |
| 27 | 62 | M | 7 | Yes | Fluticasone and albuterol |
| 28 | 84 | F | 11 | No | Fluticasone |
| 29 | 34 | F | 10 | No | Fluticasone and albuterol |
| 30 | 45 | M | 8 | Yes | Fluticasone, salmeterol, and albuterol |
| 31 | 38 | F | 6 | No | Fluticasone, salmeterol, and albuterol |
| 32 | 64 | F | 8 | No | Fluticasone and albuterol |
| 33 | 45 | F | 16 | No | Triamcinolone and salmeterol |
| 34 | 47 | F | 8 | No | Salmeterol and albuterol |

**ECT = electroconvulsive therapy; F = female; M = male. *Inhalants unless otherwise indicated.**

actively wheezing. For the first several days after admission, she received scheduled inhaled β-agonist treatments more frequently than her usual regimen, resulting in prompt resolution of her symptoms. She started and completed her course of ECT without delay.

## DISCUSSION

Little extant medical literature informs clinicians about the risk and management of pulmonary complications in patients with asthma who are undergoing ECT. Such reports exist, however, for the surgical setting. In the surgical setting, risk factors for postprocedure pulmonary complications include recent asthma symptoms, recently added medications, therapy in a medical facility for asthma symptoms, and a history of endotracheal intubation for asthma.[7] Airway instrumentation (specifically endotracheal intubation) may cause intraoperative bronchospasm in patients with asthma.[8-10] The overall risk of bronchospasm and other pulmonary complications appears to be low in patients with stable asthma.[11] Face masks and laryngeal mask airways are associated with less airway hyperreactivity.[12,13] Our report is the first to consider a series

of patients with asthma who have had ECT. We found ECT to be safe and well tolerated by 34 asthmatic patients who underwent 459 ECT sessions. Only four patients experienced five postprocedure asthma exacerbations, all of which were successfully treated, allowing all four patients to complete their respective courses of ECT. Our findings suggest that for patients with currently active and medically managed asthma, there is a low risk of pulmonary complications during or after ECT, which does not involve routine intubation and lasts only a few minutes. On the basis of the literature and our findings, we have several recommendations for the medical management of patients with asthma who are being considered for ECT. Before ECT, each patient should have a thorough medical history taken and undergo a complete physical examination which, in turn, should provide guidance about the need for additional testing. The patient should be asked about asthma exacerbation triggers (e.g. cold or exertion), the frequency of asthma exacerbations, and the intensity of the treatment required after exacerbation (e.g. visits to hospital emergency department). Patients should be asked about their current medication use (e.g. type, dose, and frequency) and their need for systemic corticosteroids. Patients should also be asked about their current symptoms and any recent history of upper respiratory tract infections. Many clinicians obtain PFTs in asthmatic patients before surgical and other procedures (including ECT). However, PFTs may have findings that are within the normal limits in patients who have well-controlled asymptomatic asthma, and normal findings of PFTs do not rule out bronchial hyperreactivity.[14] Furthermore, PFTs do not always produce findings that correlate with the severity or frequency of asthma symptoms.[15] Nevertheless, PFTs may provide useful information to clinicians who are managing patients undergoing ECT. For example, if the forced expiratory volume in one second improves more than 15% after administration of an inhaled β-agonist, the patient should receive treatment with an inhaled β-agonist before surgery; if the patient is already being treated with an inhaled β-agonist, the patient's asthma regimen should be intensified.[16] However, prospective data are not available on the utility of this approach for patients with asthma undergoing ECT. The medical management of patients with persistent asthma, regardless of severity, should include inhaled corticosteroids, and evidence suggests that adding a long-acting β-agonist to an inhaled corticosteroid improves lung function, lessens asthma exacerbations, and reduces the need for rescue therapy.[17] Indeed, most of our patients were taking this combination of medications. Although it seems reasonable to administer inhalers prophylactically before an ECT session, there is little published support for this practice. However, a study in adult patients with asthma who were not already using daily asthma medications found that those who were given a combination of both oral steroids and inhaled β-agonists had a marked reduction in bronchospasm evoked by tracheal intubation, which supports the notion that such patients should receive preoperative therapy.[18] Actively wheezing patients require more aggressive treatment, such as regular and more frequent administration of inhaled β-agonists.[11] Precipitating factors (e.g. respiratory infection) should be treated. In fact, the five asthma exacerbations that occurred in four of our patients following ECT sessions were treated successfully, allowing all four patients to ultimately complete their courses of ECT. Smokers who have moderate to severe airway obstruction on preprocedure PFTs have more bronchospasm during and after anaesthesia for surgical procedures, which suggests a low threshold for intensifying asthma regimens in these patients.[8] However, only one smoker in our series experienced pulmonary complications after an ECT session. Our series is too small to determine whether the four patients who experienced pulmonary complications differ from those who did not experience complications. However, three of the four patients in our series were managed with three asthma medications; the other patient was a smoker managed with two asthma medications. These features suggest more active asthma. However, many other patients who were managed with three or more asthma medications or were smokers or both did not experience pulmonary complications. Special mention should be made of the methylxanthines (e.g. theophylline). These agents are no longer the first-line medication for management of asthma, and they have the potential for clinically significant toxicity.[19] Theophylline has a narrow therapeutic index, and clinicians should consider discontinuing this agent 24 hours before ECT to reduce the risk of status epilepticus.[20-23] In addition, fluorinated volatile anaesthetics can cause ventricular arrhythmia in patients receiving theophylline, so it would be best to use intravenous induction in such patients.[24] None of our patients were taking theophylline. Notably, there is some evidence that induction of general anaesthesia with propofol substantially reduces the incidence of wheezing after induction compared with barbiturate induction, probably because thiobarbiturates may release some histamine.[25,26] Our study has a number of limitations. An important limitation is its retrospective design. For example, asthmatic patients with depression may not have been offered ECT because of their asthma. Also, some asthmatic patients offered ECT may have refused it out of concern about exacerbating their asthma. These patients would not be included in our analysis. Furthermore, although we used an algorithm described previously[4] to identify patients with asthma for our study, we excluded patients with a history of asthma that had been inactive for more than one year (e.g. not using asthma medicines). Hence, these patients who might have experienced peri-ECT pulmonary complications related to their prior

histories of asthma would not be included in our analysis. If anything, however, excluding these patients from our analysis likely biases our results toward finding more pulmonary complications because our patient population had currently active and managed asthma. Yet, we found that only four of our patients (12%) experienced pulmonary complications while undergoing a large number of ECT sessions. Nevertheless, only a prospective study would be able to determine with precision the risk of pulmonary complications in patients with asthma who undergo ECT.

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CASE REPORT

# Successful treatment of myelodysplastic syndrome-induced pyoderma gangrenosum

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## ABSTRACT

**We report successful treatment of a refractory myelodysplastic syndrome-associated pyoderma gangrenosum with the combination of thalidomide and interferon-α2a in a single patient. A non-healing wound developed on a 40-year-old woman's left thumb after minor trauma. Massive ulcerovegetative lesions developed after reconstruction surgery. Histopathological examination of the bone marrow and cytogenetic studies revealed an atypical myeloproliferative/myelodysplastic syndrome. The skin lesions resolved dramatically after two months of thalidomide and interferon-α2a combination therapy and the haematological status improved.**

## KEYWORDS

Melodysplastic syndrome, pyoderma gangrenosum, thalidomide, trisomy 8

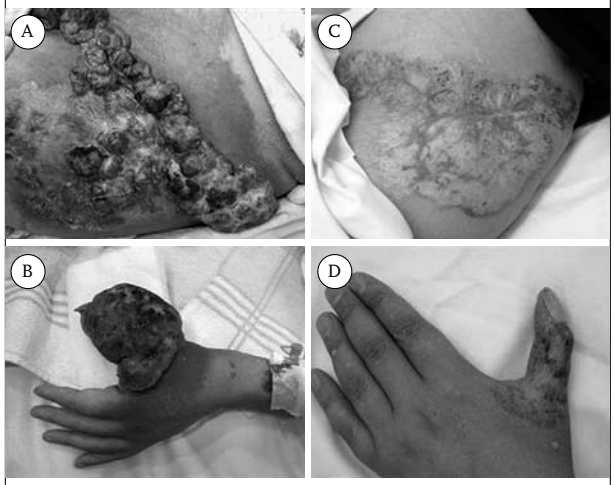
## INTRODUCTION

Pyoderma gangrenosum is a painful, noninfectious, ulcerovegetative skin disorder which may be associated with myelodysplastic syndromes (MDS).[1] Angiogenesis and immunobiological abnormalities are among the key events sticking the pathological pieces of MDS and pyoderma gangrenosum together.[1-3] Clinical management of both pyoderma gangrenosum and MDS represents a great challenge.[1,4-5] We report here the successful treatment of a refractory MDS-associated pyoderma gangrenosum with the combination of thalidomide and interferon-α2a in a single patient. This combination of antiangiogenic, immunosuppressive, and biological response modifier drugs resulted in the resolution of massive ulcerovegetative lesions of pyoderma gangrenosum and the dyshaematopoiesis and cytopenias of MDS.

## CASE REPORT

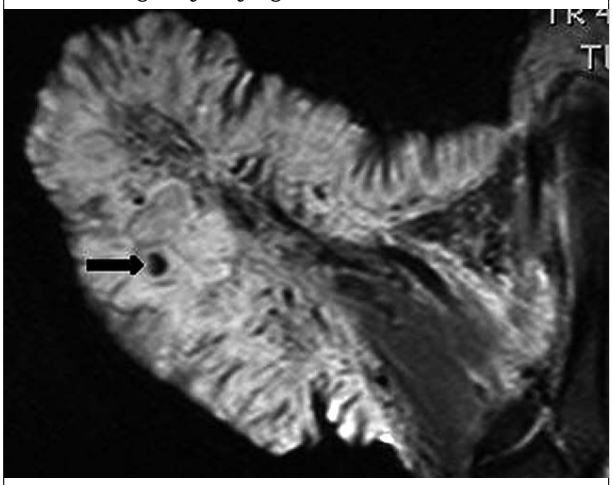
A 40-year-old woman with documented antiphospholipid syndrome (APS) associated with a history of recurrent abortions was admitted to a rural hospital complaining of non-healing wounds. Three months before the admission, she had sustained a minor knife cut on her left thumb which had not healed. A graft from her left inguinal region was implanted to the wound on her hand in the rural hospital. After the surgery, massive ulcerovegetative lesions developed both in the graft region and on her thumb. She was then admitted to the Department of Plastic Surgery in our hospital. During this admission, her left thumb and left inguinal region were oedematous with numerous verrucous papules and purulent discharge (*figure 1*). The lesions, which were compatible with pyoderma gangrenosum, were situated from the pubis to the anterior iliac spine. Magnetic resonance imaging revealed a villous hyperintense lesion surrounding the first finger (*figure 2*). Multiple biopsies were taken from the lesions and anti-infective therapy with amoxicillin/clavulonic acid was started as her body temperature was over 38.7°C. Biopsy of the lesion demonstrated multiple pyogenic granulomas.
Haematological laboratory investigations revealed leukemoid reaction and normochromic normocytic anaemia (white blood cells (WBC) 58,000/mm$^3$, haemoglobin 7.0 g/dl and peripheral blood smear: 20% promyelocytes, 8% myelocytes, 12% band, 60% polymorphonuclear leucocytes with normal erythrocyte morphology and platelets). The leucocyte alkaline phosphatase (LAP) score was increased. Bone marrow aspirate was hypercellular and morphological analysis disclosed

**Figure 1.** *Lesions before and after treatment*



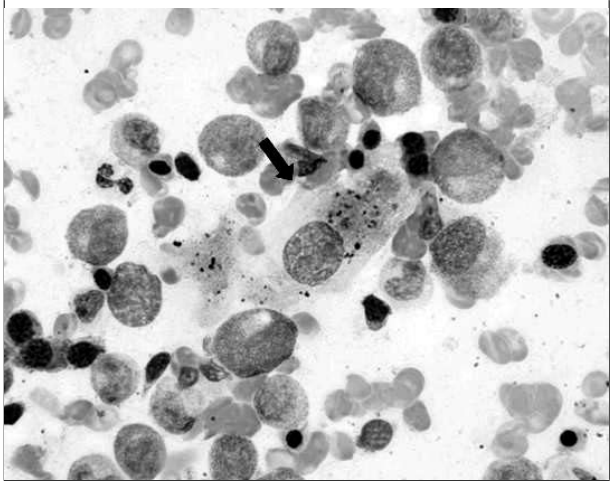

**Verrucous papules with purulent discharge on inguinal region (A) and the oedematous left thumb with a similar lesion on admission (C). Marked improvement of lesions on the inguinal region (B) and on her left thumb after treatment with IFN and thalidomide (D).**

**Figure 2.** *Coronal T2 weighted image with fat saturation reveals a villous hyperintense lesion surrounding the first finger*



**The lesion demonstrates low intensity foci representing flow void.**

**Figure 3.** *Bone marrow aspirate showing sea-blue histiocytes (arrow) and dysplastic changes in erythroid precursors*



prominently increased atypical hypergranular promyelocytes (42%) with granulocytic hyperplasia, dysplastic suppressed erythropoiesis, and increased atypical megakaryocytes. A small number of sea-blue histiocytes were also seen (*figure 3*). On the histopathological examination of the bone marrow biopsy, increments in the myeloid/erythroid ratio (8/1), reticulin fibres, megakaryocytes and iron store were noted. Cytogenetic studies revealed clonal trisomy 8 abnormality. All of those findings were found to be compatible with an atypical myeloproliferative/myelodysplastic syndrome presenting as a leukemoid reaction in the presence of pyoderma gangrenosum. During her follow-up, deep vein thrombosis also developed in her left superficial femoral and popliteal vein, which was successfully treated with low-molecular-weight heparin.

High-dose intravenous methylprednisolone as a 1 gram pulse and oral prednisone 60 mg/day was started for the treatment of pyoderma gangrenosum and MDS. *E. coli, K. pneumonia* and *E. feacalis* were isolated from the wound cultures. Bacterial infections were controlled with amikacin and imipenem treatments. After the steroid therapy, haemoglobin values reached 10 g/dl without transfusion. Erythrocyte sedimentation rate decreased from 143 mm/h to 34 mm/h. WBC counts were between 5000/mm$^3$ and 11,000/mm$^3$ but no marked improvement in the lesions could be achieved.

The patient underwent palliative surgery one month after admission for lesions in the left inguinal region. However, the operation failed to be completed because of bleeding from the giant vegetative lesions. Postoperative interferon-α2a was initiated at a dose of 5 MU/day as a biological response modifier. However, no improvement in the lesions was evident. Thalidomide was started at the dose of 200 mg/day as an antiangiogenic drug three weeks later. The steroid dosage was reduced slowly and discontinued in four weeks. The massive ulcerovegetative skin lesions resolved dramatically after four months of interferon-α2a plus thalidomide combination therapy (*figure 1*), and the haematological status of the patient improved (WBC 8500/mm$^3$, haemoglobin 12.8 g/dl, platelets 125,000/mm$^3$ and peripheral blood smear findings consistent with dysplastic changes especially in granulocytes). Thalidomide was withdrawn after 14 months following the healing of all the lesions with scarring.

## DISCUSSION

In this report, successful treatment of massive ulcerovegetative lesions of pyoderma gangrenosum and the dyshaematopoiesis and cytopenias of MDS with a combination of thalidomide and interferon-α2a was described. Neutrophilic dermatoses, including

ulcerovegetative necrotic pyoderma gangrenosum, may be associated with myelodysplasia in transition to leukaemia. The distinctive cutaneous symptoms sometimes precede MDS.[6] Pyoderma gangrenosum presented initially as a 'leukemoid reaction' in our MDS patient. Moreover, our patient also had APS, which was associated with recurrent abortions. Skin manifestations have been described in lupus anticoagulant (LA) positive patients. A report on 33 LA-positive patients indicated that three patients developed pyoderma gangrenosum-like ulcers.[7] Laboratory investigations failed to demonstrate antiphospholipid antibodies in our patient during the last clinical presentation of pyoderma gangrenosum and MDS.

The combination of antiangiogenic, immunosuppressive, and biological response modifier drugs was successful in the clinical management of our patient. There are currently no guidelines for the treatment of pyoderma gangrenosum but high-dose corticosteroids are usually the first choice.[5] Immunosuppressive drugs such as cyclosporine A, azathioprine, cyclophosphamide, chlorambucil, sulphasalazine, dapsone, minocycline, clofazamine and thalidomide are used in steroid-refractory cases, alone or in combination with steroids.[5] Autoimmune manifestations of MDS and pyoderma gangrenosum frequently respond to immunosuppressive agents and occasional haematological responses to steroid therapy have been reported in MDS.[3] Daily wound oxygenation increases collagen production by fibroblasts to support capillary angiogenesis in pyoderma gangrenosum.[8] Surgical procedures could have precipitated the generation of pyoderma gangrenosum lesions[9] as in our patient. Thalidomide is used in pyoderma gangrenosum for its antiangiogenic and anti-inflammatory effects.[5] Many successful anecdotal treatments of pyoderma gangrenosum with thalidomide have been reported.[10-12] Two of these patients had pyoderma gangrenosum associated with Behcet's disease.[10,11] Thalidomide is also effective in treating mucocutaneus lesions of Behçet's syndrome.[13] Several immunomodulatory mechanisms of action of thalidomide have been suggested, such as inhibition of TNF-$\alpha$, chemotaxis of monocytes and leucocytes, and inhibition of phagocytosis by neutrophils.[14] It affects human keratinocyte viability, proliferation and migration, which is critical for the re-epithelialisation of skin wounds.[15] Thalidomide is also effective in the management of MDS.[4] Haematological improvement usually occurs after a median of two months of treatment,[4] as in our patient. It exerts heterogeneous biological effects on haematopoiesis in MDS. Some recent clinical trials have confirmed that thalidomide may improve anaemia and less frequently other cytopenias in some younger patients with low-risk MDS (11-56%, on intention-to-treat analysis). How thalidomide acts in MDS is not clear. Some data suggest several mechanisms possibly involving stimulation of erythropoiesis through activation of physiological compensative mechanisms and reduction of apoptosis.[4]

In summary, distinct pathobiological pathways comprised the challenging clinical course of APS, pyoderma gangrenosum, leukemoid reaction, and MDS in our cytogenetically handicapped patient. Nevertheless several drugs affecting distinct molecular crossroads of inflammation, neoplasia, angiogenesis, cytokine response, and cellular events have served to provide a successful clinical outcome.

## NOTE

A written informed consent was taken from the patient for the photographs.

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CASE REPORT

# Thalidomide as treatment for digestive tract angiodysplasias

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## ABSTRACT

**An 80-year-old man with von Willebrand's disease was admitted with severe melaena. Despite suppletion with von Willebrand concentrate he continued to be dependent on blood transfusions. Endoscopic examination did not show a bleeding focus. Video capsule endoscopy showed active bleeding from angiodysplasias in the proximal section of the small intestine. Ultimately, treatment with thalidomide was initiated at a dose of 100 mg/day. Soon after starting treatment his stools became normal and his haemoglobin level stabilised. No bleeding problems occurred for 11 months, after which the thalidomide treatment was stopped because of the potential side effects. Two months later he again developed melaena and treatment with thalidomide was restarted with a successful outcome. Trying to lower the dose to 50 mg resulted in rebleeding after three months with stabilisation after increasing the dose to 100 mg again. Monotherapy with thalidomide improves the clinical picture but may not be sufficient in the long term. Additional therapy, such as argon plasma coagulation or the use of the novel drug lenalidomide, might be necessary.**

## KEYWORDS

Angiodysplasias, gastrointestinal bleeding, thalidomide

## INTRODUCTION

Blood loss from the upper digestive tract is a common problem. Frequently, bleeding from ulcers in the stomach or the duodenum or from reflux oesophagitis is observed. Angiodysplasias or arteriovenous malformations are seldom the cause of bleeding. Angiodysplasias or arteriovenous malformations are mainly found in the small bowel, especially in the lower ileum.[1,2] At present the treatment of choice is endoscopic intervention with argon plasma coagulation. This treatment is not always possible, especially when angiodysplasias are located in the lower section of the small bowel. A new but to date not frequently used therapy in these patients is treatment with thalidomide. Recently we saw a patient with severe gastrointestinal blood loss due to angiodysplasias and von Willebrand's disease type II-a who was successfully treated with thalidomide.

## CASE REPORT

An 80-year-old man was admitted to our hospital with severe melaena in May 2004. As a child he had had poliomyelitis; furthermore he had documented von Willebrand's disease type II-a and a bleeding duodenal ulcer was diagnosed 50 years ago. Three years before this admission he had been examined for black coloured stools for which no explanation was found at that time.

On presentation he admitted having black coloured stools and had experienced progressive fatigue over the past few days. He was not on oral anticoagulation or NSAIDs. On physical examination we saw a tired patient with a blood pressure of 160/60 mmHg, a regular heart rate of 80 beats/min and a peripheral saturation of 99%. Abdominal examination was normal. Rectal digital examination showed black/brown faeces. Laboratory results showed a haemoglobin level (Hb) of 5.4 mmol/l (8.5 to 10.9 mmol/l) and a mean corpuscular volume (MCV) of 81 fl. (80 to 100 fl). Iron level was 5 µmol/l (10 to 25 µmol/l), ferritin 12.0 µg/l (20.0 to 250.0 µg/l) and transferrin 2.86 g/l (2.00 to 4.00 g/l) with 7% iron saturation. Platelet counts were normal. Additional work-up (gastroscopy, colonoscopy, computed tomography scan of the abdomen and enteroclysis of the small bowel) did not show a focus for his bleeding. During admission he remained dependent on blood transfusions. Treatment with tranexamic acid was initiated

with transfusion of a total of 20 units of red blood cells (RBC) and three units of fresh frozen plasma (FFP). As treatment of his von Willebrand's disease desmopressin (DDAVP) was infused. Finally his haemoglobin level became stable and the patient could be discharged.

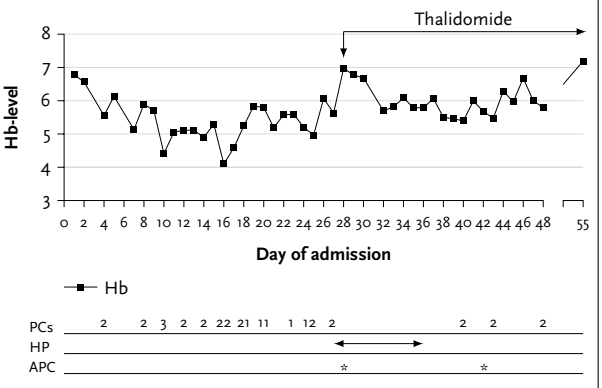
Late July 2004 he was readmitted with complaints of fatigue and an Hb level of 3.5 mmol/l. Examination of the faeces for occult blood turned out to be positive. Again additional endoscopic examination failed to localise the bleeding, although gastroscopy did show oozing blood in the pars descendens of the duodenum. A Meckel's scan was negative. During this admission he was again treated with tranexamic acid, DDAVP and a total of 15 units of RBCs and one unit of FFP. Because of the persistent bleeding without an obvious focus he was transferred to Leiden University Medical Centre. The next day a video capsule endoscopy showed several angiodysplasias in duodenum and jejunum which were not actively bleeding. Because he did not respond to DDAVP he was treated with von Willebrand's factor concentrate (HaemateP), in addition to RBC. Again stabilisation occurred.

In September 2004 he was readmitted with the same problem. Video capsule endoscopy showed fresh red blood in the duodenum and upper jejunum. Argon plasma coagulation intervention (double balloon endoscopy was not available at that time) was not successful so treatment with thalidomide (100 mg/day) was initiated. Five days after commencing thalidomide treatment, our patient started passing normal coloured stools. Two weeks after starting treatment, the patient again developed melaena. Again there was active blood loss from an angiodysplasia in the duodenum. A single argon plasma coagulation was performed, after which the Hb level stabilised (*figure 1*). During treatment with thalidomide during the next 11 months our patient remained free of symptoms with a stable Hb level. He was examined several times by a neurologist and several electromyograms were performed. No (progressive) neurological problems were found, although interpretation was hampered due to the documented poliomyelitis in the patient's history. Because of the potentially severe side effects of thalidomide, especially the neurotoxicity, and the poliomyelitis in the patient's past, the decision was made to stop the thalidomide treatment in August of 2005.

Two months later he again experienced melaena with complaints of fatigue, and a low Hb level. The possibility of performing a double balloon endoscopy was discussed. He refused further endoscopic treatment. Therefore, he was again treated with thalidomide (100 mg/day) with instant success (*figure 2*). At the time of his first outpatient control in February 2006 the patient was free of symptoms with an Hb level of 8.5 mmol/l. Trying to lower the dose to 50 mg resulted in rebleeding in May 2006 with stabilisation after increasing the dose to 100 mg again.

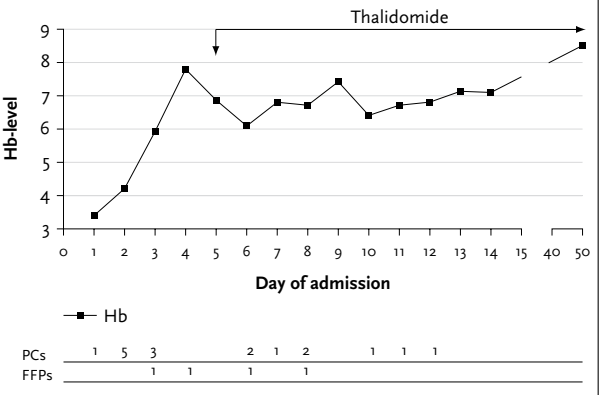
In July 2006 he was readmitted with rebleeding despite the use of thalidomide 100 mg/day. Gastroscopy showed active bleeding from an angiodysplasia in the jejunum. A single argon plasma coagulation was performed and the thalidomide dose was increased to 150 mg/day. In the near future he may be put on a similar drug, lenalidomide.

**Figure 1.** *Admission September 2004: course of Hb in mmol/l, time of blood transfusion (PCs), treatment with HaemateP (HP), argon plasma coagulation (APC) and start of treatment with thalidomide*




**The patient became independent of blood transfusions with a stable Hb level after starting treatment with thalidomide.**

**Figure 2.** *Admission December 2005: course of Hb in mmol/l, time of blood transfusion (PCs), fresh frozen plasma (FFPs) and time of restarting treatment with thalidomide*




**The patient became independent of blood transfusions with a stable Hb level after restarting treatment with thalidomide.**

## DISCUSSION

Angiodysplasias are newly formed blood vessels in the mucosa of the bowel. They can be part of several syndromes such as the Klippel-Trenaunay-Weber syndrome, the syndrome of Ehlers-Danlos, the CREST variation of sclerodermia and the inheritable haemorrhagic

telangiectasia. They also occur sporadically, especially at higher age, and can be associated with considerable morbidity. Chronic mucosal ischaemia may play a role. The most frequently observed angiodysplasias are found in the colon, but they also occur in the small bowel, with a location preference for the lower ileum.[1,2] The standard treatment at present is argon plasma coagulation. Hormone treatment with oestrogens used to be used;[3,4] however, the effect of this treatment is at best doubtful.[4]

Thalidomide (also known as Softenon) was used between 1950 and 1970 as a sleeping pill and an antiemetic drug during pregnancy. At the end of the 1960s its use was abandoned worldwide due to severe teratogenic effects.[5-7] However, during the past few years thalidomide has been shown to be effective in a number of diseases: multiple myeloma,[8] erythema nodosum leprosum,[9] Behçet's disease,[10] graft-versus-host disease in allogenic bone marrow transplantation,[11] Crohn's disease,[12,13] HIV-wasting syndrome in AIDS patients and stomatitis aphthosa in HIV patients.[14,15] The effect of thalidomide is also being evaluated in other forms of cancer, such as renal-cell carcinoma, glioblastoma multiforme and Kaposi sarcoma.[16-18]

Thalidomide is on the list of 'orphan drugs' of the European Agency for the Evaluation of Medicinal Products (EMEA) for the treatment of multiple myeloma and erythema nodosum leprosum and is a non-registered drug in the Netherlands. The exact working mechanism of thalidomide is as yet unknown but considering the success in the treatment of the various disorders mentioned above it is likely that thalidomide has anti-inflammatory, immune-modulating and antiangiogenic properties. Especially this last feature seems to be important in the treatment of multiple myeloma.[8] Besides its anti-inflammatory effects by suppression and modulation of the production of multiple cytokines, such as TNF-α in diseases like Crohn's disease,[19,20] thalidomide can also inhibit angiogenesis, which is probably most important in the treatment of angiodysplasias.[21] This inhibition most likely takes place through two pathways. First the suppression of the production of vascular endothelial growth factor (VEGF) plays an important role.[22] Serum VEGF is greatly increased when angiodysplasias of the colon are present.[23] Because VEGF is an important angiogenic factor in the development/growth of cancer cells and normal cells in hypoxaemic circumstances,[24] VEGF could play an important role in the pathophysiology of angiodysplasias.[25] Especially in elderly patients, hypoxaemia of the mucosa cells of the bowel might induce the forming of angiodysplasias through production of VEGF. Secondly, thalidomide inhibits the transcription factor NF-κB, which plays a role in apoptosis. It is thought that a metabolite of thalidomide is able to inactivate NF-κB and subsequently slows the growth of cells and induces apoptosis.[20]

In the literature a relation has been suggested between the occurrence of angiodysplasia and the presence of severe aortic stenosis,[26-28] which could not be confirmed by systematic prospective investigations.[29,30] In some patients a dramatic clinical improvement was observed after replacement of the stenosed aortic valve. On physical examination there were no signs of aortic stenosis in our patient. Warkentin *et al.* suggested a relation between acquired von Willebrand's disease type II-a, aortic stenosis and angiodysplasia.[31,32] Our patient had documented congenital type II-a von Willebrand's disease and the possible contribution of an acquired aggravation is only speculative.

Recently, the use of thalidomide in refractory gastrointestinal bleeding due to angiodysplasias was reported.[25,33] The 2004 article in Gut described three patients with severe gastrointestinal bleeding of the small bowel, at least one of whom had video capsule endoscopy proven angiodysplasias of the jejunum and ileum. All three patients were treated with thalidomide (100 mg/day) for four months. In all these patients the bleeding stopped within two weeks after the onset of treatment. Despite the limited follow-up, the effect of thalidomide treatment seemed to have lasted 22 to 33 months, during which no blood loss was observed. A recent case report described a 54-year-old patient with von Willebrand's disease II-b and angiodysplasia, who was successfully treated with thalidomide at a dose of 150 mg daily with a follow-up of six months.[34]

Our patient was also free of symptoms soon after (re)starting the thalidomide. In 2004 the combined effect of the argon plasma coagulation of the angiodysplasia in the duodenum and thalidomide initially stopped the bleeding successfully. Later on, the 11-month period without bleeding and the success after restarting the thalidomide in 2005 proved the thalidomide to be effective. After this initial success the most recent rebleeding indicates that monotherapy with thalidomide improves the clinical picture but may not be sufficient in the long term. Additional therapy such as argon plasma coagulation or the use of the novel drug lenalidomide might be necessary. Due to the side effects of thalidomide, such as sleepiness, dizziness, constipation and especially peripheral neuropathy, the compliance of this drug is not very good.[35,36] The use of adequate laxatives and strict neurological control is necessary when using this drug. A new thalidomide-like drug (lenalidomide) is believed to be more potent than thalidomide with possibly less side effects. The first results of this drug in patients with multiple myeloma are encouraging.[37,38]

## CONCLUSION

Angiodysplasias of the digestive tract can cause severe blood loss. It is not always possible to treat these bleeds by endoscopic intervention and local haemostatic procedures. Case reports of treatment with thalidomide show that this

drug offers a treatment option in patients with difficult to treat gastrointestinal blood loss due to angiodysplasias. It is assumed that the effect of thalidomide is based on inhibition of the VEGF production and inactivation of NF-κb. Unfortunately, the use of this drug is limited due to the side effects, especially neurotoxicity, and it may not be sufficient as monotherapy in the long term. Perhaps the more potent successors of thalidomide which cause less side effects, such as lenalidomide, will offer a solution for these problems in the future.

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PHOTO QUIZ

# Right subclavian vein cannulation?

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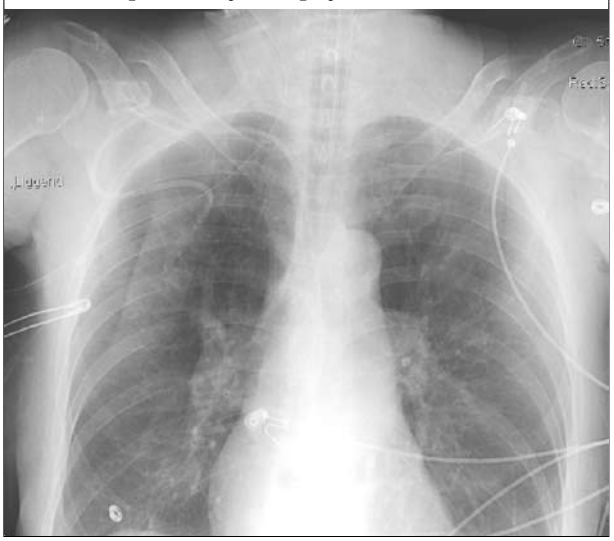
## CASE REPORT

A 57-year-old female patient presented with respiratory failure and sepsis. On admission a central venous catheter was inserted into the right subclavian vein. The procedure was unremarkable and the postinsertion chest X-ray showed a properly placed central venous catheter. However, after connection, infusion proved to be impossible.

## WHAT IS YOUR DIAGNOSIS AND WHAT IS YOUR NEXT STEP?

See page 430 for the answer to this photo quiz.

**Figure 1.** *Conventional chest radiograph with abnormal position of the tip of central venous catheter*



## ANSWER TO PHOTO QUIZ (ON PAGE 429)
## RIGHT SUBCLAVIAN VEIN CANNULATION?

In hindsight, the nearly symmetrical chest X-ray (*figure 1*) showed an aspecific position of the central line: deviation of the catheter to the midline and the position of the tip above the left ventricle. Cannulation of the right subclavian artery was confirmed by pressure tracings. The catheter was removed surgically without further complications.

### DISCUSSION

Arterial puncture, pneumothorax and haematoma are the most common mechanical complications during the insertion of central venous catheters. The frequency of puncture of subclavian artery varies between 3 and 5%.[1] After cannulation of the subclavian or carotid artery, there are usually no adverse complications.[2] Some authors advocate the use of ultrasound guidance.[3] However, Mansfield *et al.*[4] showed no difference in prevention of iatrogenic cannulation using ultrasound guidance in a prospective randomised trial.
In our hospital insertion of a central venous catheter is not performed routinely with the use of ultrasound guidance.

### DIAGNOSIS

Insertion of a central venous catheter with inadvertent cannulation of the subclavian artery.

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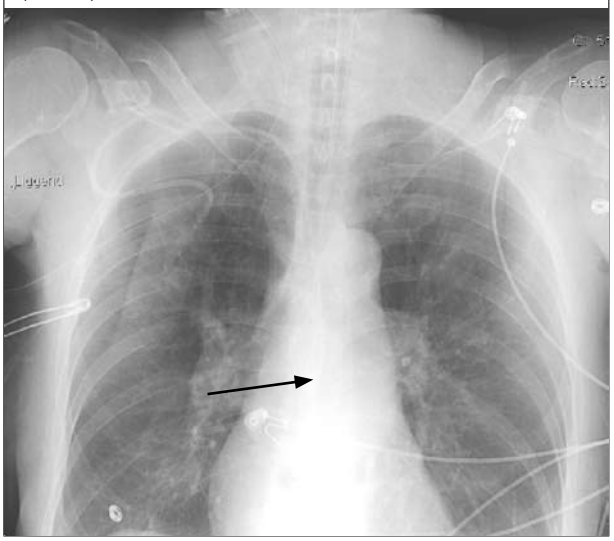
**Figure 1.** *Conventional chest radiograph with abnormal position of the tip of central venous catheter (arrow)*



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NOTE

# The blue rubber bleb nevus syndrome co-existing with celiac disease

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## ABSTRACT

**Background: Anaemia caused by iron deficiency is one of the most common disorders in the world. We describe a patient with iron deficiency anaemia in whom absorption was limited due to celiac disease, superimposed to chronic blood loss due to the blue rubber bleb nevus syndrome, a rare syndrome characterised by multiple cutaneous venous malformations in association with visceral lesions.**
**Case report: A 54-year-old patient with severe iron deficiency anaemia showed marked rubbery cutaneous lesions on the body surface, extremities, under and on the left side of the tongue as well as in the stomach and duodenum. The appearance and pathological examination of the lesions were consistent with the diagnosis of blue rubber bleb nevus syndrome (BRBNS). Biopsy of the mucosa of the duodenum showed celiac disease. No association between celiac disease and BRBNS has been previously described.**
**Conclusion: Combined loss of iron and malabsorption from the gastrointestinal tract can lead to severe iron deficiency. Early recognition of both diseases can result in early treatment. Patients can recover completely with iron suppletion and a gluten-free diet. Recognising typical BRBNS skin lesions would provide a potential diagnosis and could prevent unnecessary procedures or invasive surgery.**

## KEYWORDS

Blue rubber bleb nevus syndrome, celiac disease, iron deficiency anemia

## INTRODUCTION

Anaemia caused by iron deficiency is one of the most common disorders in the world. The World Health Organisation estimates that more than 30% of the population suffer from iron deficiency anaemia (http://www.who.int/nut/ida.htm). Causes of iron deficiency include an increased demand for iron e.g. in pregnancy, an increased iron loss, e.g. chronic blood loss from the gastrointestinal tract, or decreased iron intake, absorption or use, e.g. such as resulting from an inadequate diet. In this report, we describe a patient with severe iron deficiency anaemia, in whom absorption was limited due to the presence of celiac disease, superimposed to chronic blood loss from the gastrointestinal tract due to the blue rubber bleb nevus syndrome, a rare syndrome characterised by multiple cutaneous venous malformations in association with visceral lesions, affecting predominantly the gastrointestinal tract.

## CASE REPORT

A 54-year-old female patient was evaluated because of iron deficiency anaemia. Medical history included an unconfirmed encephalitis at the age of 6, a pulmonary abnormality which possibly resulted in a pulmonary haemorrhage when she was 23 years, and periods of iron deficiency anaemias for which she had received multiple courses of iron suppletion. She developed a hemiparesis at the age of 43, after an episode of atrial fibrillation. Her last menstrual bleeding had occurred ten years ago. On presentation, she complained of painful rhagades in the corners of her mouth, which had not healed despite the use of several topical applicants. Her defecation occurred twice daily and consisted of loose stools. There was no obvious blood loss, and her weight was stable at 59 kg. On examination, there were marked rubbery cutaneous lesions on the body surface of the trunk and on the extremities (*figure 1*). Similar lesions were found under and on the left side of the tongue.
Laboratory examination revealed a microcytic anaemia with a haemoglobin level of 4.4 mmol/l and mean corpuscular volume of 62 fl. Serum iron concentration was 2 mmol/l

with a ferritin level of 4 µg/l consistent with the diagnosis of anaemia caused by iron deficiency.

On gastroscopy, angiodysplastic lesions were found in stomach and duodenum (*figure 2*). Biopsy of the mucosa of the duodenum showed a picture of gluten-induced enteropathy grade III, according to the modified Marsh criteria, consistent with the diagnosis of celiac disease.[1]

Cutaneous biopsy of a lesion on the trunk showed vascular proliferations, suspicious of arteriovenous malformation (*figure 3*). The appearance and pathological examination of the lesions were consistent with the diagnosis of blue rubber bleb nevus syndrome.

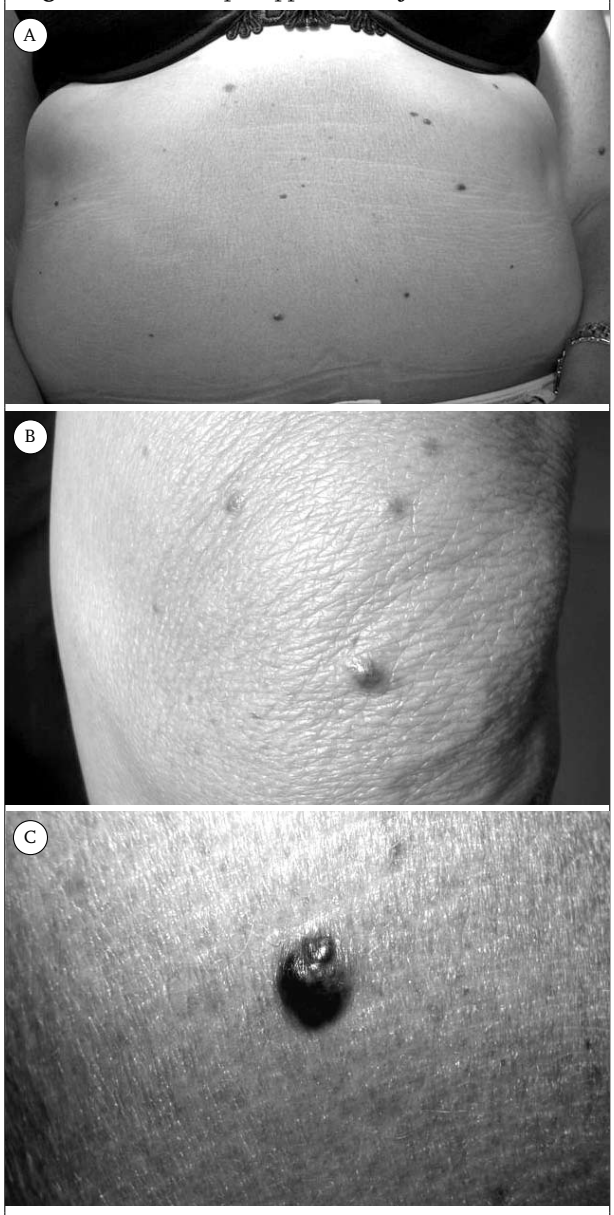
Because of the history of a possible pulmonary haemorrhage and the development of a hemiparesis, additional radiological examinations were performed. Computed tomography of the chest showed a large vascular malformation, while magnetic resonance imaging of the brain showed no malformations.

Treatment was initiated with a gluten-free diet and iron suppletion, after which she had an uneventful recovery, without any complaints.

## DISCUSSION

The blue rubber bleb nevus syndrome (BRBNS) is a syndrome characterised by multiple vascular, mostly venous, blebs or nodules. Involved organ systems include the skin and visceral organs, most commonly the gastrointestinal tract. Less often, other organ systems are

**Figure 1.** *Macroscopic appearance of BRBNS lesions*




**A. Localisations on the abdomen. B. Localisation on the knee. C. Detail of localisation on the knee.**

**Figure 2.** *Endoscopic appearance of BRBNS lesions*

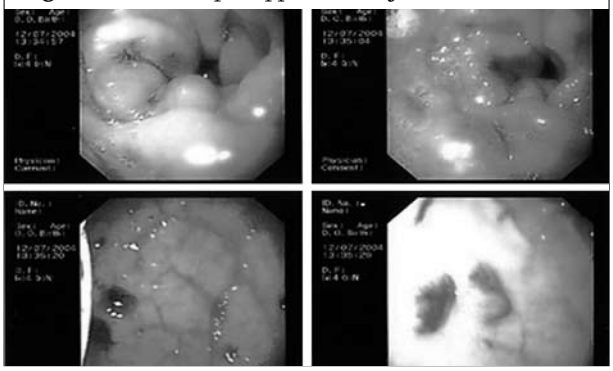
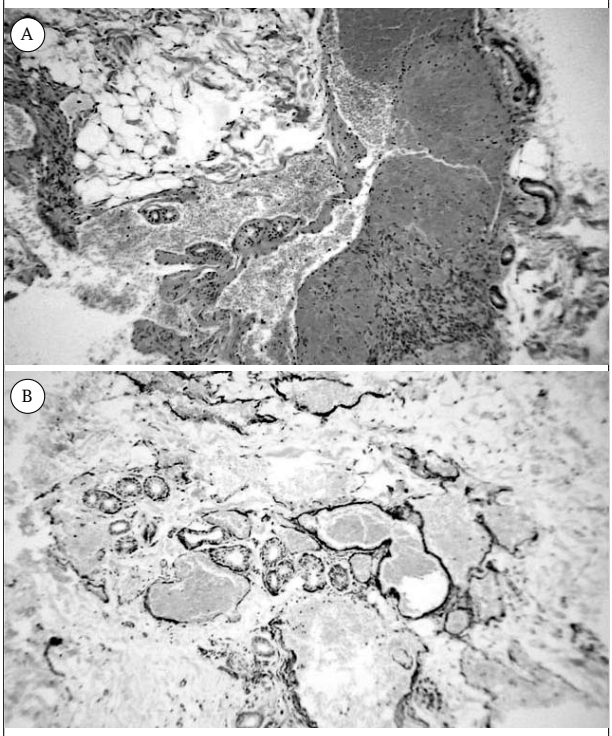


**Figure 3.** *Histopathological examination of BRBNS lesions*




**A/B. Curled, ectatic vessels with single layer epithelium and connective tissue.**

involved, including the central nervous system (CNS), musculoskeletal system, thyroid, parotid, eyes, oral cavity, spleen, lungs, kidney, liver, and bladder.[2-10] The syndrome was first described in 1860, when Gascoyen noticed an association between cavernous haemangiomas of the skin and similar lesions in the gastrointestinal tract.[11] In 1958, Bean, after further research, named this association the 'blue rubber bleb nevus syndrome'.[12] The BRBNS is a rare or under-recognised disorder: to date, fewer than 150 cases of BRBNS have been reported.

Cutaneous lesions are the main indicators for the diagnosis; however, they have a variable macroscopic appearance. The most classic cutaneous lesion consists of a nipple-like lesion, which is easily compressible and refills slowly on release of pressure. The lesion is mostly asymptomatic, but can be associated with pain and hyperhydrosis.[12] Histopathological examination of such lesions shows blood-filled ectatic vessels, lined by a single layer of endothelial cells, surrounded by thin connective tissue. The lesions show irregular cavernous spaces, located in both the deep dermis as well as subcutis, and often show smooth muscle fibres in vessel walls. In some cases, these vessels show an intimate relation with the sweat glands.[3,5] The diagnosis of BRNBS is initially based on the clinical cutaneous findings of characteristic lesions. However, other clinical conditions characterised by vascular abnormalities of the skin should be differentiated from BRBNS. Osler-Weber-Rendu disease (hereditary hemorrhagic telangiectasia) is a disease in which cutaneous lesions may look like the lesions in BRNBS. In addition, they are associated with similar lesions in the lungs and gut. However, the visceral and cutaneous lesions are typically smaller (2-5 mm) and more punctiform. The subungual lesions, nail-bed involvement, and spider and punctate telangiectases found in Osler-Weber-Rendu disease can help in distinguishing it from BRBNS. Maffucci's syndrome, also a disease with widespread cutaneous and visceral vascular lesions, is distinguishable from BRBNS by the bony abnormalities resulting from chondroplasia and defective ossification. Klippel-Trénaunay-Weber syndrome is identified by venous varicosities, soft tissue and bony hypertrophy, and cutaneous vascular malformations which are typically confined to one extremity. Other vascular disorders with cutaneous and visceral involvement are von Hippel-Lindau disease in which retinal and cerebellar angiomatosis occurs and the Sturge-Weber syndrome which is associated with meningeal angiomatosis. The unique cutaneous and extracutaneous findings can help distinguish these disorders from BRBNS.[2,3,13-18]

In BRBNS, the associated gastrointestinal venous malformations predominantly occur in the small intestine, but lesions may be found elsewhere in the digestive tract.[17,19-21] Gastrointestinal tract malformations are subject to frequent bleeding, potentially resulting in occult blood loss and iron-deficiency anaemia, as in the presented case.[4,5,13,19]

Most cases of BRBNS occur spontaneously; however, hereditary patterns with autosomal inheritance have also been reported in several case reports.[13,22] Some evidence suggests that the mutation for some cases of BRBNS may occur on chromosome 9p, because venous malformations were found to occur in association with an activation mutation in the receptor tyrosine kinase tie-2 also located at this same locus on chromosome 9p. However, tie-2 mutations have not yet been directly linked to BRBNS.[23-26] Complications of BRBNS include acute or, mostly, chronic blood loss, resulting in anaemia or pain in the affected organs. The most feared complication is CNS involvement resulting in CNS bleeding.[27,28] The prognosis depends on the extent of visceral organ involvement. Most patients have a normal lifespan.

Treatment options of cutaneous lesions include laser treatment, curettage or cryotherapy.[29-32] Surgical removal is usually not necessary. Depending on the presentation, extracutaneous lesions require symptomatic treatment, such as iron suppletion, endoscopic coagulation or surgery.[13,32-34]

Other conditions associated with cutaneous lesions as well as gastrointestinal blood loss include hereditary haemorrhagic teleangiectasia, in which epistaxis is often the initial manifestation. Pseudoxanthoma elasticum is a condition associated with yellow papules in intertriginious zones, angioid streaks in the eye, hypertension, premature atherosclerosis, uterine haemorrhage and vascular calcification, associated with upper or lower gastrointestinal bleeding. The Ehlers-Danlos syndrome type IV, an autosomal dominant inherited disease resulting in deficiency of type III collagen can be associated with upper gastrointestinal haemorrhage due to arterial rupture or intestinal perforation. The Gardner's syndrome (associated with epidermoid cysts, lipomas and desmoid tumours), the Peutz-Jeghers syndrome (associated with melanotic macules on mucosal surfaces) and Cowden's disease (multiple facial periorificial papules, cobblestoning of the oral mucosal surface, and acral keratotic papules) are associated with polyps in the gastrointestinal tract from which bleeding can occur. In addition, vasculitis syndromes can present with both cutaneous lesions and gastrointestinal haemorrhages. Scurvy, due to vitamin C deficiency, presents with perifollicular purpura and corkscrew hair and gingivitis and results in collagen degeneration in vasculature, which can lead to gastrointestinal blood loss. Inflammatory bowel syndromes such as ulcerative colitis and Crohn's disease can also be associated with cutaneous lesions such as erythema nodosum and pyoderma gangrenosum.[35]

In conclusion, our case demonstrates that combined loss of iron and malabsorption from the gastrointestinal tract can lead to severe iron deficiency. Early recognition of both diseases can result in early treatment. Patients can recover completely with iron suppletion and a gluten-free diet. Recognising typical BRBNS skin lesions would provide a potential diagnosis and could prevent unnecessary procedures or invasive surgery.

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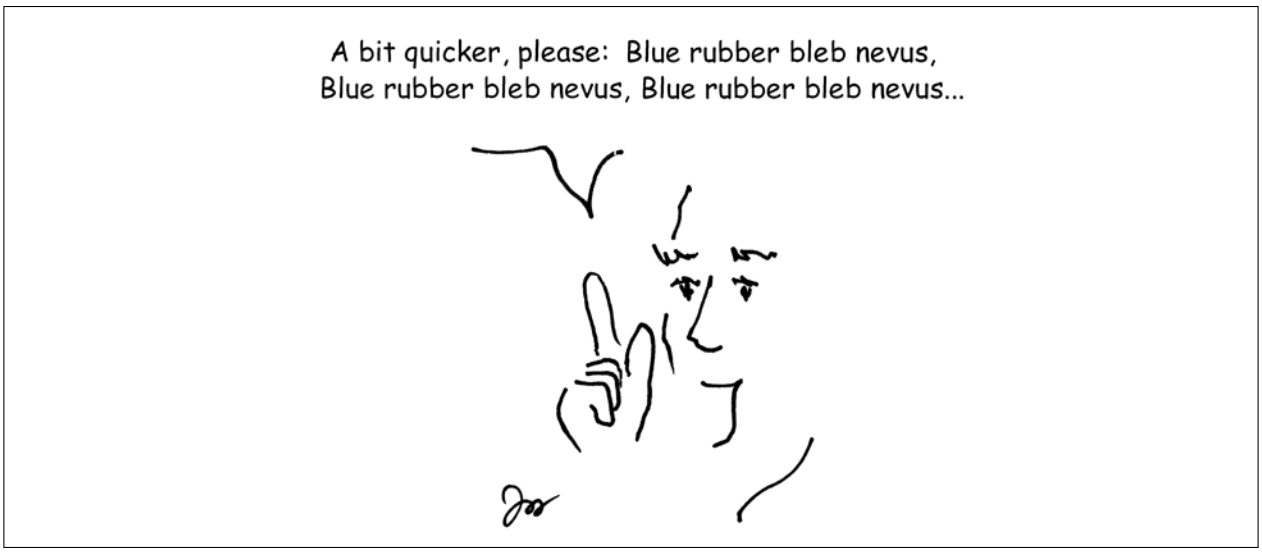


Oosterheert, et al. The blue rubber bleb nevus syndrome combined with celiac disease.

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ABOUT THE COVER

# Duesme

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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.

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*Keywords*: Include three to five keywords.

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*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.

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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.

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