

Strategy for Antibiotic Therapy in Febrile Neutropenic Patients on Selective Antibiotic Decontamination

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In a non-randomized prospective study the need for broad-spectrum antibiotic therapy was evaluated in selectively decontaminated neutropenic patients with fever. Fifty-two adult patients with a neutrophil count $< 0.5 \times 10^9/l$ suffered 77 febrile episodes while receiving oral antibiotics for selective decontamination. Antibiotic treatment was only initiated if additional clinical signs or the microbiological culture results pointed to the likelihood of an infection. Treatment was either empirically based (broad-spectrum) or specific (narrow-spectrum). If a causative agent was identified, therapy was adjusted accordingly. If evidence of infection was lacking after 72–96 hours, the antibiotics were discontinued, and these patients were reexamined meticulously and repeatedly. For the 40 episodes without confirmed infection, the median duration of therapy was three days (range 0–13 days) and the survival rate 100 %; for the 37 episodes with confirmed infection, the median duration of therapy was 12 days (range 1–49 days, $p < 0.0001$) and the survival rate 85 %. After adjustment of therapy the final regimen was broad-spectrum in only 18 % of treated episodes. None of the six deaths could be attributed to the withholding or stopping of broad-spectrum therapy. It is concluded that in febrile neutropenic patients on selective decontamination a standard therapy regimen with prolonged administration of broad-spectrum antibiotics is not necessary. After initial intervention antibiotic therapy can safely be tailored to the needs of the individual patient.

Neutropenic cancer patients are at a high risk of acquiring severe bacterial and fungal infections, especially when the neutrophil count is less than $0.1 \times 10^9/l$ (1, 2). In such cases the specific signs of infection seen in other patients are often missing (3). When neutropenic patients become febrile, it is universally recommended that an empirical regimen of antibiotics active against gram-negative bacteria be started immediately (4–12). Such an approach is based on the assumption that most episodes of fever in the neutropenic patient are caused by bacterial infections. Studies show that the empirical administration of new, potent antibiotics has resulted in a reduction in mortality compared to previous studies (13). However, these antibiotics are expensive, may interfere with diagnostic procedures and – most important-

ly – increase the risk of toxicity as well as of colonization and infection with resistant bacteria and fungi.

It has been demonstrated that the prophylactic administration of oral antibiotics for selective decontamination results in a marked reduction in the rate of serious infections with gram-negative microorganisms (14–23). This marked decrease in the risk of fulminant infections should lead to a reappraisal of the classical approach to the management of fever in patients on selective decontamination, especially the administration of prolonged broad-spectrum antibiotics in the case of unexplained fever (24, 25). In these patients application of a restrictive antibiotic policy may avoid the above-mentioned risks arising from standard empirical antibiotic regimens.

At the University Hospital in Leiden, the Netherlands, a conservative strategy has been adopted in the therapy of these patients: (a) systemic antibiotics are only administered to febrile neutropenic patients when it is judged necessary on the basis of additional clinical and microbiological findings,

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(b) antibiotic therapy is specific if there are focal signs of infection or culture results are available, and (c) treatment is discontinued when evidence of an infection, other than the fever, is not found. In this prospective study the efficacy of this restrictive strategy was assessed by evaluating the clinical and microbiological outcome of all febrile episodes occurring in a one-year period in hospitalized neutropenic patients receiving selective decontamination.

Patients and Methods

Patients. Patients older than 15 years with a hematologic disorder who were admitted to the Bone Marrow Transplantation Unit or Hematology Department of University Hospital Leiden were prospectively studied when they became febrile during a period of severe neutropenia while receiving antibiotics for selective decontamination. Only patients with an expected duration of neutropenia of more than one week were included in the study. The study started on 1 May 1987 and ended on 1 May 1988. Fever was defined as an axillary or oral temperature of 38 °C or higher on at least two readings taken four hours apart. Febrile reactions obviously caused by the infusion of blood or blood components were excluded. Neutropenia was defined as a neutrophil count of less than $0.5 \times 10^9/l$. The end of a non-fatal febrile episode was indicated by temperatures below 38 °C without evidence of infection. A prophylactic selective decontamination regimen was given orally throughout the period of neutropenia, and consisted of 250 mg neomycin, 100 mg polymyxin B and 250 mg amphotericin B four times daily and 400 mg pipemidic acid twice daily. All patients were nursed in protective isolation. If patients were not able to swallow, 960 mg cotrimoxazole was administered intravenously twice daily to preserve the state of decontamination during that interval. Antibiotic prophylaxis was adjusted in accordance with the results of bacteriological surveillance which included regular culture of samples of skin and mucosa from different sites, as described previously (17). Some patients on high-dose cytarabine-C therapy received benzylpenicillin intravenously for a two-week period following the end of chemotherapy to prevent streptococcal septicemia, as this appears to be a frequent and serious complication in these patients (26).

Strategy for Antibiotic Therapy. At the onset of fever a decision was made as to whether to initiate treatment or not; treatment was initiated if one of the following criteria applied: 1) Physical examination by the infectious diseases consultant (i.e. the investigator or one of his colleagues) revealed an acute deterioration of the patient's general condition, the presence of hypotension or chills, an abrupt rise in temperature of 2 °C or more, or signs of focal infection. Local signs of infection included oropharyngeal mucositis, redness, swelling and/or pain at the site of insertion or along the route of the subcutaneous tunnel of a central venous catheter, painful swelling in the perianal region, and signs of upper or lower respiratory tract infection. 2) Microbiological in-

vestigations yielded a positive Gram stain and/or a positive culture of (a) blood (for *Staphylococcus epidermidis* and *Corynebacterium* spp. at least two sets of blood cultures had to be positive), (b) urine (except for concentrations $< 10^3/ml$ of enterococci, *Staphylococcus epidermidis*, *Corynebacterium* spp. or *Candida* spp), (c) sputum (except for normal pharyngeal bacterial flora), (d) material obtained by puncture. 3) Specific potential pathogenic microorganisms such *Staphylococcus aureus*, β -hemolytic streptococci or gram-negative bacteria, were detected in surveillance cultures. 4) X-ray studies of the chest and sinuses showed abnormalities suggestive of infection. Culture results were not usually available at the onset of fever except in the case of surveillance cultures taken prior to the febrile episode.

For the purposes of this study, an infection was defined as a disease caused by a bacterial or fungal pathogen. If an infection was judged likely on the basis of the above criteria, drugs for antimicrobial therapy were chosen taking into account previous antibiotic therapy and the following requirements: 1) Initial antibiotic treatment had to be specific when examination pointed to a focal infection or a specific pathogen (e.g. penicillin for pharyngitis, vancomycin for infected site of entry of i.v. catheter) and the general condition did not warrant the use of broad-spectrum antibiotics. 2) In the absence of evidence of the nature and location of the infection, standard empirical treatment with broad-spectrum antibiotics including gentamicin and cefamandole had to be started. 3) As soon as the pathogen was identified and susceptibility tests were completed, antibiotic therapy was adjusted to agents with specific activity against the pathogen. Antibiotics were continued until the neutrophil count rose above $0.5 \times 10^9/l$ and the signs of infection disappeared. Antibiotic therapy was defined as inappropriate when susceptibility tests showed resistance to the agents used. Antibiotic therapy was considered to lack efficacy if there was no clinical response after 48 to 96 hours, despite susceptibility of the pathogen isolated; therapy was changed either to more potent antibiotics (e.g. penicillin replacing cefamandole for streptococcal septicemia) or to broad-spectrum antibiotics or antifungal agents if the patient's condition so demanded.

If cultures remained negative and clinical evidence of a serious infection was lacking 72 to 96 hours after initiation of therapy, whether empirical or specific, the systemic antibiotics were discontinued even if fever persisted and the patient kept under close surveillance. If an infection was considered unlikely at the onset of fever, antibiotics were withheld and the patient re-examined daily to re-evaluate the need for treatment.

The outcome of all febrile episodes was evaluated in relation to the antibiotic treatment and pathogens isolated. Mortality during or within two weeks after the end of the febrile episode was taken as the primary endpoint for determining the success of the treatment. Follow-up evaluation in the case of survival was made four weeks after the end of the febrile episode.

Results

Patient Characteristics. A total of 77 febrile episodes occurred in 52 neutropenic patients

receiving oral selective decontamination. The mean age of the patients was 39.3 years (range 19–65 years). Their underlying hematological diseases and chemotherapy received prior to febrile episodes are summarized in Table 1. In 6 of the 77 episodes, the hematological disease was refractory to anti-cancer treatment. In only 25 of the 77 (33 %) episodes the neutrophil count was more than $0.01 \times 10^9/l$ at the onset of fever. The duration of neutropenia prior to fever was known in 75 episodes, being in 8 episodes (10.4 %) less than 5 days, in 40 episodes (51.9 %) between 5 and 15 days and in 27 episodes (35.1 %) more than 15 days, with a median of 12 days. The temperature at the onset of fever ranged between 38.0 °C and 41.2 °C, with a median of 38.8 °C. Chills or hypotension accompanied 14 of the 77 (18.2 %) episodes; in 33 (42.9 %) episodes illness was judged clinically to be moderately severe or severe. In addition to abdominal and gastrointestinal symptoms in 15 episodes, there were also focal signs in 26 (36.6 %) episodes consisting of nonspecific pharyngitis (11), i.v. catheter-related skin lesions (4), herpetic mucosal lesions (3), other skin lesions (2), perianal lesions (2), severe pharyngeal candidiasis (1), external otitis (1), rhinitis (1), and pulmonary symptoms (1). In 36 (46.8 %) episodes no focal signs or symptoms were recorded. In 22 episodes both general and focal signs were absent at the onset of fever.

In nine episodes surveillance cultures were positive for gram-negative bacteria at the onset of fever; in two of them the findings were associated with bacteremia with the same pathogen (*Escherichia coli* and *Pseudomonas aeruginosa* respectively). In two other episodes surveillance cul-

tures became positive for *Pseudomonas aeruginosa* early during fever; both pathogens corresponded with the blood isolates.

Antibiotic Therapy Strategy. Flow sheets depicting our strategy are presented in Figures 1 and 2. Antibiotic therapy was started immediately in 43 febrile episodes (Figure 1). In 9 episodes therapy

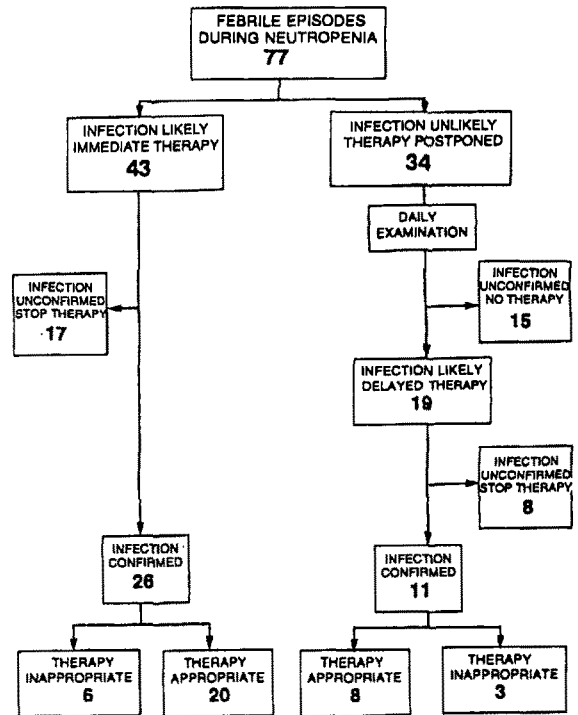


Figure 1: Strategy for management of 77 febrile episodes during selective decontamination.

Table 1: Characteristics of 52 neutropenic patients receiving selective oral decontamination.

Underlying disease	Hematologic treatment prior to febrile episode (no. of episodes)							
	No. of patients	No. of episodes	No therapy	Medium-dose cytarabine ^a	High-dose cytarabine ^b	Allogeneic BMT	Autologous BMT	Other therapy
Acute myeloid leukemia	25	42	1	17	12	8	2	2
Acute lymphatic leukemia	6	7	1	0	3	2	0	1
Chronic myeloid leukemia	13	18	1	2	0	15	0	0
Non-Hodgkin's lymphoma	6	7	1	0	3	1	2	0
Other	2	3	0	0	0	3	0	0
Total	52	77	4	19	18	29	4	3

^a Medium-dose: 2g/m²/day.

^b High-dose: 6g/m²/day.

BMT = bone-marrow transplantation.

was specific from the beginning; in 34 episodes therapy was broad-spectrum. The initial median temperature of these 43 patients was 39.0 °C (range 38.0 °C – 40.2 °C). A final diagnosis of infection could be made in 26 of the 43 episodes (60.5 %). Twenty of these 26 episodes were treated appropriately from the onset of therapy, and 6 were not.

In 34 episodes an infection was judged unlikely at the onset of fever, and antibiotics were withheld although the temperature (median 38.7 °C, range 38 °C – 39.9 °C) was comparable to that of the other subset (Figure 1). In 11 (32.4 %) of these 34 episodes a final diagnosis of infection could be established. This percentage differs significantly from that found for the other subset (32.4 % versus 60.5 %, $p < 0.02$ according to the Chi-square test). In a total of 15 episodes no antibiotics were given at all despite high maximum temperatures (median 39.0 °C, range 38.6 °C – 39.8 °C). Extensive and frequent examinations did not provide any evidence of a bacterial or fungal infection during these 15 episodes. Later observations and microbiological investigations led to the delayed initiation of antibiotic therapy in 19 episodes. The delay in administration of antibiotics varied between 1 and 4 days (median 2.5 days). Infection was confirmed in 11 of the 19 episodes. The initial therapy in 8 of these 11 confirmed infections was appropriate (Figure 1).

The 9 episodes for which initial therapy was inappropriate (Figure 1) included 4 cases of systemic fungal infections, 2 cases of gram-negative bac-

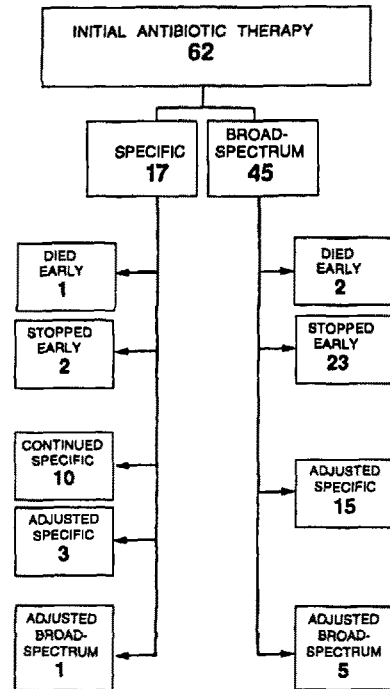


Figure 2: Antibiotic therapy in 62 febrile episodes showing spectrum of activity and adjustments.

Table 2: Data on fatal outcome of six febrile episodes.

Causative agent and condition	Hematologic therapy	Initial antibiotic therapy*	Time of starting appropriate antimicrobial therapy	Day of death
<i>Clostridium perfringens</i> parapharyngeal cellulitis	other	immediate, broad-spectrum (+ penicillin)	immediate	1
<i>Staphylococcus epidermidis</i> ARDS	high dose cytarabin	immediate, broad-spectrum	day 3: vancomycin added	11
<i>Candida albicans</i> cerebral hemorrhage?	BMT	immediate, broad-spectrum	day 3: fluconazole day 8: amphotericin B	23
<i>Candida albicans</i> disseminated candidiasis (autopsy)	BMT	delayed, specific	day 3: fluconazole	8
<i>Aspergillus fumigatus</i> sinusitis & pneumonia	refractory	immediate, broad-spectrum	antifungal therapy abandoned	10
<i>Aspergillus fumigatus</i> pneumonia	refractory	delayed, broad-spectrum	antifungal therapy abandoned	23

* Immediate therapy: started at the onset of fever; delayed therapy: started after 1–3 days. BMT = bone-marrow transplantation; ARDS = adult respiratory distress syndrome.

teremia, 2 cases of *Staphylococcus epidermidis* bacteremia and 1 case of necrotizing stomatitis.

A total of 62 episodes were treated, either immediately or after a delay (Figure 2). The initial choice of antibiotics was specific and narrow-spectrum in 17 and empirical and broad-spectrum in 45 episodes.

In 25 episodes no clinical or microbiological evidence of a bacterial infection could be demonstrated, and therefore antibiotic therapy was stopped early after a median duration of five days (range 2–13; mean 5.0 ± 2.5 days). The maximum temperature during these episodes ranged between 39.0° and 41.2°C with a median of 39.7°C .

The decision to continue therapy was based on the presence of a microbiologically documented infection in 33 episodes and a clinically documented infection in four episodes. Three of the patients died without ineffective therapy being changed due to immediate death in one patient and abandonment of appropriate therapy in two patients (Figure 2, Table 2). In a total of 24 episodes antibiotic therapy was adjusted. In addition to changes from broad-spectrum to specific therapy, antibiotics were changed because of resistance of causative pathogens in seven episodes and lack of a rapid clinical response in eight episodes. These latter eight included candidemia which did not respond to initial fluconazole therapy ($n = 1$), unexplained fatal adult respiratory distress syndrome (ARDS) following *Staphylococcus epidermidis* septicemia which did not respond to vancomycin therapy ($n = 1$), *Pseu-*

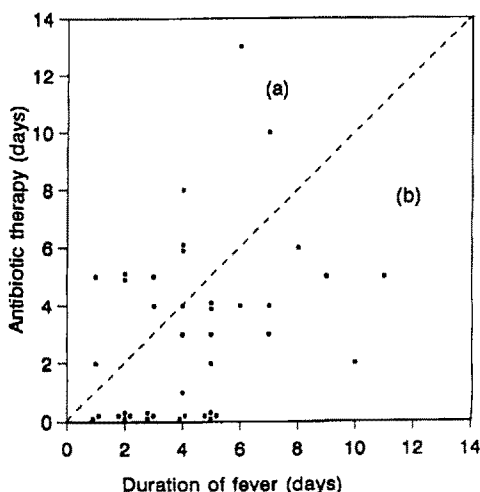


Figure 3: Duration of fever and antibiotic therapy for 40 episodes of unconfirmed infection. (a) therapy was stopped after the patient became afebrile; (b) therapy was stopped before the patient became afebrile.

Table 3: Cause of fever in 52 neutropenic patients with 77 febrile episodes.

Cause of fever	No. of episodes
Episodes with positive blood cultures ($n = 29$)	
Alpha-hemolytic streptococci	10
<i>Staphylococcus epidermidis</i>	7*
<i>Pseudomonas aeruginosa</i>	4
<i>Escherichia coli</i>	3
<i>Candida albicans</i>	2
<i>Enterococcus</i> spp.	3*
<i>Streptococcus pneumoniae</i>	1*
<i>Corynebacterium</i> JK	1*
<i>Clostridium perfringens</i>	1
Episodes with other cultures positive ($n = 4$)	
<i>Aspergillus fumigatus</i> (sputum)	2
<i>Candida</i> sp. (liver tissue)	1
<i>Staphylococcus aureus</i> (cellulitis)	1
Episodes with no positive cultures, infection clinically confirmed ($n = 4$)	
Perianal abscess	1
Tonsillitis	1
Oropharyngitis	1
Necrotizing stomatitis	1
Episodes in which infection not confirmed ($n = 40$)	

*Polymicrobial bacteremia: *Staphylococcus epidermidis* plus *Corynebacterium* JK ($n = 1$), *Staphylococcus epidermidis* plus *Enterococcus* sp. ($n = 1$), *Enterococcus* sp. plus *Streptococcus pneumoniae* ($n = 1$).

domonas aeruginosa septicemia which did not respond to imipenem monotherapy ($n = 1$), and septicemia due to alpha-hemolytic streptococci ($n = 6$). Although these streptococci were sensitive in vitro to the agents used for initial therapy (including cefamandol and ceftazidime), the clinical response was unsatisfactory with persistence of high fever, prompting a switch to penicillin or vancomycin.

On the basis of the microbiological results the final therapy in 28 of the 34 episodes with continued or adjusted therapy was specific and narrow-spectrum (Figure 2). In only six episodes final broad-spectrum therapy was required because of *Pseudomonas aeruginosa* infection (4 episodes), allergy to cephalosporins (1 episode) and clinical deterioration (ARDS in 1 episode).

Causes of Fever. The pathogens isolated in the 37 documented infections are summarized in Table 3. The ten cases of streptococcal septicemia occurred in four episodes after medium-dose cytarabine therapy, three episodes after high-dose cytarabine therapy and three episodes after

allogeneic bone marrow transplantation. None of the patients had received penicillin prophylaxis, but five were on cotrimoxazole.

A presumed or definite non-infectious cause of fever was established in a total of 29 of 40 episodes. In another two episodes a viral infection was diagnosed. The final diagnoses in 15 episodes which were not treated with antibiotics were: cancer chemotherapy-associated toxicity ($n = 4$), acute graft-versus-host disease (GVHD) of the skin ($n = 2$), aseptic thrombophlebitis ($n = 1$), herpes simplex virus infection ($n = 1$), cytomegalovirus infection ($n = 1$) and fever of unknown origin ($n = 6$). The final diagnoses in 25 cases of discontinued antibiotic therapy were: acute GVHD ($n = 10$), cancer chemotherapy-associated toxicity ($n = 6$), allergy to cotrimoxazole ($n = 4$), vasculitis ($n = 2$) and fever of unknown origin ($n = 3$).

Course and Outcome of the Febrile Episodes. All of the patients who had fever which was not treated ($n = 15$) or treated only for a short period of time ($n = 25$) survived. Two of the episodes were followed within one week of normalization of the temperature by a second febrile episode due to streptococcal and enterococcal septicemia, respectively; both were treated successfully. In Table 4 the clinical characteristics of these 40 epi-

sodes are summarized and compared with those of the 37 episodes of confirmed infection. These data indicate that the majority of episodes with unconfirmed infection were not characterized by mild fever of short duration or by rapid recovery of the bone marrow. In 13 of the 25 treated episodes antibiotic therapy was discontinued before the temperature dropped below $38\text{ }^{\circ}\text{C}$ (Figure 3). The duration of therapy in the 40 episodes was significantly shorter than in the episodes with confirmed infection ($n = 37$) (median 3 [range 0–13] days versus 12 [range 1–49] days; $p < 0.0001$ according to the Wilcoxon Rank Sum test) (Table 4).

In four of seven episodes, streptococcal septicemia following cytarabine therapy was complicated by transient ARDS; all four patients were treated successfully. Six febrile episodes had a fatal outcome (Table 2). One patient died of fulminant *Clostridium perfringens* septicemia within a few hours despite appropriate antibiotic therapy from the very beginning. One patient died 13 days after the onset of fever of unexplained progressive ARDS after an appropriately treated *Staphylococcus epidermidis* bacteremia, despite broad-spectrum antibiotic and antifungal therapy. Four patients died of invasive fungal disease (disseminated candidiasis in 2, invasive pulmonary aspergillosis in 2) more than one week

Table 4: Comparison of characteristics of 37 episodes of confirmed infection and 40 episodes of unconfirmed infection. Unless otherwise stated the median (range) of values is given.

Clinical characteristic	Confirmed infection ($n = 37$)	Unconfirmed infection ($n = 40$)	p value ^a
Neutrophil count	$0 \times 10^9/l$ (0–0.32)	$0.01 \times 10^9/l$ (0–0.5)	< 0.0001
Duration of prior neutropenia ($< 0.5 \times 10^9/l$)	11 days (2–98)	14 days (1–99)	0.48
Initial temperature	$38.8\text{ }^{\circ}\text{C}$ (38.0–40.2)	$38.8\text{ }^{\circ}\text{C}$ (38.0–41.2)	0.9
Maximum temperature	$39.1\text{ }^{\circ}\text{C}$ (38.0–40.7)	$39.6\text{ }^{\circ}\text{C}$ (38.6–41.2)	0.08
Chills or hypotension (proportion)	6/37 (16.2 %)	8/40 (20.0 %)	$> 0.05^b$
Poor clinical condition (proportion)	21/37 (56.8 %)	12/40 (30.0 %)	$< 0.02^b$
Duration of antimicrobial therapy	12 days (1–49)	3 days (0–13)	< 0.0001
Duration of fever ($T > 38\text{ }^{\circ}\text{C}$)	4 days (1–23)	4 days (1–11)	0.61
Persistence of neutropenia ($< 0.5 \times 10^9/l$)	12 days (1–50)	14 days (4–90)	0.34

^a Wilcoxon Rank Sum test used to compare median values.

^b Chi-square test used to compare proportions.

after the onset of fever (on days 23, 8, 9, and 23 respectively). All four remained persistently neutropenic; two of them were not treated with antifungal agents at all because their underlying illnesses were refractory to any hematological therapy. None of these deaths were due to gram-negative or other bacteria which were not covered by the spectrum of the antibiotics used.

Discussion

Recent guidelines continue to indicate that prompt treatment with broad-spectrum antibiotics is required in all febrile patients with neutropenia (11, 12). They do not recommend adaptation of treatment to culture results with narrowing of the antibiotic spectrum. With respect to the duration of systemic broad-spectrum antibiotic therapy, Pizzo (12) argues for continuing treatment until neutropenia resolves. The guidelines of the Infectious Diseases Society of America allow discontinuation of (broad-spectrum) antibiotics only in two instances: (a) if neutropenia continues and the patient is clinically well, after a total of five to seven afebrile days, and (b) if the neutrophil count rises over $0.5 \times 10^9/l$ and antibiotics have been given for a total of seven days (11). Unfortunately, in both sets of US guidelines the benefits of prophylactic administration of oral antibiotics for selective decontamination are not taken into consideration. In neutropenic patients on selective decontamination febrile episodes still occur and remain unexplained in about 50 %. As there is a marked reduction in the rate of gram-negative infections the organism spectrum has changed with a predominance of gram-positive infections. Whether the use of selective decontamination allows more restrictive systemic antibiotic therapy has not yet been established, although it was suggested by Joshi et al. (25). In many European centers nowadays patients are receiving oral prophylaxis and there may therefore be a need for more specific guidelines.

In our study we have shown that there was an excellent survival rate in febrile episodes when applying a restrictive strategy of antibiotic use based on additional clinical and microbiological data and tailored to individual needs. Although clinical findings appear to have a low positive predictive value as far as the existence of infection is concerned (3), these findings were used in this study to select patients who did not need therapy

immediately. As these patients were at risk for fulminating infections, it is the outcome of the episodes in terms of survival which should justify this approach, not just whether infections were treated appropriately (27). Surprisingly, antibiotics were withheld in 20 % of the episodes without any complications; and in another 33 % therapy was discontinued after a median of five days without any deterioration in the patient's condition. An infection could not be demonstrated in any of these episodes and all of the patients survived. In two episodes the abatement of fever was followed within one week by a new febrile episode caused by bacteremia; both episodes were subsequently treated successfully. The remaining episodes (47 %) were caused by a confirmed infection and antibiotic therapy was instituted either immediately or after some delay.

The classical rule states that initial broad-spectrum therapy – if necessary together with additional antibiotics or antifungal therapy – should be maintained throughout the neutropenic period (12). This recommendation is based on the observation that secondary infections can occur in the course of prolonged neutropenia due to continuing colonization with potentially pathogenic micro-organisms (11, 12, 24, 28, 29). Continuation of initial broad-spectrum therapy should therefore be considered as continuous systemic prophylaxis until the neutrophil count rises and the danger of endogenous infections is over (8, 10). However, after selective decontamination there is no need for such systemic prophylaxis (14, 17, 20). Instead of continuing the broad-spectrum antibiotics, we therefore gave specific narrow-spectrum antibiotics as soon as indicated by clinical or microbiological data. This resulted in the administration of broad-spectrum antibiotics to only 6 of the 34 (18 %) patients who received therapy for a longer period of time (median 14 days), which represents 8 % of the total number of episodes. In the other 28 episodes final therapy became specific as soon as the culture and susceptibility testing results were known.

This study was not performed to establish the efficacy of our selective decontamination regimen, which has already been described in detail (17). As seen in other studies using selective decontamination, local bacterial infections were mostly restricted to catheter related infections caused by *Staphylococcus epidermidis*, while localized gram-negative infections such as perianal infections or hematogenous pneumonia are rare. In this study, the isolation of seven gram-negative bacteria from the blood in a total of 77 episodes

(9 %) is not favourable compared to the results of studies that used quinolones, such as norfloxacin, ciprofloxacin or ofloxacin (18, 19, 21–23). Nevertheless, the specific approach to fever, as described in our study, may also be fully applicable in patients on quinolone prophylaxis.

The combination of gentamicin and cefamandole used for empirical therapy in this study does not cover a very wide spectrum of gram-negative pathogens. In neutropenic patients the activity of gentamicin alone is not sufficient to treat gram-negative infections effectively. However, the indication for empirical use of antibiotics with an extended spectrum of activity such as third generation cephalosporins or carbapenems depends mainly on the rate of isolation of gram-negative bacteria from neutropenic patients in a particular institution. In our study *Pseudomonas aeruginosa* bacteremia did occur but, in contrast to the well known life-threatening form, it was not fulminant. In neutropenic patients not receiving antibiotics for decontamination we would always recommend that the spectrum of the antibiotic regimen covers *Pseudomonas* at the onset of fever. A recent study showed that imipenem was superior to the combination of gentamicin and cefuroxime (another second generation cephalosporin with activity comparable to that of cefamandole) but this was due to the fact that gram-positive infections responded more favourably to imipenem (30). In that study ciprofloxacin was used as prophylaxis with a very low incidence of gram-negative infections.

Streptococcal septicemia after cytarabine therapy appears to be a serious infection, patients often presenting with chills and high fever, and resulting in ARDS in a large proportion of the patients (in our series 4 of 7) (26, 31). Therefore, specific prophylaxis with benzylpenicillin or roxithromycin has been recommended in patients on cytarabine therapy (21, 31). Even with this prophylaxis, the clinician must remain on the alert because resistant alpha-hemolytic streptococci may emerge. In cases of presumed penicillin resistance we would recommend administration of vancomycin or teicoplanin. In five of the ten episodes of streptococcal septicemia in our study, cotrimoxazole was given prophylactically and thus failed to prevent this disease. Moreover, the use of cotrimoxazole as well as quinolones has been recognized as a predisposing factor (32). Because of the fulminant character of the disease immediate institution of appropriate therapy is required. However, commonly recommended

regimens using third generation cephalosporins are not the most appropriate for these streptococci (33). The above observations also support the notion of an individual approach in each patient rather than a standard therapy aimed primarily at gram-negative infections.

The six deaths in this study could not have been prevented, even if broad-spectrum antibiotic therapy had been administered early. Four were due to invasive fungal infections which indicates the importance of these infections in selectively decontaminated patients. Patients who have received such a regimen no longer seem to be in extreme danger of acquiring fatal gram-negative infections but are still threatened by invasive fungal infections, such as disseminated candidiasis and pulmonary aspergillosis. In the literature, failure to make an early diagnosis as well as insufficient preventive and therapeutic measures against these infections are well recognized problems (11, 34). Early empirical antifungal therapy is recommended in the persistently febrile patient who remains severely neutropenic (11, 35).

The fear that nearly all febrile episodes of unknown origin will turn out to be cryptogenic infections which should be treated immediately could not be confirmed by our study. On the contrary, some febrile episodes resolved spontaneously without any antibiotic therapy and others resolved after only a few days of antibiotic therapy. Whether these febrile episodes were associated with an obscure infection cannot be answered with certainty, but apparently recovery was possible without a full course of antibiotic therapy. In addition, as a result of the withholding of or early discontinuation of antibiotics, the etiology of 75 % of all unconfirmed infections could be presumed or established. This is a very high percentage compared to figures in other studies (7, 8). A large proportion of febrile episodes appeared to be drug-related. Neutropenic cancer patients are prone to such reactions, partly because of the nature of the treatments they receive (cytostatics, allopurinol, antibiotics, blood and serum components) and perhaps also because of their altered immunological status. In view of this finding, it is important to warn against overtreatment with antibiotics, especially in patients receiving cytokines and hematopoietic growth factors, as they frequently induce fever (36).

Our study was performed in an institution where there was careful assessment and follow-up of

these potentially septicemic patients. Such careful and continuous supervision to determine when antibiotics could be withheld is not available at all centers and the impact of this information could have an adverse effect in settings where a more casual approach is taken to the patient's fever. Therefore, we cannot recommend withholding antibiotics at the time of initial fever in every clinical setting. As a general rule, it would be wise to make decisions about continuation or adjustment of antibiotic therapy once the results of clinical examinations, radiography and microbiological investigations are available. On the basis of our findings we therefore recommend the following guidelines for the antibiotic treatment of selectively decontaminated neutropenic patients with fever: (a) discontinue systemic antibiotics after three to five days if infection has not been demonstrated or is doubtful; (b) adjust antibiotic therapy, with a narrower antibiotic spectrum according to the culture results; and (c) consider empirical antifungal therapy if fever persists for more than five to seven days. Because of the possibility of rapid deterioration of the patient in case of bacteremia, it is essential in all situations that repeated frequent evaluation of the patient's condition be continued until the bone marrow has recovered. Our study demonstrates that with an intensified patient-oriented approach many neutropenic patients can be spared the potential complications of unnecessary prolonged broad-spectrum antibacterial therapy. Because our study was not controlled it would be important to see whether our results could be confirmed in a controlled study which compares the conventional strategy of empirical continuous broad-spectrum antibiotic therapy with our strategy of restricted use of systemic antibiotics.

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