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# Three-day treatment with imipenem for unexplained fever during prolonged neutropaenia in haematology patients receiving fluoroquinolone and fluconazole prophylaxis: A prospective observational safety study

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ABSTRACT

*Background:* Guidelines advocate >7 d of broad-spectrum antibiotics for unexplained fever (UF) during neutropaenia. However, effective antimicrobial prophylaxis reduces the incidence of gram-negative infections, which may allow shorter treatment. This study evaluates the safety of discontinuing empirical broad-spectrum antibiotics if no microbial source is documented after an initial work-up of 72 h.

*Methods:* Prospective observational study at a tertiary-care haematology-unit in patients suffering from haematologic malignancies and treatment-induced prolonged neutropaenia of $\geqslant$10 d. Oral fluoroquinolone and fluconazole prophylaxis was given from day 1. Fever was empirically treated with imipenem which was discontinued after 72 h if, following a standardised protocol, no infectious aetiology was documented. Duration of fever, antimicrobial therapy and overall mortality were registered.

*Results:* One hundred and sixty six patients were evaluated during 276 neutropaenic episodes. One hundred and thirty six patients (82.5%) experienced $\geqslant$1 febrile episode. A total of 317 febrile episodes were observed, of which 177 (56%) were diagnosed as UF. In 135 febrile episodes (43%), a probable/definite infectious origin was documented. Mean duration of fever in neutropaenic periods with 1 febrile episode was 5 d, and mean time of treatment with imipenem was 4.7 d. In patients without documented infection, mean time of imipenem treatment was only 3.7 d. Overall mortality 30 d after neutrophil recovery was 3.6% (6/166); no patient died from untreated bacterial infection.

*Conclusion:* Discontinuation of broad-spectrum antibiotics during neutropaenia in haematology patients on fluoroquinolone and fluconazole prophylaxis is safe, provided that no infectious aetiology is established after 72 h.



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## 1. Introduction

Severe and possibly life-threatening bacterial and fungal infections constitute a major cause of morbidity and mortality in patients with haematological malignancies treated with intensive chemotherapy, especially when the neutrophil count drops below $0.5 \times 10^9$/l for $\geqslant 10$ d.[1–5] In case of fever, current guidelines universally recommend immediate empirical treatment with broad-spectrum antibiotics for at least 7 but even up to 14 d.[6] This approach is based on the assumption that most febrile episodes in these patients are due to bacterial infections. However, there is no evidence from randomised clinical trials that neutropaenic patients with unexplained fever (UF), in whom evidence of a bacterial infection is lacking after a thorough diagnostic work-up, will benefit from prolonged antimicrobial therapy.

Although gram-positive bacteria account for the majority of all microbiologically documented infections, the more fulminant gram-negative infections result in a much higher attributable mortality.[3,5,7,8] The prophylactic administration of antibiotics, especially fluoroquinolones, has been demonstrated to result in a marked reduction of bacteraemia due to gram-negative micro-organisms[9–13] and to reduce mortality,[14] probably by lowering the intestinal burden of these micro-organisms. The argumentation in the current literature that prolonged empiric broad-spectrum antibiotic therapy in case of UF during neutropaenia will prevent recurrence of bacteraemia and other bacterial infections does not take into account the efficacy of the administration of such antibiotic prophylaxis.

Moreover, apart from substantial extra costs and an increased amount of adverse events, continuing unnecessary treatment harbours additional disadvantage of antibiotic resistance selection. Also, it may falsely temper the scrutiny in the search for the real cause of the febrile episode. In fact, a significant proportion of these patients suffer from invasive fungal infections, especially invasive pulmonary aspergillosis (IPA), during the course of continuous neutropaenic fever.[3]

The antibiotic strategy in case of prolonged neutropaenia developed in our hospital over the last 10 years differs from most international recommendations. It is based on continuous fluoroquinolone and fluconazole prophylaxis, in combination with non-absorbable antibiotics for the first 10 d. In case of fever during neutropaenia, patients are treated with a considerably shorter course of empirically started broad-spectrum antibiotics. This has been suggested as an alternative approach previously,[15,16] but the safety of such a strategy clearly needs to be evaluated in more detail before it can be widely accepted.

In our hospital, patients with prolonged neutropaenia due to intensive chemotherapy or stem cell transplantation receive empirical treatment with imipenem when neutropaenic fever is documented.[6,17] Imipenem is discontinued irrespective of the temperature response if after a standardised diagnostic work-up of 72 h no infectious aetiology is identified. In case of a documented infection, patients receive directed therapy based on the susceptibility pattern of the identified pathogen (if available).

The primary objective of this prospective observational study was to investigate the safety of early discontinuation of empirically started broad-spectrum antibiotics for fever in neutropaenic haematology patients during fluoroquinolone and fluconazole prophylaxis. As a secondary goal, we registered the outcome and duration of all febrile episodes within each neutropaenic period.

## 2. Methods

### 2.1. Patient population

The study was performed at the Erasmus MC, a university tertiary care hospital in Rotterdam, The Netherlands. From March 2005 until June 2008, all consecutive adult haematology patients (>17 years) with expected duration of neutropaenia (neutrophil count $<0.5 \times 10^9$/l) of $\geqslant 10$ d, induced by intensive chemotherapy or haematological stem cell transplantation were studied. Excluded were patients with a carbapenem allergy. Patients had direct bloodstream access by means of a tunnelled Hickman catheter and were nursed in rooms with High Efficiency Particulate Air (HEPA)-filtration. All patients gave written informed consent and the institutional review board approved the protocol.

### 2.2. Antimicrobial prophylaxis

All patients were on antimicrobial prophylaxis, which was started 1 to 5 d before chemotherapy or conditioning in case of stem cell transplantation, until neutrophil recovery was observed (neutrophil count $\geqslant 0.2 \times 10^9$/l on 2 consecutive days). The standard oral regimen consisted of ciprofloxacin 500 mg BID and fluconazole 400 mg once daily. For the first 10 d of neutropaenia, we added also colistin capsules 200 mg QID combined with 5 mg oral colistin suspension QID to accelerate the eradication of gram-negatives and to minimise the theoretical risk of developing fluoroquinolone resistance in case of ciprofloxacin monotherapy. Prophylaxis was only given parenterally when oral intake was impaired (e.g. severe mucositis). Patients already initially at high risk for mucositis (e.g. in case of treatment with high-dose cytarabine, etoposide or methotrexate) also received a 10-d course of intravenous benzyl-penicillin from day 5 after the start of chemotherapy or longer in case of persisting mucositis, aimed to reduce the occurrence of bacteraemia with oral streptococci. Bowel surveillance cultures consisting of mouth wash and rectal and vagina swabs were taken twice weekly. If surveillance cultures revealed ciprofloxacin-resistant gram-negative bacteria, ciprofloxacin was preferably replaced by sulphametoxazole-trimethoprim, and tobramycin was added or colistin was reintroduced, based on the susceptibility pattern, to aim for successful bowel decontamination.

### 2.2. Diagnostic and therapeutic protocol for neutropaenic fever

Fever was defined as an ear temperature of >38.2 °C during 2 subsequent occasions 1 h apart, or a single measurement of

>38.7 °C. Disappearance of fever was defined as a temperature of <37.8 °C for at least 24 h following a febrile episode.

At the onset of fever, treatment with imipenem 500 mg QID was initiated and a physical examination and microbiological work-up to detect any sign of clinical or a microbiological documented infection were performed. Signs of infectious sources that were specifically documented were oropharyngeal mucositis, erythema and/or tenderness or purulence of the insertion site or tunnel tract of the central venous catheter, tenderness in the perianal region and signs of respiratory tract infection, including standard chest X-ray and imaging of sinuses if indicated. Microbiologically documented infection was defined as a microbiological investigation yielding a positive culture from blood (Bactec system BD, Franklin Lakes, USA; preferably incubating an amount of 10 ml both aerobically and anaerobically), urine (except for concentrations $<10^3$/ml enterococci, coagulase-negative staphylococci (CNS), *Corynebacterium* spp. or *Candida* spp.), sputum or other respiratory secretions (except for normal pharyngeal flora) or material obtained by puncture. Definitions of catheter-related bacteraemia (CRB) from current guidelines were followed in case of suspected CRB.[18] For this purpose, CVC blood cultures, together with peripheral blood cultures were taken for any new episode of fever. CRB was defined as $\geqslant 1$ positive blood culture obtained from either CVC or peripheral vein (in case of CNS or other skin colonisers $\geqslant 2$ CVC cultures were required) in patients with fever or other clinical manifestations of infection, lacking apparent other source for infection except the catheter, combined with a culture of the catheter tip demonstrating the same phenotypic micro-organisms in case of catheter removal, or a differential time to positivity (DTTP) $\geqslant 2$ h of the peripheral minus the central venous catheter blood culture.

If this initial diagnostic work-up did not reveal a clinically or a microbiologically documented infection, treatment with imipenem was stopped after 72 h regardless of the presence or absence of fever. If a causative pathogen was identified or a clinical source of infection was documented, therapy was tailored according to the susceptibility pattern or clinically documented focus. In case of bacteraemia, tailored treatment was continued for 14 d, or at least 7–10 d in case of recovery from neutropaenia.

Prolonged treatment with imipenem occurred in predefined specific occasions. Imipenem was continued in patients with clinically documented pneumonia or sinusitis without a microbiologically documented pathogen. It was also continued in patients with fever and known unsuccessful gram-negative bowel decontamination. Patients with symptoms of septic shock (i.e. systolic blood pressure <90 mm Hg despite intravenous colloid administration and/or oliguria (<3 ml/kg/6 h)) were treated with imipenem and once-daily amikacin 15 mg/kg for 1–3 d; in case of septic shock among patients with severe mucositis, intravenous vancomycin was added to assure adequate treatment in case of penicillin-resistant streptococci.

At day 5 of ongoing neutropaenic fever, blood cultures for *Candida* spp. (Bactec Mycosis IC/F BD, Franklin Lakes, USA) were taken and patients underwent a high-resolution CT-scanning (HRCT) of the thorax, which was repeated 5–7 d later if fever persisted. In case of documented intrapulmonary abnormalities, patients underwent bronchoscopically guided broncho-alveolar lavage (BAL) of the most representative lung lesion. BAL was cultured for bacteria, mycobacteria and fungi. Also, galactomannan level in BAL was measured to detect IPA. If bronchoscopy was not feasible because of the location or very small size of the lung lesion, galactomannan level was measured in serum. If these diagnostic procedures were inconclusive, a biopsy of the lung lesions was performed if feasible and not contraindicated. Patients were diagnosed with IPA following updated EORTC-MSG definitions.[19] The presence of ongoing neutropaenic fever without any abnormalities on HRCT was not considered as an indication for empirical antifungal therapy.

### 2.3. *Data collection and patient evaluation*

Per patient data were collected for all consecutive neutropaenic periods. Baseline information included age, sex, underlying haematological malignancy, type of stem cell transplantation and co-morbidity. Cases were evaluated by LS and BJR, who were not involved in patient management. For each patient, the outcome and mean duration of all febrile episodes within each neutropaenic period were registered, together with the mean duration of imipenem use. All-cause mortality during neutropaenia or within 30 d after neutrophil recovery was registered as a primary marker to determine the safety of our neutropaenic fever treatment policy. Data were analysed by means of descriptive statistics, using SPSS version 15.0 (Chicago, IL, USA).

## 3. Results

We included 166 patients receiving chemotherapy with an expected neutropaenia duration of $\geqslant 10$ d. In total, these patients experienced 276 periods of prolonged neutropaenia.

**Table 1 – Characteristics of 166 haematologic patients with prolonged neutropaenia.**

| Characteristic | Value |
|---|---|
| Age, mean years (range) | 53.9 (19–80) |
| Male sex | 98 (59.0) |
| *Underlying haematologic disorder* | |
| AML/MDS[a] (137 neutropaenic periods) | 64 (38.6) |
| Multiple myeloma (47 neutropaenic periods) | 47 (28.3) |
| Non-Hodgkin lymphoma (64 neutropaenic periods) | 36 (21.7) |
| Acute lymphatic leukaemia (16 neutropaenic periods) | 8 (4.8) |
| Other[b] (12 neutropaenic periods) | 11 (6.6) |
| *Co-morbidity* | |
| Cardiovascular | 42 (25.3) |
| Respiratory | 7 (4.2) |
| Other[c] | 5 (3.0) |

Data presented are numbers (%) of patients unless otherwise indicated.

a AML/MDS, acute myeloid leukaemia/myelodysplastic syndrome.

b Other, Hodgkin lymphoma ($n = 6$), chronic myeloid leukaemia ($n = 3$), aplastic anaemia ($n = 2$).

c Other, autoimmune disorders requiring regular immunosuppressive therapy ($n = 3$), ulcerative colitis ($n = 1$), HIV ($n = 1$).

Characteristics of the patient population are presented in Table 1 and characteristics of these 276 neutropaenic periods are shown in Table 2. One hundred and eighty two (65.9%) of these neutropaenic periods were related to high-dose chemotherapy and 94 were in the context of a haematological stem cell transplantation. The mean duration of neutropaenia was 20.5 d. The longest mean neutropaenic period (28.2 d) was observed in patients with acute myeloid leukaemia/myelodysplastic syndrome (AML/MDS) treated with remission and/or consolidation chemotherapy.

Of all 166 patients, 29 (17.5%; accounting for 39 neutropaenic periods) did not develop fever during their entire haematological treatment. One hundred and thiry seven patients (82.5%) experienced 1 or more febrile episodes in the remaining 202 periods of neutropaenia (Table 2). Mean duration of all-cause fever in neutropaenic periods with only 1 febrile episode ($n = 113$) was 5.5 d and in these patients imipenem was given for a mean duration of 4.7 d (SD 4.3). A clinical or a microbiological infection was documented in 48 of these episodes; 64 episodes were diagnosed as UF and in 1 case a non-infectious origin of fever was registered. If only taking into account the 64 UF episodes, the observed duration of fever was 4.3 d (SD 3.6) and imipenem was administered for 3.7 d (SD 1.8). For neutropaenic periods with 2 febrile episodes, the mean total duration of fever was 9.9 d and the total duration of imipenem use was 6.6 d (SD 4.0). Finally, for periods of neutropaenia with >2 febrile episodes, mean total duration of fever was 16.8 d and total imipenem use was 10.5 d (SD 6.0).

Of all 276 neutropaenic periods, 74 passed without fever. In the remaining periods, treatment with imipenem was started on 317 occasions of fever (Fig. 1). In 169 episodes, imipenem was discontinued after 72 h as the diagnostic work-up revealed no bacterial aetiology ($n = 155$). Directed therapy, based on microbiological culture results or clinically documented infection, was started on 92 occasions of fever. In the majority of all cases in which tailored therapy was administered, a switch to a glycopeptide, mainly vancomycin, was made because of gram-positive infections. Prolonged treatment with imipenem was given for 56 instances, including 22 episodes of unexplained fever in which patients were considered too ill to stop empirically started imipenem safely, despite the absence of any clue of a bacterial aetiology. Other reasons to continue imipenem were clinically documented infection, especially pneumonia and typhlitis (neutropaenic enterocolitis). In 18 patients, antifungal therapy was eventually started at the time a diagnosis of possible or probable/proven invasive fungal infection was made.

In Fig. 2, the presumed aetiology of all 317 febrile episodes in the 202 neutropaenic periods is provided. Distinct febrile episodes caused by the same aetiologic origin (e.g. pulmonary aspergillosis) during a single period of neutropaenia were counted only once. The vast majority of all febrile episodes were diagnosed as UF ($n = 177$). Episodes of primary bacteraemia were due to CNS ($n = 21$), *Enterococcus* spp. ($n = 2$), combined CNS and *Enterococcus faecalis* ($n = 1$), *Streptococcus* spp. ($n = 3$), *Escherichia coli* ($n = 1$) and *Rothia mucilaginosa* ($n = 1$). In the patient with *E. coli* bacteraemia, surveillance cultures did not detect gram-negative micro-organisms before the onset of bacteraemia.

Sources of secondary bacteraemia were catheter-related bacteraemia ($n = 13$), bacteraemia in the context of severe mucositis and/or typhlitis ($n = 11$), respiratory tract infection ($n = 4$), cellulitis ($n = 1$), diverticulitis ($n = 1$) and infected venous thrombus ($n = 1$). Infections without bacteraemia were catheter exit-site infection ($n = 12$), invasive aspergillosis ($n = 18$, of which 7 probable/proven and 11 possible), typhlitis ($n = 4$), viral infection ($n = 5$), urinary tract infection ($n = 2$), wound infection ($n = 2$) and tonsillitis, folliculitis, meningitis, *Rhodotorula* pleuritis and disseminated mucormycosis (all $n = 1$). In 5 episodes of fever, a non-infectious aetiology was the most likely explanation, i.e. fever due to blood transfusion ($n = 3$), exacerbation of gout and acute graft-versus-host disease (both $n = 1$).

Six of the 166 patients (3.6%) died within 30 d after neutrophil recovery; 4 patients died while being neutropaenic and 2 patients were already recovered from neutropaenia (Table 3). No differences in outcome were observed when taking into account the original decision to stop or to continue empirical treatment with imipenem (Fig. 1). Infectious complications contributed to death in 2 patients (invasive aspergillosis and severe typhlitis). The cause of death in the other patients was cardiac death after electromechanical dissociation (autopsy refused), cardiogenic shock due to myositis with left ventricular dysfunction, acute respiratory distress syndrome (no documented infectious origin in BAL) and progressive AML/MDS (all $n = 1$).

**Table 2 – Main characteristics of the neutropaenic[a] periods (n = 276).**

| Characteristic | Value |
|---|---|
| *Haematological treatment course* (%) | |
| High-dose chemotherapy | 182 (65.9) |
| Autologous stem cell transplantation | 86 (31.2) |
| Allogeneic stem cell transplantation | 8 (2.9) |
| *Mean days of neutropaenic period* (SD[b]) | |
| All neutropaenic periods | 20.5 (11.5) |
| AML/MDS[c] (remission and consolidation, $n = 127$) | 28.2 (11.3) |
| MM[d], autologous stem cell transplantation ($n = 47$) | 12.7 (4.0) |
| Non-Hodgkin lymphoma ($n = 64$) | 14.6 (6.7) |
| Acute lymphatic leukaemia ($n = 16$) | 18.3 (11.7) |
| Allogeneic stem cell transplantation ($n = 8$) | 11.9 (1.7) |
| *Neutropaenic periods classified according to febrile episodes* | |
| Neutropaenia without fever | 74 |
| Neutropaenia with 1 febrile episode | 113 |
| Neutropaenia with 2 febrile episodes | 57 |
| Neutropaenia with >2 febrile episodes | 32 |

Data presented are numbers of neutropaenic periods.
a Neutropaenic, neutrophil count $<0.5 \times 10^9$/l.
b SD, standard deviation.
c AML/MDS, acute myeloid leukaemia/myelodysplastic syndrome.
d MM, multiple myeloma.

## 4. Discussion

Current guidelines recommend prolonged use of broad-spectrum antibiotics in febrile patients with prolonged neutropaenia, although also emphasising that these recommendations

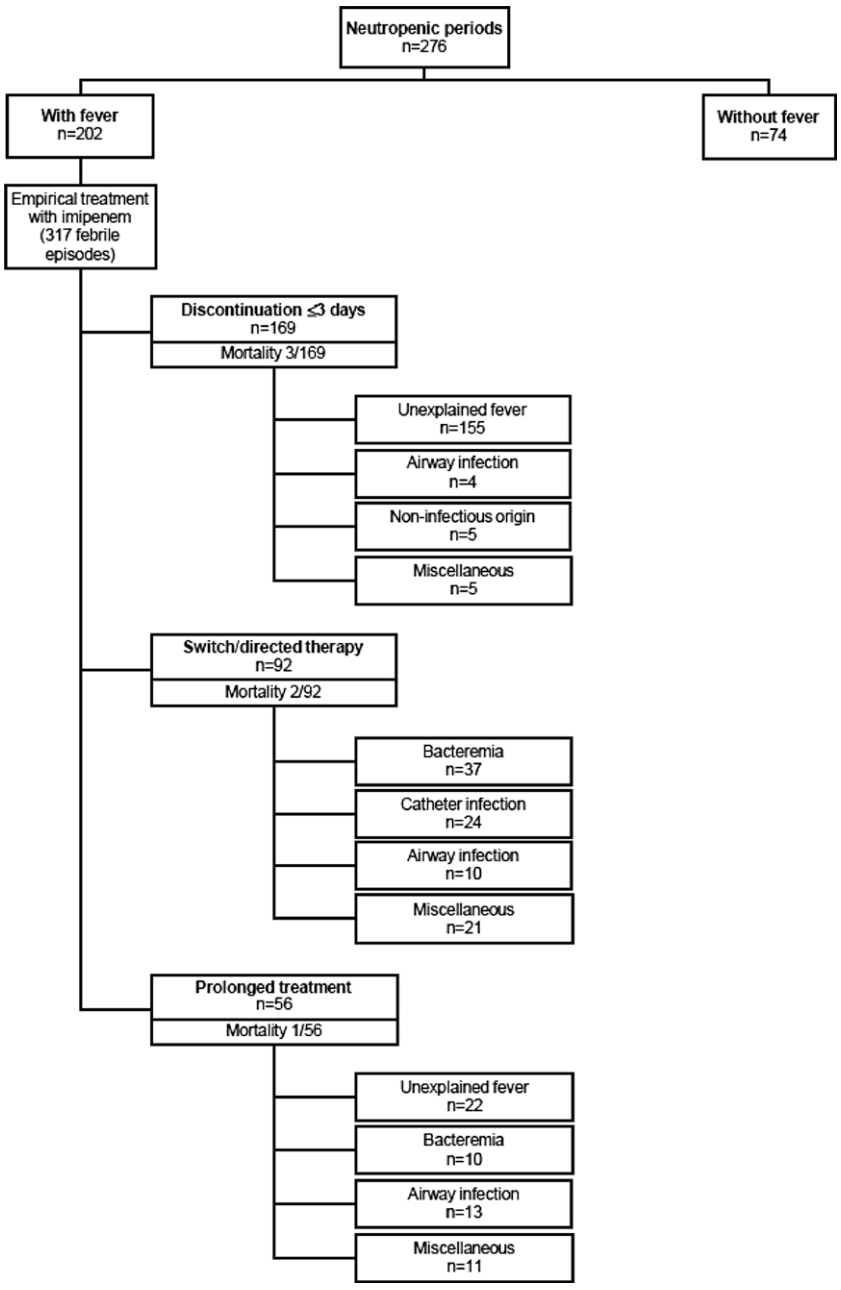


**Fig. 1 – Antibiotic strategy in 276 neutropaenic periods (317 febrile episodes).**

are general and should be applied taking into account the different treatment settings, patient populations and antimicrobial susceptibility patterns.[6] Even in patients already non-febrile after 3–5 d of treatment, cautious recommendations are to continue antibiotics in these high-risk patients for at least 2 weeks.

Indeed, progression of infection in patients with prolonged neutropaenia can be rapid, and signs and symptoms of inflammation may be minimal or even absent. However, we are unaware of any convincing evidence from randomised clinical trials that non-febrile or even febrile patients, in whom proof of a bacterial infection is lacking after a scrupulous clinical and diagnostic work-up, will benefit from continued antimicrobial therapy. A considerable amount of febrile episodes in patients with chemotherapy induced neutropaenia have a non-infectious aetiology. Neutropaenic haematology patients might be prone to febrile reactions in general, due to the nature and consequences of treatment with high-dose chemotherapeutics and transfusions with blood or plasma products. Moreover, a significant proportion of these patients are diagnosed with invasive fungal infections, especially pulmonary aspergillosis, in case of persisting neutropaenic fever. Continuation of broad-spectrum antibiotics may falsely temper the scrutiny in the search for the real cause of the febrile episode in such cases.

This study suggests that in patients receiving fluoroquinolone and fluconazole prophylaxis, broad-spectrum antimicrobial therapy started empirically for neutropaenic fever can be

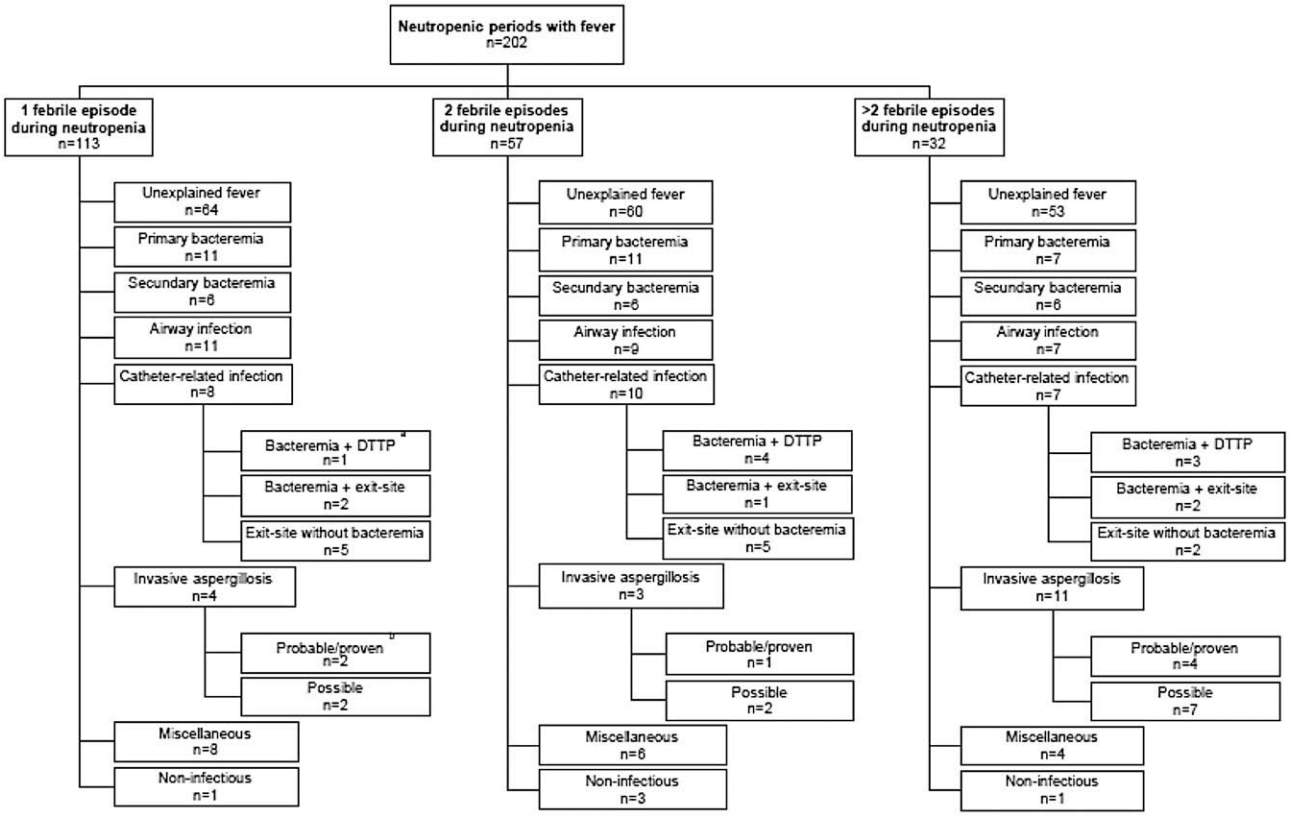


**Fig. 2 – Cause of fever in 202 neutropaenic periods (137 patients). Febrile episodes due to same aetiology during a single neutropaenic period were counted once; therefore, adding up totals may result in different numbers compared to the multiplication of the number of neutropaenic periods with the febrile episodes. [a]DTTP, differential time to positivity and [b]for diagnosis, updated EORTC-MSG definitions were used.**

safely discontinued after 72 h if no infectious origin is documented, provided that patients are hemodynamically stable. Following this policy, the all-cause mortality in our study population was 3.6% (6 out of 166 patients). At least 1 and possibly 2 of these deaths were related to a non-bacterial infection (aspergillosis) and another one was due to refractory AML/MDS. In the 4 other patients, an infectious aetiology could not be established although autopsy was not performed.

The major advantage of a more restrictive antimicrobial treatment strategy would be an important reduction in the amount of days on which patients receive broad-spectrum antibiotics. Following latest IDSA guidelines for these high-risk patients would imply an additional prescription of at least another 5–7 d of broad-spectrum antibiotics after defervescence. This study suggests that fluoroquinolone prophylaxis effectively prevents gram-negative infections. In only 1

**Table 3 – Data on fatal outcome of 6 patients.**

| Infectious cause | Underlying disease | Cause of death | Days after start of neutropaenia[f] |
|---|---|---|---|
| Yes | AML/MDS | Proven/probable aspergillosis jaw and Iung | 36 |
| Yes | AML/MDS | Refractory AML, typhlitis and possible IPA | 48 |
| No | AML/MDS[b] | ARDS[d] no infectious origin | 41[a] |
| No | AML/MDS | Reanimation after EMD[e] no autopsy | 15 |
| No | AML/MDS | Progressive AML | 28 |
| No | HL[c] | Cardiogenic shock due to left ventricular dysfunction induced by myositis | 16[a] |

a Patients already recovered from neutropaenia.
b AML/MDS, acute myeloid leukaemia/myelodysplastic syndrome.
c HL, Hodgkin lymphoma.
d ARDS, acute respiratory distress syndrome.
e EMD, electromechanic dissociation.
f Neutropaenia, neutrophil count $<0.5 \times 10^9$/l.

patient a gram-negative bacteraemia was documented; however, no gram-negative micro-organisms were detected in preceding surveillance cultures. In contrast, the large majority of bacterial infections were caused by gram-positive micro-organisms, and microbiological confirmation of gram-positive bacteraemia was straightforward in these cases. Therefore, early discontinuation of empirically started broad-spectrum antibiotics could be done safely in the absence of an infectious origin after a thorough diagnostic work-up. Although disadvantages of antibiotic prophylaxis are conceivable, the results of a recent meta-analysis on antibiotic prophylaxis during chemotherapy induced neutropaenia demonstrated that the reduction in mortality and infection rates outweighs the risk of developing resistance, costs and adverse events.[14]

The present study has several limitations that should be noticed. This study lacked a control arm because the strategy as described has historically become the present standard of care in our hospital. Further studies should therefore compare this policy with the more widely advocated approach of continued broad-spectrum antibiotic therapy for another 7 d after defervescence. Also it should be stressed that effective antibiotic prophylaxis, which was monitored twice weekly with surveillance cultures, is an essential part of our strategy.

From a historical point of view, the management of unexplained fever during neutropaenia has been an evolving landscape over the previous 20 years. Not even 10 years ago, vancomycin was part of the empiric therapy in many centres, but subsequent randomised trials showed that vancomycin containing regimens did not lead to a better outcome.[20] More recently, the need for empirical antifungal therapy in case of unexplained fever of >5 d has been questioned due to the improved outcome with voriconazole treatment as well as the possibility to diagnose invasive aspergillosis earlier by means of new diagnostic tools, such as galactomannan measurement and HRCT of the lungs. These developments improved the outcome of invasive aspergillosis considerably.[21–24] In this historical perspective, our present study could be a cautious next step in this evolving field on the management of neutropaenic fever.

In conclusion, our study shows that discontinuation of empirically started broad-spectrum antimicrobial therapy given for unexplained fever during neutropaenia in haematology patients on continuous fluoroquinolone and fluconazole prophylaxis is safe if no infectious origin is found after 72 h.

## Conflicts of interest statement

None declared.

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