

# Management of febrile neutropenia in low risk cancer patients

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## Introductory articles

### A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy

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**Background.** Among patients with fever and neutropenia during cancer chemotherapy who have a low risk of complications, oral administration of empirical broad-spectrum antibiotics may be an acceptable alternative to intravenous treatment. **Methods.** We conducted a randomized, double-blind, placebo-controlled study of patients (age 5–74 years) who had fever and neutropenia during chemotherapy for cancer. Neutropenia was expected to be present for no more than 10 days in these patients, and they had to have no other underlying conditions. Patients were assigned to receive either oral ciprofloxacin plus amoxicillin-clavulanate or intravenous ceftazidime. They were hospitalized until fever and neutropenia resolved. **Results.** A total of 116 episodes were included in each group (84 patients in the oral-therapy group and 79 patients in the intravenous-therapy group). The mean neutrophil counts at admission were 81 per cubic millimetre and 84 per cubic millilitre, respectively; the mean duration of neutropenia was 3.4 and 3.8 days, respectively. Treatment was successful without the need for modification in 71% of episodes in the oral-therapy group and 67% of episodes in the intravenous therapy group (difference between groups 3%, 95% confidence interval –8% to 15%;  $p=0.48$ ). Treatment was considered to have failed because of the need for modifications in the regimen in 13% and 32% episodes, respectively ( $p<0.001$ ) and because of the patients' inability to tolerate the regimen in 16% and 1% of episodes, respectively ( $p<0.001$ ). There were no deaths. The incidence of intolerance of the oral antibiotics was 16% as compared with 8% for placebo ( $p=0.07$ ). **Conclusions.** In hospitalized low-risk patients who have fever and neutropenia during cancer chemotherapy, empirical therapy with oral ciprofloxacin and amoxicillin-clavulanate is safe and effective. (N Engl J Med 1999; 341:305–11)

### Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy

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**Background.** Intravenously administered antimicrobial agents have been the standard choice for the empirical management of fever in patients with cancer and granulocytopenia. If orally administered empirical therapy is as effective as intravenous therapy, it would offer advantages such as improved quality of life and lower cost. **Methods.** In a prospective, open-label, multicentre trial, we randomly assigned febrile patients with cancer who had granulocytopenia that was expected to resolve within 10 days to receive empirical therapy with either oral ciprofloxacin (750 mg twice daily) plus amoxicillin-clavulanate (625 mg three times daily) or standard daily doses of intravenous ceftriaxone plus amikacin. All patients were hospitalized until their fever resolved. The primary objective of the study was to determine whether there was equivalence between the regimens, defined as an absolute difference in

the rates of success of 10% or less. **Results.** Equivalence was demonstrated at the second interim analysis, and the trial was terminated after the enrolment of 353 patients. In the analysis of the 312 patients who were treated according to the protocol and who could be evaluated, treatment was successful in 86% of the patients in the oral-therapy group (95% confidence interval 80 to 91%) and 84% of those in the intravenous-therapy group (95% confidence interval 78 to 90%;  $p=0.02$ ). The results were similar in the intention to treat analysis (80% and 77%, respectively;  $p=0.03$ ), as were the duration of fever, the time to a change in the regimen, the reasons for such a change, the duration of therapy, and survival. The types of adverse events differed slightly between the groups but were similar in frequency. **Conclusions.** In low-risk patients with cancer who have fever and granulocytopenia, oral therapy with ciprofloxacin plus amoxicillin-clavulanate is as effective as intravenous therapy. (*N Engl J Med* 1999;**341**:312–8)

Infection continues to be a major complication of neutropenia following cytotoxic chemotherapy and, despite significant advances in the scope of antimicrobial drugs, it is still responsible for considerable morbidity and a small, but significant, mortality.

Both the presentation and management of infection in the neutropenic patient differ from infection in other settings. A typical presentation is of fever with no other accompanying signs or symptoms, although about one third of individuals may have some evidence of a source of infection. Microbiological testing is also often disappointingly unhelpful, with a positive culture in less than 50% of patients. Once established, the course of infection during neutropenia can be extremely rapid and fulminating and it has become clear over the years that it is essential to initiate antibiotic treatment as soon as a pyrexia is noted, and that it is dangerous to wait to review the evolution of the process or to obtain a microbiological diagnosis. From these findings the concept of empirical antibiotic treatment arose and the challenge has been to develop protocols for regimens that are safe and effective that can respond to the changing patterns of infection and the development of antimicrobial resistance.

#### Conventional management of febrile neutropenia

The rationale behind the very large numbers of published clinical trials dealing with empirical treatment of febrile neutropenia can be traced to the changing pattern of infection in neutropenic patients, the availability of new antimicrobial agents and, more recently, attempts to improve safety and convenience of administration of these agents.

The changing pattern of infection in neutropenic patients has been well documented.<sup>12</sup> During the 1970s Gram negative bacilli were the predominant pathogens, but this trend was reversed during the 1980s when Gram positive bacteria began to account for some two thirds of documented infections and this pattern has continued throughout the 1990s. The two major Gram positive bacteria accounting for this change have been the coagulase negative staphylococci, which are mainly related to the use of central venous catheters, and the viridans streptococci which seem to be associated with intensive chemotherapeutic regimens, particularly those which cause severe mucositis. *Pseudomonas aeruginosa*, which was previously an extremely important pathogen in this setting, is now isolated only infrequently. Relevant advances in new antimicrobial agents have focused particularly on the beta-lactam group, including the carbapenems, and the new fluoroquinolones.

Early studies of treating febrile neutropenia showed poor results with aminoglycosides alone, even when the

organism was fully susceptible,<sup>3</sup> and this led to the requirement for synergistic combinations of antimicrobial agents to give the bactericidal effect needed to treat infections in neutropenic individuals. The combination of a beta-lactam with an aminoglycoside appeared particularly suitable and, wherever possible, agents with activity against *P aeruginosa* were chosen. When extended spectrum penicillins such as piperacillin and azlocillin became available, combinations of one of these with an aminoglycoside became widely used.<sup>4</sup> The changing pattern of infections, concerns about potential toxicity from the aminoglycosides, and the availability of new broad spectrum, highly bactericidal antibiotics led to renewed interest in the possibility of monotherapy. Broad spectrum cephalosporins such as cefoperazone and ceftazidime were the first contenders to be studied, but a large trial carried out by the European Organisation for Research and Treatment of Cancer (EORTC) comparing ceftazidime with short or prolonged duration amikacin suggested that a full course of combination therapy was more effective in individuals with Gram negative bacteraemia.<sup>5</sup> This somewhat surprising result led to concerns about monotherapy which were not able to be addressed until the availability of the carbapenem group of antimicrobial agents which have an extremely broad spectrum of activity and are highly bactericidal. Studies which looked initially at imipenem/cilastatin<sup>6,7</sup> and subsequently at meropenem<sup>8</sup> were able to confirm that these agents were as effective as combination regimens and had the potential for reduced toxicity.

With the increasing use of central venous catheters, the frequency of isolation of Gram positive bacteria, and the advent of widespread resistance to beta-lactam antibiotics by coagulase negative staphylococci and, in some centres, *Staphylococcus aureus*, the question arose as to whether a glycopeptide – either vancomycin or teicoplanin – should become part of the initial empirical regimen. This issue has been widely studied, including a randomised trial coordinated by the EORTC,<sup>9</sup> and the general conclusion has been that a glycopeptide should not be routinely added to the initial regimen, although individual centres with particular problems with methicillin resistance might wish to consider adding one of these agents.

New fluoroquinolones were another class of broad spectrum antimicrobial agents with antipseudomonal activity which came under consideration for use as empirical treatment for neutropenic fevers. Ciprofloxacin was the first of these agents to be developed in the mid 1980s and was obviously attractive for this indication because of its spectrum, lack of resistance, and the possibility of both intravenous and oral formulations. The first studies of ciprofloxacin for the treatment of neutropenic fever were in the context

of combinations of agents and used the intravenous formulation, although step down to the oral formulation was possible when patients had improved sufficiently. The EORTC<sup>10</sup> undertook a prospective study comparing intravenous ciprofloxacin alone (200–300 mg every 12 hours) with piperacillin plus amikacin in patients with lymphoma and solid tumours, but this study was discontinued prematurely because patients treated with ciprofloxacin had a significantly lower overall success rate than patients treated with piperacillin plus amikacin (65% versus 91%), as well as having a poor outcome in those with Gram positive bacteraemia. By this time fluoroquinolones were being widely used for prophylaxis of bacterial infections in neutropenic patients, and the authors concluded that empirical monotherapy with ciprofloxacin should not be recommended, even in patients with neutropenia of short duration.

The Infectious Diseases Society of America<sup>11,12</sup> has attempted to produce comprehensive, evidence based guidelines for the use of antimicrobial agents in febrile neutropenia, and the most recently revised version of these continues to recommend that all febrile patients with neutrophil counts of  $<500/\text{mm}^3$  and those with counts of  $500\text{--}1000/\text{mm}^3$  in whom a further decrease can be anticipated should be treated with broad spectrum bactericidal antibiotics by the intravenous route, although they acknowledge that a number of new issues need to be addressed including the identification of “lower risk” patients and the drive to reduce costs and enhance quality of life.

### Rationale for a risk based approach

Most of the large studies of various antibiotic regimens for febrile neutropenia have included patients with a wide variety of underlying diseases and expected duration of neutropenia. In some cases patients perceived to have a different likely outcome, such as those with solid tumours, were stratified into subgroups to ensure that they would be equally represented in the different trial arms but, in general, analyses have been of the full group of patients entered.

However, it is well known that individuals with neutropenic fever are an extremely heterogeneous group and many factors are likely to influence the course of their infection and its outcome. In the mid 1960s Bodey and colleagues<sup>13</sup> identified the association between depth of neutropenia and likelihood of infection and, since then, it has become clear that both degree and duration of neutropenia have a profound effect on risk of poor outcome from infection. Individuals with solid tumours are also considered to be at lower risk of serious complications, probably because chemotherapeutic regimens for these conditions usually result in shorter periods of neutropenia. Episodes where a site of infection or causative organism cannot be identified (fevers of unknown origin) tend to be associated with improved outcome,<sup>14</sup> but this cannot, of course, be identified until some time after presentation. Other factors which might play a role in determining risk of poor outcome had not, however, been carefully considered until the work of Talcott and colleagues.<sup>15–17</sup> In an attempt to identify at presentation of fever a group of individuals at low risk of complications or death, they distinguished four subgroups of patients – group 1: individuals who were already inpatients when fever developed; group 2: outpatients who had significant comorbidity other than the fever and neutropenia; group 3: outpatients who did not have significant comorbidity but who did have

uncontrolled malignancy; and group 4: outpatients with fever and neutropenia who did not have the additional risk factors of groups 2 and 3. In two studies which attempted to validate whether the risk was different in these patient groups they were able to show a significantly higher risk of serious complications in groups 1, 2, and 3 than in group 4. In addition, no deaths were noted in individuals identified as belonging to group 4, whereas death rates in groups 1, 2, and 3 were between 9% and 23%. It is interesting that neither underlying disease nor expected duration of neutropenia formed part of this risk assessment, and clinical characteristics which are often considered to be associated with additional risk – such as leukaemia (which may be related to expected prolonged duration of neutropenia), older age, bacteraemia, or hepatic dysfunction – were noted in individuals in the low risk group 4.

If this risk based approach was to be used to identify a group of patients who were able to be managed as outpatients, other non-clinical risk factors such as availability of a capable carer, transport, and proximity to hospital would also need to be taken into account. To date, none of the studies attempting to validate a risk based strategy has assessed the potential numbers of patients with non-clinical risk factors that would make outpatient treatment dangerous or difficult.

### Options for management of low risk febrile neutropenia

If a group of individuals at low risk of serious complications can be identified, then a number of options exist for lower intensity antimicrobial treatment. Clearly, to maximise benefits of cost saving and improved quality of life and to alleviate problems of access to healthcare facilities, particularly in developing countries, outpatient treatment for all or part of the antimicrobial course is the ultimate goal. This could be achieved by sequential intravenous followed by oral antibiotics, outpatient intravenous treatment, or outpatient oral treatment. A number of studies of all these approaches have now been undertaken, but the major problem remains the limited number of antimicrobial agents suitable for such use.

#### OUTPATIENT INTRAVENOUS TREATMENT

While it may be possible to train patients or their carers to administer multiple daily doses of intravenous antibiotics, this is unlikely to find widespread acceptability, so the only realistic options for home intravenous treatment revolve around agents which can be administered once a day. Once daily aminoglycoside administration is well accepted and once daily amikacin has been part of the regimen in a number of EORTC studies of febrile neutropenia.<sup>8,18</sup> However, regardless of the dosing regimen, serum levels of aminoglycosides must be regularly monitored and this may prove to be an added inconvenience in the outpatient setting.

There are few options for beta-lactam agents which could be used either in combination with an aminoglycoside, another agent, or on their own. Ceftriaxone has a long half life and its spectrum of activity includes many Gram positive cocci and Gram negative rods, but not *P aeruginosa*. The efficacy and toxicity of single daily doses of ceftriaxone and amikacin were studied in a large prospective randomised trial coordinated by the EORTC and compared with their “gold standard” regimen of multiple daily doses of ceftazidime and amikacin.<sup>18</sup> The single daily dosing regimen of ceftriaxone

and amikacin proved to be as effective and safe as the standard treatment, and the authors noted that this could pave the way to a convenient intravenous treatment which could be used on an outpatient basis. Karthaus *et al*<sup>19</sup> studied 126 episodes of febrile neutropenia in clinically stable outpatients which were treated with ceftriaxone alone in 100 episodes or in combination with other antibiotics in 26 episodes. The initial empirical regimen was successful in 78% of episodes and 76% of the episodes were managed entirely in the outpatient setting. There were no infective deaths. A number of other studies using ceftriaxone either alone or in combination with an aminoglycoside or a glycopeptide have also shown promising results.<sup>20-22</sup>

#### ORALLY BASED REGIMENS

Where intravenous followed by oral or entirely oral regimens are considered, the major class of antibiotics likely to be candidates are the fluoroquinolones. These agents have a broad spectrum of activity, excellent oral bioavailability, and are well tolerated. However, the question of their safety in children remains controversial.<sup>23,24</sup> The first fluoroquinolone to be developed was ciprofloxacin, and ofloxacin and levofloxacin have since become widely available. A number of other newer agents are at various stages of development. In most of these newer agents the aim has been to improve activity against Gram positive pathogens, in some cases at the expense of activity against Gram negative organisms such as *P aeruginosa*. A major concern with the use of fluoroquinolones has been the development of resistance in Gram negative organisms, particularly *E coli*, in neutropenic cancer patients,<sup>25-27</sup> and this is considered to be at least in part the result of the widespread practice of using these agents as prophylaxis against bacterial infections in these patient groups. A number of studies using ciprofloxacin in combination with other intravenous agents have been reported,<sup>28,29</sup> and in a study comparing ciprofloxacin plus netilmicin against piperacillin plus netilmicin, step down to oral ciprofloxacin therapy was possible in 64 of 115 (56%) episodes.<sup>30</sup>

If an entirely orally based regimen is to be considered, the options are to use a fluoroquinolone on its own or to combine it with another agent. Malik and colleagues have conducted a number of studies looking into the feasibility of using oral ofloxacin alone for neutropenic cancer patients deemed to belong to low risk groups. These studies were carried out in Pakistan where the availability of adequate medical services for the management of cancer is problematic and where many individuals do not have adequate access to specialist facilities. In an initial small randomised study they noted that oral ofloxacin at a dose of 400 mg twice daily was as effective as their current parenteral regimens using a beta-lactam together with amikacin.<sup>31</sup> However, patients with neutropenia of less than one week duration had better responses to both treatment regimens than patients with longer lasting neutropenia. Mortality was 7% in the ofloxacin group and 10% in the parenteral therapy group. In two subsequent multicentre prospective trials the same group then addressed the issue of oral ofloxacin administered as an outpatient treatment. In the first study<sup>32</sup> a prerequisite of entry was inaccessibility to or non-affordability of conventional management. Neutropenic patients who were able to swallow, had no other comorbidities requiring admission to hospital, and in whom there was an expectation that neutropenia would not be prolonged beyond seven days,

were given ofloxacin and instructed to self-administer it if fever developed. In this group 83% of the febrile episodes responded to oral ofloxacin and did not require hospital admission, 15% failed and did need to be admitted to hospital, and in 2% the two patients did not respond and died before reaching hospital. Overall, treatment was successful for 97% of all evaluable patients. In the second study<sup>33</sup> 182 low risk febrile neutropenic episodes were randomised to receive oral ofloxacin either at home or in hospital. Close monitoring and follow up was undertaken for all cases. Overall, 78% of inpatient and 77% of outpatient fevers resolved with no modification of initial treatment; 21% of patients originally assigned to outside management required admission to hospital. The mortality was 2% among inpatients and 4% among outpatients. One early death occurred in a non-hospitalised patient who developed vomiting and became unable to take oral medication but refused admission to hospital. Response rates were significantly higher in cases of pyrexia of unknown origin than in proven infections and there were two cases of breakthrough infections with *P aeruginosa*, calling into question whether ciprofloxacin would have been more effective than ofloxacin.

In the United States, workers at the MD Anderson Cancer Centre<sup>34</sup> studied a group of patients who did not require inpatient care for any other reason and compared two outpatient regimens, one using intravenous clindamycin and aztreonam and the other oral clindamycin together with oral ciprofloxacin 750 mg eight hourly. The patients studied included individuals with leukaemia and other haematological malignancies as well as those with solid tumours. Although the response rates were similar in both arms, the study was terminated early because of unacceptable toxicity in the oral regimen. With this regimen there were four episodes of acute renal failure which was attributed to one or more of several factors including the high dose of ciprofloxacin, a nephrotoxic interaction between clindamycin and ciprofloxacin, subclinical dehydration, or pre-existing diminished renal function.

A prospective randomised trial of outpatient treatment for low risk neutropenia was reported by Hidalgo *et al*.<sup>35</sup> Patients with solid tumours who presented with fever (>38°C) on two occasions four hours apart or 38.5°C on one occasion and neutropenia of <500 cells/μl were randomised to receive hospital inpatient treatment with intravenous ceftazidime and amikacin or outpatient oral ofloxacin. Exclusion criteria were ECOG performance status 3-4, hypotension, oliguria, altered mental status, tachypnoea, respiratory failure, clotting abnormality, acidosis, serious local infection, hypercalcaemia, and liver or renal failure. Patients were also excluded if they had received antibiotics in the last 96 hours. Ninety five of 100 randomised episodes were evaluable; 89% of outpatients and 91% of inpatients recovered uneventfully. Eight patients (16%) in the outpatient group needed to be admitted to hospital because of treatment failure. No patients died during the study. The authors concluded that oral ofloxacin was safe and similar in efficacy to broad spectrum parenteral antibiotics for low risk patients.

#### Myeloid growth factors in the treatment of neutropenia

Several guidelines have been published advising on how myelopoietic colony stimulating factors (CSFs) should be used.

## CHILDREN

Secondary prophylaxis has been recommended for children receiving regimens which have previously caused prolonged neutropenia (>7 days) or severe neutropenia with associated proven bacterial or fungal infection which led to a modification of their chemotherapy regimen, or two previous episodes of prolonged and severe neutropenia with or without infection. G-CSF 5 µg/kg/day (Filgrastim) or 150 µg/m<sup>2</sup> per day (Lenograstin) or 5 µg/kg/day (Molgramostim) should begin 1–5 days after chemotherapy, with a later start for regimens with a long half life, and should continue until the absolute neutrophil count exceeds  $0.5 \times 10^9/l$  for two days.<sup>36</sup>

Intervention therapy probably improves quality of life rather than survival as antibiotics are so effective. Two placebo controlled trials in children have shown a statistically significant reduction of antibiotic days and duration of inpatient stay. Interventional use of CSFs is recommended for chemotherapy induced febrile neutropenia, together with antibiotics for children considered to be at high risk (proven pseudomonas or fungal infection, multi-organ dysfunction or pneumonia), and they are also recommended for prolonged neutropenia of >28 days, with or without sepsis. Treatment is given until neutrophil counts are  $>0.5 \times 10^9/l$  for two consecutive days and sepsis has resolved.

## ADULTS

The American Society of Clinical Oncology (ASCO)<sup>37,38</sup> and the EORTC<sup>39</sup> guidelines do not recommend use of CSFs in afebrile neutropenia, nor is routine use recommended in febrile neutropenic patients. Exceptions are patients at high risk of clinical deterioration – for example, those with pneumonia, hypotension, multiorgan dysfunction or fungal infection – where the use of CSFs is thought to be reasonable although the benefits are not proven. The dose should be G-CSF 5 µg/kg/day (Filgrastim) or 250 µg/m<sup>2</sup>/day GM-CSF (Sargramostatin) intravenously or subcutaneously. The EORTC guidelines recommended CSFs for secondary prophylaxis after infections or neutropenia lasting more than seven days following the first cycle of chemotherapy where treatment is given with curative intent and dose intensity should be maintained.

## Introductory articles

Both of the introductory articles address the same issue – an evaluation of the efficacy of oral antibiotics in the management of fever associated with neutropenia after cancer chemotherapy.

Patients were only included in the studies if they were perceived to be at low risk – that is, had neutropenia that was expected to last no more than 10 days and were haemodynamically stable. Freifeld *et al*<sup>40</sup> excluded patients with abdominal pain, nausea or vomiting, or diarrhoea more than six times daily whereas Kern *et al*<sup>41</sup> excluded patients who had signs or symptoms necessitating intravenous supportive therapy. Both groups excluded patients with intravascular catheter infection, catheter tunnel infection, neurological or mental status changes, or those who had received antibiotics within the last 72 hours<sup>40</sup> or seven days.<sup>41</sup> Patients with new pulmonary infiltrates<sup>40</sup> or respiratory insufficiency<sup>41</sup> were also excluded from entry into the study. Patients also had to be able to swallow oral medication, have adequate hepatic function (aminotransferase less than five times normal<sup>40</sup>), and adequate renal function (creatinine clearance of more than 30 ml/min,<sup>40</sup> not in renal failure<sup>41</sup>).

Patients who had received autologous stem cell transplants were excluded from entering the study. Freifeld *et al* allowed patients to be randomised for more than one episode, whereas Kern *et al* only enrolled patients once.

The two groups had a different definition of neutropenia –  $<500/ml^3$  in the study by Freifeld *et al* and  $<1000/ml^3$  in the study by Kern *et al*. The latter group stratified patients on entry to the study according to neutrophil count ( $<500$  or  $\geq 500$ ). Fever was defined as  $\geq 38^\circ C$  on three oral measurements more than four hours apart during a 24 hour period or a single temperature of  $\geq 38.5^\circ C$  by Freifeld *et al*<sup>40</sup> or using the EORTC definition of  $\geq 38.5^\circ C$  on one occasion or  $\geq 38^\circ C$  on two or more occasions within 12 hours by Kern *et al*.<sup>41</sup>

Both groups used oral ciprofloxacin but the dose regimens were different – 30 mg/kg/day in three divided doses (max 750 mg eight hourly) in the study by Freifeld *et al* or 15 mg/kg if weight  $<40$  kg or 750 mg 12 hourly in the study by Kern *et al*. Neither paper stipulated the timing of the first dose of oral treatment. Both groups also used amoxicillin and clavulanate 40 mg/kg/day in three divided doses (maximum 500 mg eight hourly in the study by Freifeld *et al*) or 625 mg eight hourly or 15 mg/kg eight hourly if weight  $<40$  kg in the study by Kern *et al*. The standard intravenous antibiotic was different in the two trials; ceftazidime 90 mg/kg (max 2 g eight hourly) was used by Freifeld *et al* whereas ceftriaxone 2 g was used in adults and amikacin 20 mg/kg with dosage adjustment according to renal function was used by Kern *et al*. The Freifeld study was double blind whereas the Kern study was of open label design.

A total of 211 patients were randomised in the Freifeld study with 284 episodes of fever of which 52 (18%) were not evaluable, leaving 232 evaluable episodes. Kern *et al* randomised 370 patients of whom 17 (5%) were ineligible, giving 353 evaluable episodes. In both studies just over 70% of patients in each arm had solid tumours. However, most of the patients in the Freifeld study had breast cancer and their mean age was 41–42 years, while in the study by Kern *et al* the median age was 52 years in each arm.

In both groups central venous lines were present before the fever (170 (73%) episodes in the study by Freifeld *et al* and 143 (41%) episodes in the study by Kern *et al*). In addition, both groups had a high usage of myelopoietic growth factors. Freifeld *et al* used GM-CSF in 34 episodes (15%) and G-CSF in 163 episodes (70%) while Kern *et al* administered either G-CSF or GM-CSF in 223 patients (63%). The reason for using CSF is not obvious but is assumed to be part of the chemotherapy protocol.

The mean neutrophil count was  $81/ml^3$  for patients receiving oral antibiotics and  $84/ml^3$  for patients randomised to receive intravenous therapy in the study by Freifeld *et al* whereas 78% of patients on oral antibiotics and 75% of those on intravenous antibiotics in the study by Kern *et al* had a neutrophil count of  $<100/ml^3$ . The mean (Freifeld *et al*) or median (Kern *et al*) duration of neutropenia was 3–4 days in both studies with no difference between the treatment groups. The cause of approximately two thirds of febrile episodes was unexplained in both studies.

The efficacy of antibiotic treatment was 71% for the oral route and 67% for the intravenous route in the study by Freifeld *et al*, while Kern *et al* reported efficacy rates according to the protocol of 138/161 (86%) for oral treatment and 127/151 (84%) for intravenous treatment. There were 41 protocol violations (fever unrelated

to infection (8), protocol violations (26), other reasons (7)) so Kern *et al* also reported efficacy rates on an intention to treat basis with a success rate of 80% for oral treatment and 77% for intravenous treatment. Freifeld *et al* reported that intolerance of the antibiotics occurred in 16% of episodes with oral treatment and 1% with intravenous treatment ( $p < 0.001$ ), and that 13% of patients receiving oral treatment and 32% receiving intravenous treatment had additional treatment which resulted in one third of patients in each group needing treatment modifications. Fever of unknown origin was successfully treated by oral and intravenous antibiotics in approximately 85% of patients in each study, whereas microbiologically documented infection was successfully treated in only 41% of episodes treated with oral antibiotics and 33% with intravenous antibiotics.<sup>40</sup> Kern *et al*<sup>41</sup> reported a success rate for bacteraemia and microbiologically documented infection without bacteraemia of 54% and 78%, respectively, for oral antibiotics and 50% and 67%, respectively, for intravenous antibiotics.

Finberg and Talcott<sup>42</sup> wrote an accompanying editorial to these two articles which states that “the results of these studies show that oral antibiotics may be safely substituted for intravenous antibiotics in low-risk patients with fever and neutropenia”. However, in both of these studies patients were hospitalised and discharged after resolution of fever and recovery of neutropenia to  $\geq 500/\text{ml}^3$  (Freifeld *et al*, not defined by Kern *et al*). The frequency of blood pressure, temperature, pulse, and respiration rate is not documented for either study but patients were under close supervision with the ability to institute rapid changes in medication should they deteriorate. One third of the patients in the study by Freifeld *et al* needed modifications to the antibiotic regimen and both studies reported a lower efficacy for both oral and intravenous antibiotics in the presence of microbiologically documented infection. There were no deaths in the study by Freifeld *et al* but Kern *et al* reported six deaths – two on oral antibiotics and four on intravenous antibiotics. The authors caution the extrapolation of these results to the use of oral antibiotics in outpatients.

### Conclusions

There is now mounting evidence to suggest that it is possible to identify a subset of neutropenic patients with cancer who have febrile episodes where the risk of complications or a poor outcome is low, and in whom

oral or intravenous antibiotics, possibly administered in the home setting, may be safe. This exciting development holds out the prospect for enhanced quality of life, particularly in individuals who may have a severely limited lifespan, for better use of healthcare resources, and for delivering cancer chemotherapy in developing countries.

The precise identification of the low risk subgroup is not yet clear. In some cases, as in the two publications reviewed, the decision making was based largely on predicted duration of neutropenia, whereas in the model developed by Talcott and colleagues comorbidity and the stage of malignancy were the major considerations. Further work on validating various rule based approaches would be helpful. In addition, if outpatient treatment is considered, non-clinical criteria for acceptability of such an approach would need to be developed, such as the maximum distance from a healthcare facility that the patient might be expected to travel, availability of carers, telephone and transport, and optimal timings for follow up to allow monitoring of other myelotoxicities such as anaemia and thrombocytopenia. It may be advisable to recommend supervision of the first dose of oral treatment to ensure that it is taken promptly.

A major problem with oral treatment of febrile neutropenia is that all regimens to date rely heavily on the use of a fluoroquinolone, either alone or in combination with another agent. This is happening against a background of increasing availability of new quinolones, many of which are being targeted for respiratory infections and are likely to be widely used both in hospitals and the community. This will inevitably increase the potential for the development of resistance to this class of antimicrobial drug. Questions will arise as to whether it is safe to use repeated courses of the same agents in a patient, or whether one could prescribe a fluoroquinolone for outpatient febrile neutropenia to an individual who has recently received one for another indication. Freifeld *et al*<sup>40</sup> and Kern *et al*<sup>41</sup> looked at ciprofloxacin in combination with co-amoxiclav, whereas other workers have used a fluoroquinolone alone with apparently equivalent results. If the treatment of febrile neutropenia with fluoroquinolones is to become widespread, their use in both prophylaxis and treatment of other conditions in cancer patients will have to be carefully reviewed and surveillance of susceptibility patterns among clinical isolates from these patients will be essential.

Regardless of whether oral or even outpatient based

## LEARNING POINTS

- \* Neutropenic sepsis is a medical emergency with a significant risk of mortality
- \* A low risk group of patients may be identified, either on the basis of expected duration of neutropenia of <10 days, the absence of significant comorbidity, or both
- \* Local policies should dictate the treatment approach based on patterns of infecting organisms and microbial susceptibility
- \* Oral treatment for low risk patients appears to be as effective as intravenous treatment in randomised studies conducted in a hospital setting, although in some patients treatment will need to be modified because of intolerance or failure
- \* There are few data on outpatient oral treatment in low risk patients, the feasibility of which must consider non-clinical variables such as suitable home circumstances

therapies become established in routine use, precise recommendations of drugs and doses must be driven by local guidelines which take into consideration local patterns of infecting organism and bacterial susceptibility.

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