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The New Fluorinated Quinolones for Antimicrobial Prophylaxis in Neutropenic Cancer Patients

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Fluoroquinolones are the most attractive agents for prophylactic use in neutropenic cancer patients, due to their broad antimicrobial spectrum, high concentration in the faeces, systemic bactericidal activity, uncommon emergence of resistant strains and good tolerability. They have proved to be more effective than placebo, oral non-absorbable antibiotics or cotrimoxazole in the prevention of Gram-negative infections. In a prospective, randomised multicentre study performed by the *GIMEMA* infection program, ciprofloxacin was demonstrated to be more effective than norfloxacin for the reduction of febrile episodes, use of systemic antibiotics, and Gram-negative infections in neutropenic patients with haematological malignancies. The greater efficacy may be related to its better systemic or greater antibacterial activity. The potential problems related to the prophylactic use of fluoroquinolones are the increasing prevalence of Gram-positive infections caused by streptococci and coagulase-negative staphylococci; the reported emergence and nosocomial spread of resistant strains, especially among coagulase-negative staphylococci; the lack of their usefulness as empirical therapy in febrile neutropenic patients. Fluoroquinolones are today the better choice for preventing Gram-negative infections in neutropenic patients and ciprofloxacin should probably be preferred. More information on their efficacy and their relationship to the overall susceptibility of micro-organisms in patients with cancer would be valuable, and careful monitoring of patients treated with these drugs is therefore warranted.
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INTRODUCTION

BACTERIAL INFECTIONS are a major cause of morbidity and mortality in cancer patients during prolonged neutropenia [1]. Since these infections are most often caused by micro-organisms that colonise the gastrointestinal tract (most frequently Gram-negative bacilli) and enter the bloodstream through the epithelial surfaces damaged by cytotoxic chemotherapy, antimicrobial agents active against the intestinal flora should prove useful in preventing these infections [2].

The goals of a prophylactic antibacterial regimen in neutropenic patients are to lower infection-related morbidity and mortality, particularly those due to Gram-negative infections, and reduce the empirical use of systemic antibiotics.

Patients that should most benefit from prophylaxis are those with prolonged and severe neutropenia (neutrophils count $< 0.1 \times 10^9$/l) who are receiving aggressive cytotoxic chemotherapy.

The several different prophylactic strategies that have been tested [3] were recently reviewed by a panel of experts at the Consensus Meeting on Antimicrobial Prophylaxis in Immunocompromised Patients during the 6th International Symposium on Infections in the Immunocompromised Host that was held on 3–6 June 1990 in Peebles, Scotland (Table 1).

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Among oral absorbable agents cotrimoxazole has been widely used and shown to reduce the number of infections due to aerobic Gram-negative bacilli [4]. However, a high incidence of side-effects, prolongation of neutropenia and the emergence of resistant bacterial strains are major drawbacks to its use [5]. More recently, the new fluorinated quinolones have proved to be effective in the prevention of Gram-negative infections in neutropenic patients with haematological malignancies or undergoing bone marrow transplantation [6].

Owing to their antimicrobial activity and pharmacokinetic characteristics, fluoroquinolones are the most attractive agents for prophylactic use in these patients. They have bactericidal activity and a broad antimicrobial spectrum that includes enterobacteriaceae, *Pseudomonas* spp., and some Gram-positive cocci, but little or no activity on intestinal anaerobic flora [7]. Although the sparing effect on anaerobic intestinal flora seems to be important in inhibiting new colonisation by potentially pathogenic aerobic bacteria [8], the hypothesis of colonisation resistance of human intestinal microflora has not been confirmed in normal volunteers [9].

Most fluorinated quinolones are well absorbed by the oral route and, probably due to active intestinal secretion, are excreted in high concentration in the faeces. Emergence of resistant strains during treatment seems at present an uncommon event. In addition, as fluoroquinolones are usually well tolerated, they favour patient compliance.

REVIEW OF CLINICAL TRIALS

The clinical experience with the prophylactic use of fluoroquinolones in neutropenic patients is ever increasing. Uncontrolled [10–14], placebo controlled [15–17] and comparative

*Table 1. The role of different prophylactic antibacterial strategies in neutropenic patients**

1—Reversed isolation It is costly, it has many psychological burdens and probably has no meaningful purposes
2—Reversed isolation plus oral non-absorbable antibiotics Can lead to prevention of infections if the patient's compliance is good
3—Oral non-absorbable antibiotics Are directed against the aerobic enteric microflora, but their efficacy and tolerability have been found to be unsatisfactory
4—Oral absorbable antibiotics Are more effective and can prevent infections due to intestinal decontamination and due to their systemic effects

*Consensus Meeting on Antimicrobial Prophylaxis in Immunocompromised Patients. *6th International Symposium on Infections in the Immunocompromised Host.* 3–6 June 1990, Peebles, Scotland.

trials with other active compounds [18–25] have been published and their results will be shortly reviewed.

All the new fluorinated quinolones, norfloxacin [10], ciprofloxacin [11], pefloxacin [12], enoxacin [13] and ofloxacin [14] tested in open trials for the prevention of bacterial infection in neutropenic cancer patients, have reduced infections caused by Gram-negative bacilli.

Three small randomised clinical trials compared fluoroquinolones to placebo in the prevention of bacterial infections in neutropenic cancer patients [15–17], but only one was carried out in patients with acute leukaemia and severe and prolonged neutropenia [15]. All these trials clearly indicated that fluoroquinolones were able to reduce Gram-negative infections (Table 2). Fluoroquinolones were superior to oral non-absorbable antibiotics: norfloxacin [18] and ofloxacin [19] were more efficacious than the combination of vancomycin and polymixin in reducing Gram-negative infections in neutropenic patients with acute leukaemia (Table 3).

Norfloxacin [20, 21], ofloxacin [22] and ciprofloxacin [23] are more effective than cotrimoxazole in reducing Gram-negative infections (Table 4). It is worth noting that patients receiving fluoroquinolones were found to have a relative increase in infections sustained by Gram-positive microorganisms [20].

Although the new fluorinated quinolones have been shown to be more effective than placebo, cotrimoxazole or oral non-absorbable antibiotics for the prevention of bacterial infection in neutropenic cancer patients, evidence that they do not convert Gram-negative infections into fever of unknown origin, or that they reduced the need for parenteral broad-spectrum antibiotics is less than persuasive. Due to the small number of patients enrolled, these studies were unable to identify and control factors which might influence the effectiveness of prophylaxis, determine the population of patients more likely to benefit from prophylactic treatment or document that fluoroquinolones improved survival. On the basis of these studies it is hard to discern which of the available compounds is preferable as prophylactic agent. The main question is whether a quinolone characterised by good systemic activity (such as ciprofloxacin or ofloxacin) offers any advantage over a compound with lower bioavailability and/or antibacterial activity, such as norfloxacin [6]. The comparison between norfloxacin and ciprofloxacin carried out by Maschmeyer *et al.* [24] failed to reveal any significant difference, but the population studied was too small (51 patients) to reach any firm conclusion.

The recent *GIMEMA* infection program study has provided some answers to these questions [25]. This randomised, prospective multicentre study compared the efficacy of norfloxacin and ciprofloxacin in preventing bacterial infection in neutropenic patients with haematological malignancies or undergoing bone-marrow transplantation. 619 consecutive adult patients with chemotherapy-induced neutropenia expected to be of more than 10 days duration were studied. The prophylactic regimen was started 1–3 days before chemotherapy and administered for the entire neutropenic period. Ciprofloxacin increases the number of patients remaining afebrile during neutropenia, reduces the total number of febrile episodes, reduces the number of patients requiring empiric antibiotic therapy and the mean days spent with systemic antibiotics, increases the time interval to the first febrile episode (Table 5). Ciprofloxacin-treated patients also had a lower incidence of microbiologically documented infections particularly those due to Gram-negative bacilli (Table 6). Clinically documented infections, fever of unknown origin, mortality, compliance and tolerability were similar for the two groups. The patients who benefited from ciprofloxacin prophylaxis were those whose total neutropenia lasted less than 15 days, severe neutropenia below 7 days, in treatment with antifungal prophylaxis. Patients undergoing bone marrow transplantation did not enjoy the same benefit.

Table 2. Fluoroquinolones compared to placebo

Reference Study design	Study population No. of patients	Drug tested	Results in patients treated with quinolones
Karp *et al.* [15] RCT, double-blind	Acute leukaemia 68	Norfloxacin vs. placebo	Less Gram-negative infections $P<0.02$
Casali *et al.* [16] RCT	Solid tumours 65	Norfloxacin vs. placebo	Less infections $P<0.001$
Hartlapp J.H. [17] RCT, cross-over	Testicular tumours 42	Ofloxacin vs. placebo	Less fever, less infections

RCT: Randomised clinical trial.

Table 3. Fluoroquinolones compared to non-absorbable antibiotics

Reference Study design	Study population No. of patients	Drug tested	Results in patients treated with quinolones
Winston *et al.* [18] RCT	Acute leukaemia 66	Norfloxacin vs. vancomycin + polymyxin	Less Gram-negative infections $P=0.02$
Winston *et al.* [19] RCT	Acute leukaemia 62	Ofloxacin vs. vancomycin + polymyxin	Less Gram-negative infections

RCT: Randomised clinical trial.

Table 4. Fluoroquinolones compared to cotrimoxazole (T/S)

Reference Study design	Study population No. of patients	Drug tested	Results in patients treated with quinolones
Dekker *et al.* [23] RCT	Acute leukaemia 56	Ciprofloxacin vs. T/S + colistin	Less Gram-negative infections $P<0.02$
Bow *et al.* [20] RCT	Acute leukaemia 63	Norfloxacin vs. T/S	Less Gram-negative infections $P=0.06$ More Gram-positive infections $P=0.003$
Cruciani *et al.* [21] RCT	Children with malignancies 44	Norfloxacin vs. T/S	Less febrile episodes $P<0.01$
Liang *et al.* [22] RCT	Haematologic malignancies 105	Ofloxacin vs. T/S vs. T/S	Less Gram-negative infections $P<0.05$

RCT: Randomised clinical trial.

Table 5. The Gimema infection program trial. Patient outcome

	Norfloxacin	Ciprofloxacin	*P*
Neutropenic episodes	319	300	
Patients who did not develop fever	80 (25%)	103 (34%)	0.01
Total febrile episodes	294 (92%)	237 (79%)	<0.01
Patients requiring i.v. antibiotics	239 (75%)	197 (66%)	0.01
Mean days of antibiotic therapy during neutropenia (range)	12.0 (0–72)	10.1 (0–68)	0.02
Time interval to the first fever, mean days (range)	7.2 (1–47)	8.3 (1–31)	0.05

Table 6. The Gimema infection program trial. Causative organism (bacteraemia) identified in first febrile episode

Organism	Norfloxacin (319*)	Ciprofloxacin (300*)	*P*
Streptococcus	15 (14)	13 (11)	
Staphylococcus coagulase-negative	13 (13)	16 (14)	
Staphylococcus coagulase-positive	6 (4)	2 (1)	
Total Gram-positives	37 (34)	32 (27)	>0.2
P. Aeruginosa	13 (8)	7 (5)	
Total Gram-negatives	28 (13)	12 (7)	0.03
Polymicrobial	8 (6)	4 (3)	>0.2
Candida sp.	3 (2)	3 (3)	
Overall total	75 (55)	51 (40)	0.058

*Evaluable patients

This study suggests that ciprofloxacin is preferable for preventing infection in neutropenic patients with haematological malignancies and that the greater efficacy is related to better systemic or greater antibacterial activity.

PROBLEMS WITH THE PROPHYLACTIC USE OF FLUOROQUINOLONES

Despite the advantages offered by fluoroquinolones one should not lose sight of the problems their use as prophylactic agents may entail.

The first problem is the increasing prevalence of Gram-positive infections. Although fluoroquinolones effectively decrease Gram-negative infections, they are less efficacious against those due to Gram-positive micro-organisms. Patients who received prophylactic fluoroquinolones in the *GIMEMA* trial had preponderance of bacteraemias due to Gram-positive cocci (65%) and coagulase-negative staphylococci and streptococci were the most frequent blood isolates [25]. The greater prevalence of Gram-positive organisms as major sources of infections, suggests that one should consider including other antibiotics in the prophylactic regimen. The antibiotic regimens currently under investigation in the search for an improved way of preventing Gram-positive infections are the addition of a macrolide [26] or a penicillin to the fluoroquinolones. However, while these regimens appear to be adequate against streptococci they are ineffective against coagulase-negative staphylococci. Because, when a glycopeptide antibiotic that could be active against coagulase-negative staphylococci is administered via the oral or parenteral route, it may induce resistant strains responsible for subsequent bacteraemia [27], it would seem advisable to reserve glycopeptide antibiotics for the empirical therapy of febrile neutropenic

patients or the elective therapy of documented Gram-positive infections.

The second important problem is the emergence of resistance to fluoroquinolones. It is well-known that, sooner or later after the introduction of a new antibiotic into medical practice, plasmid-mediated resistance to the compound emerges and subsequently spreads. The wide, often indiscriminate use of the antibiotic favours the selection and dissemination of resistance. The mechanism of bacterial resistance to quinolones include chromosomal mutations that either alter DNA gyrase (resistance to quinolones alone) or reduce drug accumulation in association with changes in bacterial outer-membrane proteins (pleiotropic resistance). Destruction or modification of the drug by bacteria has not yet been described, and plasmid-mediated resistance to fluoroquinolones has not yet been found in clinical isolates [28].

In the *GIMEMA* trial, 64% Gram-negative bacilli and 51% Gram-positive cocci were resistant to the quinolone used. However, the mortality rate seems not to have been influenced by resistance and resistance itself seems not to have increased over the time period of the study. Therefore, the benefit observed in our study might not be counterbalanced by the resistance. On the other hand, an alert has been sounded on the emerging resistance to fluoroquinolones in staphylococci [29]. Ciprofloxacin-resistant coagulase-negative staphylococci and septicaemia caused by these micro-organisms in immunocompromised patients on ciprofloxacin have been also reported [30, 31]. Furthermore, two oncology units who gave ciprofloxacin either prophylactically or for the empirical treatment of fever in neutropenic leukaemia patients have documented the nosocomial spread of fluoroquinolone-resistant coagulase-negative staphylococci. There were a total of 28 cases of bacteraemia caused by ciprofloxacin-resistant, coagulase-negative staphylococci; as determined by DNA and immunoblot fingerprinting, phage typing, or plasmid profiles, the responsible isolates were identical for all patients at each institution [31, 32].

Clearly, the intensive use of these antibiotics could lead to a substantial increase in resistant strains. In consequence, one would like to have more prospective information on the efficacy of fluoroquinolones and their relationship to overall susceptibility of micro-organisms in patients with cancer and it would seem wise to recommend that patients treated with these drugs be carefully monitored.

A further problem of using fluoroquinolones in prophylaxis is that they cannot be utilised as empirical therapy. Due to their wide antibacterial spectrum, good bactericidal activity, favourable pharmacokinetic characteristics and low toxicity, fluoroquinolones may rival other antibiotics (aminoglycosides, third-generation chephalosporins, monobactams or their combinations) in the therapy of bacterial infections in neutropenic patients. However, this potential disadvantage should not be overstressed since many better evaluated alternative drug regimens are available as empirical therapy, synergism between fluoroquinolones and other antibiotics seems to be infrequent, and, due to their weak activity against streptococci and coagulase-negative staphylococci, they should always be used in combination with a penicillin or a glycopeptide antibiotic. The advantage of using fluoroquinolones in prophylaxis therefore appears to outweigh the potential gains from using them in empirical therapy.

CONCLUSIONS

In conclusion enough evidence exists to suggest that new fluoroquinolones are at present the better choice for preventing bacterial infections in neutropenic cancer patients. In fact, of the various prophylactic options, they are more effective and better tolerated. A fluoroquinolone with greater systemic effect (i.e. ciprofloxacin) should probably be preferred. However, their use should be closely monitored for the emergence of resistance.

1. Young LS. Antimicrobial prophylaxis against infection in neutropenic patients. *J Infect Dis* 1983, **147**, 611–614.
2. Schimpff SC. Infection prevention during profound granulocytopenia: new approaches to alimentary canal antimicrobial suppression. *Ann Intern Med* 1980, **93**, 358–361.
3. Henry SA. Chemoprophylaxis of bacterial infections in granulocytopenic patients. *Am J Med* 1984, **76**, 645–651.
4. Martino P, Venditti M, Petti MC, Mandelli F, Serra P. Cotrimoxazole prophylaxis in patients with leukemia and prolonged granulocytopenia. *Am J Med Sci* 1984, **287**, 7–9.
5. Young LS. Antimicrobial prophylaxis in the neutropenic host: lessons of the past and perspective for the future. *Eur J Clin Microbiol Infect Dis* 1988, **7**, 93–97.
6. Young L. The new fluorinated quinolones for infection prevention in acute leukemia. *Ann Intern Med* 1987, **106**, 144–146.
7. Hooper DC, Wolfson JS. Fluoroquinolone antimicrobial agents. *New Engl J Med* 1991, **324**, 384–394.
8. Van der Waij D, Berghuis JM, Lekkerkek JEC. Colonization resistance of the digestive tract of mice during systemic antibiotic treatment. *Hygiene* 1972, **70**, 605–610.
9. Gorbach SL, Barza M, Giuliano M, Jacobus NV. Colonization resistance of the human intestinal microflora: testing the hypothesis in normal volunteers. *Eur J Clin Microbiol Infect Dis* 1988, **7**, 98–102.
10. Menichetti F, Felicini R, Bucaneve G, *et al.* Norfloxacin prophylaxis for neutropenic patients undergoing bone marrow transplantation. *Bone Marrow Transplantation* 1989, **4**, 489–492.
11. Hellriegel KP, Fulle HH, Dennig D. Prevention of bacterial infections in myelosuppressed patients with ciprofloxacin. *International Symposium on Ciprofloxacin*, Dresden, 17–20 February 1988, Abstract p. 58.
12. Leleux A, Snoeck R, Gerain J, Van der Auwera P, Daneau D, Meunier F. Prevention using pefloxacin of infections in cancer patients with granulocytopenia. *Presse Med* 1989, **18**, 21–24.
13. Leleux A, Daneau D, Defresne N, Meunier F. Prophylaxis with enoxacin in neutropenic cancer patients. *15th International Congress of Chemotherapy*, Istanbul, 19–24 July 1987, Abstract p. 15.
14. Maiche AG. Oral ofloxacin for prophylaxis in neutropenia or treatment of infections caused by multiresistant bacteria in patients with cancer. *Rev Infect Dis* 1989, **11**, 1240.
15. Karp JE, Merz WG, Hendricksen C, *et al.* Oral norfloxacin for prevention of Gram-negative bacterial infections in patients with acute leukemia and granulocytopenia. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1987, **106**, 1–7.
16. Casali A, Verri C, Paoletti G, *et al.* Chemoprophylaxis of bacterial infections in granulocytopenic cancer patients using norfloxacin. *Chemioterapia* 1988, **7**, 327–329.
17. Hartlapp JH. Antimicrobial prophylaxis in immunocompromised patients. *Drugs* 1987, **34**, 131–133.
18. Winston DJ, Ho WG, Nakao SL, Galew RP, Champlin RE. Norfloxacin versus vancomycin/polymixin for prevention of infections in granulocytopenic patient. *Am J Med* 1986, **80**, 884–890.
19. Winston DJ, Winston GH, Bruckner DA, Gale RP, Champlin RE. Ofloxacin versus vancomycin/polymixin for prevention of infections in granulocytopenic patients. *Am J Med* 1990, **88**, 36–42.
20. Bow EJ, Rayner E, Louie T. Comparison of norfloxacin with cotrimoxazole for infection prophylaxis in acute leukemia. *Am J Med* 1988, **84**, 847–854.
21. Cruciani M, Concia E, Navarra A, *et al.* Prophylactic cotrimoxazole versus norfloxacin in neutropenic children: perspective randomized study. *Infection* 1989, **17**, 65–69.

22. Liang RHS, Yung RWH, Chan TK, *et al.* Ofloxacin versus cotrimoxazole for prevention of infection in neutropenic patients following cytotoxic chemotherapy. *Antimicrob Agents Chemother* 1990, **34**, 215–218.
23. Dekker AW, Rozenberg Arska M, Verhoef J. Infection prophylaxis in acute leukemia: a comparison of ciprofloxacin with trimethoprim-sulfamethoxazole and colistin. *Ann Intern Med* 1987, **106**, 7–12.
24. Maschmeyer G, Haralambie E, Gaus W, *et al.* Ciprofloxacin and Norfloxacin for selective decontamination in patients with severe granulocytopenia. *Infection* 1988, **16**, 98–104.
25. GIMEMA Infection Program. Prevention of bacterial infection in neutropenic patients with hematologic malignancies: a randomized, multicenter trial comparing norfloxacin with ciprofloxacin. *Ann Intern Med* 1991, **115**, 7–12.
26. Rozenberg-Arska M, Dekker AW, Verhoef J. Roxithromycin prevents bacteremias caused by *S. viridans* in granulocytopenic patients receiving ciprofloxacin prophylactically. *16th International Congress of Chemotherapy*, Jerusalem, 11–16 June 1989. Abstracts p. 61.
27. Maugein J, Pellegrin JL, Brossard G, Fourche J, Leng B, Reiffers J. *In vitro* activities of vancomycin and teicoplanin against coagulase-negative staphylococci isolated from neutropenic patients. *Antimicrob Agents Chemother* 1990, **34**, 901–903.
28. Courvalin P. Plasmid-mediated 4-quinolone resistance: a real or apparent absence? *Antimicrob Agents Chemother* 1990, **34**, 681–684.
29. Trucksis M, Hooper DC, Wolfson JS. Emerging resistance to fluoroquinolones in staphylococci: an alert. *Ann Intern Med* 1991, **114**, 424–425.
30. Rozenberg-Arska M, Dekker AW, Verhoef J. Ciprofloxacin for selective decontamination of the alimentary tract in patients with acute leukemia during remission induction treatment: the effect on fecal flora. *J Infect Dis* 1985, **152**, 104–107.
31. Kotilainen P, Nikoskelainen J, Huovinen P. Emergence of ciprofloxacin-resistant coagulase-negative staphylococcal skin flora in immunocompromised patients receiving ciprofloxacin. *J Infect Dis* 1990, **161**, 41–44.
32. Oppenheim BA, Hartley JW, Lee W, Burnie JP. Outbreak of coagulase negative staphylococcus highly resistant to ciprofloxacin in a leukemia unit. *Br Med J* 1989, **299**, 294–297.

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Empirical Antibiotic Therapy in Neutropenic Cancer Patients

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EMPIRICAL THERAPY

In 1973, the European Organization for the Research and Treatment of Cancer (EORTC) International Antimicrobial Therapy Cooperative Group was founded with a protocol designed to investigate the optimal initial antimicrobial therapy for febrile neutropenic patients with malignant diseases. Before this time, the outcome of sepsis in granulocytopenic cancer patients (GCP) had been dismal. In a classic study of Gram-negative bacillary bacteraemia (GNBB), McCabe and Jackson [1] reported a 90% mortality rate in patients with rapidly fatal underlying illnesses, most of whom had neutropenia and cancer. Today, the mortality rate of Gram-negative sepsis in these patients is approximately 20% and even lower in some series. One possible explanation for the recent improvement in therapeutic outcome involves a greater awareness of the clinical importance of sepsis in these patients and improved methods for treating infectious complications. Of equal importance is reduction of the average period of time for remission induction, with a quicker return of bone marrow function.

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It was recognised early that granulocytopenia was the major factor predisposing cancer patients to frequent episodes of severe sepsis. Adequate antimicrobial coverage, in terms of susceptibility of the offending pathogen, is a major factor influencing the outcome of bacterial sepsis. This was established in several older as well as in more recent studies, especially for Gram-negative rod sepsis, which remains the major cause of morbidity and mortality in GCP. Obviously, adequate antimicrobial coverage depends on an appreciation of the changing susceptibilities of microbial pathogens over time. This factor underscores the need to develop still newer antimicrobial agents active against strains that have become resistant to older drugs.

Because the mortality for GCP patients with untreated sepsis as well as for those who received inadequate antimicrobial therapy was very high, Schimpff and colleagues [2] proposed the empiric treatment with broad-spectrum antibiotics as soon as infection was suspected or fever was noted. This approach was opposed to the basic principle of antimicrobial therapy, which required demonstration of both the infected site and the pathogen before initiating antibiotic therapy; in addition, its results have not been confirmed in controlled clinical trials. However, the observed benefits of this methodology led to its general acceptance.

Febrile episodes in GCP are caused by bacterial sepsis or bacteraemia in about 20% of patients. 10 years ago, GNBB accounted for two-thirds of these episodes; the remainder