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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

were Gram-positive infections. These observations explain the special concern of many clinicians to direct empirical therapy primarily against GNBB. *Candida fungaemia* is relatively rare as an initial cause of fever in GCP; it is reported in approximately 5% of patients. However, it is possible that undocumented fungal infections cause fever in some patients in whom no bacterial infection can be clinically documented. Over time there has been a decrease in the incidence of GNBB in GCP and a corresponding increase of bacteraemic infections caused by Gram-positive bacteria (Table 1).

The EORTC trials [3–6] resulted in some important general clinical information. When empirical antimicrobial therapy is undertaken, a microbiological cause for the febrile episode can be demonstrated in about 40% of patients, half of whom will have bacteraemia. 20% of patients will have a clinically documented infection without the identification of a specific pathogen, another 40% will have a febrile episode that can be classified as either a possible or doubtful infection.

Clinical trials in small groups of febrile GCP are often ambiguous because the number of confirmed infections is usually very low and thus cannot always statistically validate claims of efficacy of any given regimen. Moreover, the response to empirical antimicrobial therapy is usually favourable in all GCP except those with documented bacteraemia. Because these patients represent only 20% of GCP, the overall results will be biased by the more efficacious results obtained in non-bacteraemic infections that respond favourably to many antimicrobial regimens. It is still unclear, however, why non-bacteraemic GCP respond well to empirical therapy. In some patients a febrile episode may be related to non-infectious causes; in others, empirical antimicrobial therapy may effectively treat early infections associated with minimal numbers of bacteria at the infected site.

Another general observation is the effect of spontaneous changes in the neutrophil count on the response to antimicrobial therapy. Both the initial granulocyte count and the subsequent change in the level of granulocytopenia during administration of antimicrobial agents are prognostically related to the clinical response to therapy. A low and/or decreasing granulocyte count is a major determinant for the poor prognosis of a treated infection. In addition, it has been shown that a higher antibacterial activity of the serum is necessary in severely neutropenic patients compared to those with less severe granulocytopenia [7].

Finally, the EORTC trials indicated that the risk of further infection, such as superinfection, is increased with the prolonged duration of granulocytopenia. In addition, the duration of antimicrobial therapy was found to influence the frequency of further infection in patients whose granulocyte count increased; however, it was unclear as to what extent the duration of severe granulocytopenia influenced the length of antimicrobial therapy.

Table 1. Bacteraemic isolates in four consecutive trials conducted by the EORTC Antimicrobial Therapy Project Group

Microorganisms	Trial 1 (%)	Trial 2 (%)	Trial 3 (%)	Trial 4 (%)
Escherichia coli	46	33	30	63
Pseudomonas aeruginosa	18	18	15	34
Klebsiella sp.	26	14	6	9
Other Gram-negative sp.	13	9	6	23
Total	68%	64%	57%	57%
Staphylococcus aureus	28	10	10	25
Staphylococcus epidermidis	5	9	15	18
Streptococcus pneumoniae	5	6	5	6
Other Gram-positive sp.	4	12	7	41
Total	28%	32%	37%	40%
Candida sp.	7	4	5	6
Total	5%	4%	5%	3%
TOTAL	152	115	99	225

REVIEW OF THE FOUR EORTC TRIALS

The first EORTC trial [3] was a relatively simple comparison among three antimicrobial regimens: carbenicillin plus cephalothin, cephalothin plus gentamicin, and carbenicillin plus gentamicin which is the prototypic empiric antimicrobial therapy in GCP designed by Schimpff and coworkers [2]. In this study it was clearly shown that carbenicillin plus gentamicin had the best therapeutic toxic ratio and was superior to carbenicillin plus cephalothin mainly because bacterial strains doubly resistant to both of these drugs were relatively common.

The observations raised a series of basic questions, among which was the role of aminoglycosides in the treatment of sepsis in GCP. It was known that aminoglycosides alone were disappointing in the treatment of GNBB in GCP, despite their *in vitro* activity and the minimal emergence of resistance strains. There was evidence, however, that aminoglycosides were helpful as salvage therapy in patients who did not respond to double beta-lactam antibiotic combinations [8]. They also might reduce emergence of resistance to the beta-lactam when used in combination antibiotic therapy [9], and increase the bactericidal activity of the beta-lactam if synergy is present, which frequently occurs [10]. In light of these issues, including aminoglycosides in empirical antimicrobial therapy makes sense; the use of these agents may buy time, thus allowing for changes in antimicrobial therapy once the susceptibility of the bacteria is know, which may possibly prevent high mortality.

The second trial [4] was an attempt to improve clinical response by combining the types of antibiotics used in the preceding trial. The study was designed to determine whether the addition of a cephalosporin such as cefazolin would improve the response rate in GCP with a combination of an anti-pseudomonas beta-lactam such as carbenicillin plus an aminoglycoside such as amikacin. The clinical results were good with carbenicillin plus amikacin whether or not cefazolin was added: 64% of patients responded in both groups. This study suggests, then, that a triple drug combination was not more effective than a double antibiotic combination of an anti-pseudomonal broad-spectrum beta-lactam with aminoglycoside. In addition, this trial established that the early empirical use of granulocyte transfusions in combination with broad-spectrum antibiotics was not useful in the management of GCP [11].

The second trial also provided an opportunity to test the hypothesis that orally administered non-absorbable antibiotics might help to prevent infection in GCP. Although these observations were retrospective, it was suggested that patients who had received any oral chemoprophylaxis developed significantly fewer microbiologically documented infections than patients who had not been treated with oral antibiotics. The

value of oral chemoprophylaxis with cotrimoxazole as monotherapy or in combination with non-absorbable antibiotics was later evaluated in a prospective study[12].

The third trial [5] compared three different antibiotic regimens: ticarcillin plus amikacin, azlocillin plus amikacin and cefotaxime plus amikacin. In addition, the optimal duration of empirical therapy in responding patients and the possible usefulness of empirical amphotericin B in non-responding patients were also studied. The evaluation of antimicrobial therapy in the third trial compared a standard therapy, ticarcillin plus amikacin, with two newer beta-lactams in combination with amikacin: azlocillin, an anti-pseudomonal ureidopenicillin, and cefotaxime, a broad-spectrum, third-generation cephalosporin. Azlocillin plus amikacin was the most effective therapy in bacteraemic patients with 66% response rate compared with cefotaxime plus amikacin at 37% and ticarcillin plus amikacin at 47%. Azlocillin plus amikacin and ticarcillin plus amikacin were equally effective in the treatment of GNBB caused by organisms susceptible *in vitro* to azlocillin or ticarcillin; the response rate was 70 and 74%, respectively. However, in 10 episodes of GNBB caused by ticarcillin-resistant strains in the group of patients receiving ticarcillin plus amikacin, only 1 patient responded. Among the patients who received azlocillin plus amikacin, 6 cases of GNBB were caused by azlocillin-resistant strains, but 3 of these patients responded. Thus, the overall response rate was 20 out of 30, or 66%, for GNBB treated with azlocillin plus amikacin, and 15 out of 29, or 50% for those receiving ticarcillin plus amikacin, which is a statistically significant difference. These observations underscore susceptibility to the beta-lactam antibiotic of GNBB in GCP as indicated by logistic regression analysis of the data. It is clear that the efficacy of any given empirical regimen changes with time as well as the emergence of resistance.

The fourth EORTC trial [6] was designed to determine whether a cephalosporin such as ceftazidime might be as effective for empirical therapy in GCP as a combination of ceftazidime plus amikacin. It was thought that the role of synergism was important in the initial management of these patients, especially those with GNBB; ceftazidime plus a short course of amikacin (3 days) was therefore compared to ceftazidime plus a full course of amikacin (at least 9 days). In patients with GNBB, a full course of amikacin combined with cefazidime was associated with a higher response rate than a 3-day course of amikacin with ceftazidime. These results suggest that the combination of ceftazidime plus amikacin, with the aminoglycoside given as a full course, might be more therapeutically advantageous. The full course of amikacin in combination with ceftazidime was not associated with an excess of nephrotoxicity compared with the regimen that included only a short course of amikacin.

Other investigators have reported different results. Pizzo and coworkers [13] reported favourable results in GCP with ceftazidime alone; however, their study was performed with less severely neutropenic patients, predominantly young people with lymphomas and solid tumours rather than acute leukaemia. In addition, this protocol allowed for the very early addition of other antibiotics, and these patients were not classified as failures. They concluded that ceftazidime alone was as effective as a triple-drug regimen of carbenicillin plus cephalothin plus gentamicin in the total population of febrile GCP studied. However, they indicated that in GNBB these conclusions should be applied cautiously and that emergence of resistance to the beta-lactam antibiotic should be carefully monitored.

The third and fourth trials evaluated the role of empirically administered amphotericin B in patients with no proven bacterial infection who remained febrile after a course of empirical antimicrobial therapy [5, 6]. Previous studies by Pizzo and colleagues had suggested that the empirical use of amphotericin B was useful in these patients, many of whom presumably had fungal infections [14]: a group of patients who received empirical amphotericin B responded more frequently and demonstrated less frequent microbiologically demonstrated fungal infections or mortality caused by fungal infection. The EORTC trial, unlike Pizzo's study, delineates specific subgroups that might benefit from empiric amphotericin B therapy. Any patient who has not received antifungal prophylaxis with persistent, profound granulocytopenia and some evidence of a clinically documented infection may probably benefit from this approach [15]. This is distinctly different from Pizzo's conclusion, which suggests that all patients rather than just this specific subgroup be treated with amphotericin B.

Over the years, Gram-positive coccal bacteraemias have become more prevalent and the response rate of these infections to empirical antibiotic regimens aimed primarily at controlling GNBB has progressively decreased. The response to Gram-positive bacteraemia in the first trial was 80% but declined to 42% in trial 4. This is probably related both to the increasing numbers of pathogens intrinsically resistant to the drugs used in empirical regimens as well as to the increase of local infections related to intravenous catheters and gastrointestinal mucositis. The mortality rate of these infections was found to be surprisingly low (4% in trial 4). These observations suggest that the control of Gram-positive infections in GCP might be achieved through greater attention to responsible local factors rather than through extending the antimicrobial spectrum.

The fifth EORTC trial investigated whether the addition of vancomycin to ceftazidime plus amikacin would improve the response rate and reduce mortality associated with Gram-positive coccal bacteraemias [16]. Because the mortality associated with these infections is already quite low, it is possible that the use of an expensive and potentially toxic drug such as vancomycin might not be beneficial. However, recent published studies indicate that the therapeutic benefits might outweigh the risks [17].

CONCLUSIONS

The five EORTC trials conducted over the past 15 years have yielded several new concepts in treating GCP with GNBB. Early empirical therapy with broad-spectrum antibiotics directed against GNBB is necessary in febrile GCP. The level and dynamics of the granulocyte count are also extremely important in determining the clinical outcome of bacteraemia.

In addition, most empirical antimicrobial regimens may buy time to allow clinically relevant therapeutic alterations. However, only microbiologically documented infections, particularly bacteraemias, are useful in the comparison of responses to antimicrobial regimens.

The response rate of GNBB is clearly influenced by the susceptibility of the causative pathogen to the beta-lactam component of the empirical regimen, although emergence of resistance to some antibiotics has rendered these drugs less effective over time.

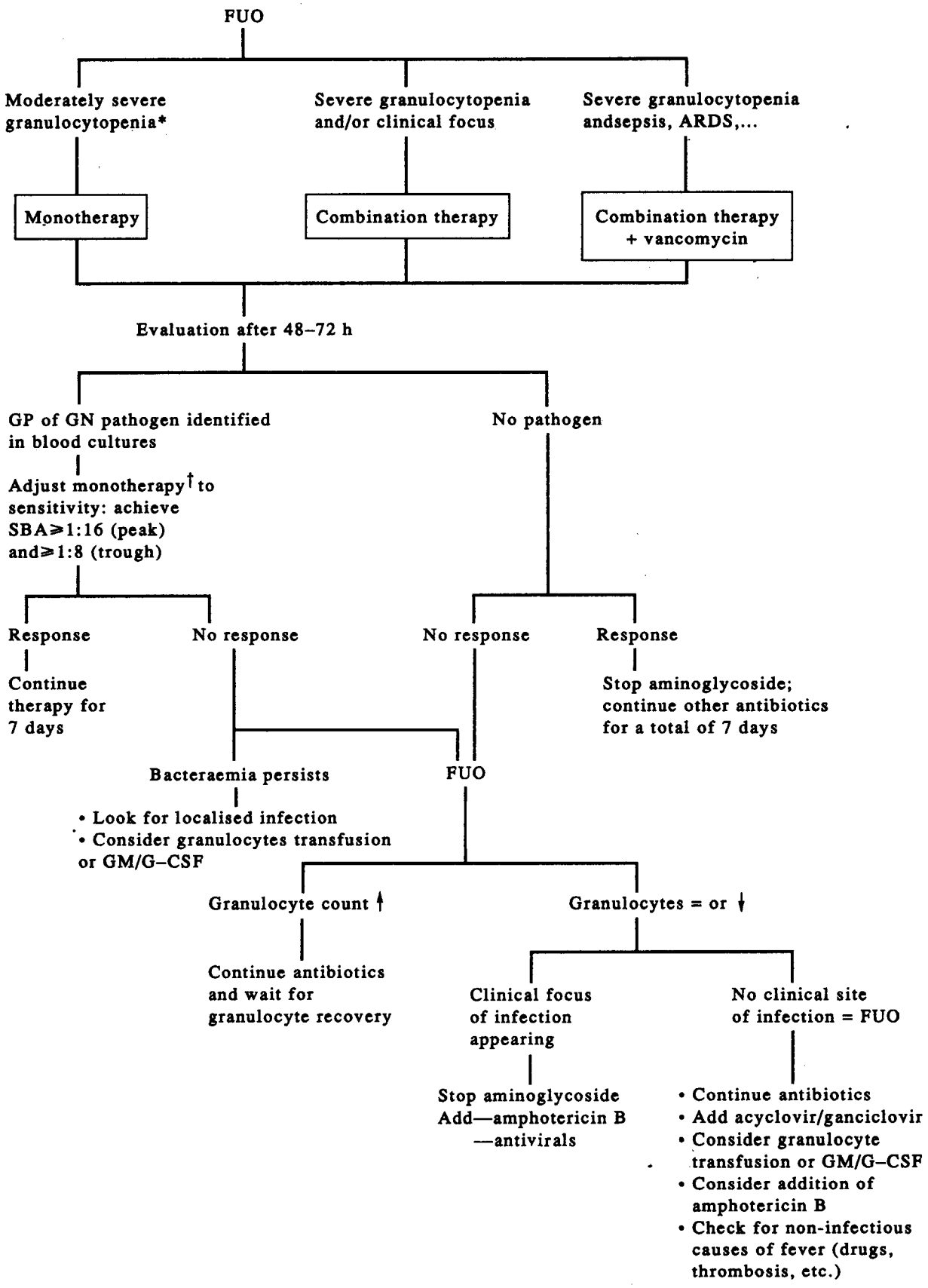

Fig. 1. Guidelines for the diagnostic and therapeutic approach of febrile episodes in granulocytopenic patients. *Granulocyte count $< 1000 \times mm^3$ but $> 100 \times mm^3$. Use combination therapy for *P. aeruginosa* infection and possibly other Gram-negative bacteraemias until SBA is known.

The combination of an anti-pseudomonal beta-lactam with an aminoglycoside is recommended as the standard for empirical therapy in febrile GCP, especially in patients with severe and persistent granulocytopenia who have suspected or demonstrated GNBB. However, patients who are less neutropenic and/or symptomatic may benefit from a monotherapy. In conclusion, Gram-positive pathogens have become a common cause of bacteraemia in GCP, and, although the response rate to empirical regimens may be marginal, the associated mortality rate is low (Fig.1).

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