

Empirical treatment of sepsis in neutropenic patients

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Mortality associated with febrile neutropenia has dramatically decreased over the last three decades; a pivotal role has been played by the concept of hospital-based empirical therapy with broad-spectrum combinations of antibiotics. Nevertheless, there is evidence that a subgroup of patients with febrile neutropenia might benefit from less aggressive treatments.

Empirical treatment, i.e. broad-spectrum antimicrobial therapy, without waiting for microbiological and/or clinical documentation of an infection, is justified in patients with febrile neutropenia (FN) by the high frequency of severe infections associated with a low granulocyte count. Moreover, signs and symptoms of infections are often inconspicuous in patients with FN, and sepsis may have a fulminant course in this setting, killing the patient before significant microbiological information is available.

The choice of empirical therapy of FN should be adapted according to the risk of developing complications during an episode of FN, as the population of patients with FN has become more heterogeneous, because chemotherapy is no longer a treatment limited to haematological neoplasia.

The criteria proposed by Talcott et al (1992) identify, within the FN population, 25% of patients with a low risk of developing serious complications. The Multinational Association for Supportive Care in Cancer (MASCC) score identifies 60% of those patients (Klastersky et al, 2000). Oral therapy — if tolerated — is probably adequate for empirical treatment of FN in those patients. It is possible that these patients might be treated as ambulatory or at home, as indicated by preliminary studies (Rubenstein et al, 1993).

Among various antimicrobial regimens tested for oral therapy of FN, amoxicillin/clavulanate plus ciprofloxacin has been tested in a large clinical trial and has been found to be highly effective (Kern et al, 1999). Other regimens likely to be effective should be further evaluated in prospective studies.

All other patients with FN should be hospitalized for empirical therapy. In patients whose

neutropenia is moderate, and especially if it is expected to be short-lived, single-agent intravenous (IV) therapy covering the most likely Gram-positive and Gram-negative pathogens, such as cefepime, ceftazidime, imipenem, meropenem or piperacillin/tazobactam, is probably adequate (*Figure 1*).

It should be stressed that none of these antibiotics covers for methicillin-resistant coagulase-negative staphylococci; these are very common in FN but have low pathogenicity, allowing specific therapy with glycopeptides to be delayed until the microbiological diagnosis is made. Monotherapy for empirical treatment of FN has thus become widely accepted. However, in patients presenting with clinical signs predictive of Gram-negative sepsis, namely high fever and hypotension, combination therapy with an aminoglycoside should remain the rule. When serious Gram-positive infection is strongly suspected, as in unstable patients with an infected IV line or extensive oral mucositis, early addition of a glycopeptide is probably warranted.

The discontinuation of aminoglycosides or glycopeptides can be decided, after 2–3 days, on the basis of microbiological findings; in this way toxicity and cost can be limited. The use of the granulopoiesis stimulating factors as a companion for empirical antibiotic therapy for the treatment of FN is still unclear; so far, it does not seem necessary if the duration of neutropenia is not expected to be prolonged.

Most patients with FN will respond favourably to the empirical strategies described here. The overall response rate has been 65% in recent International Antimicrobial Therapy Cooperative Group of the European Organisation for Research and Treatment of Cancer (IATCG-EORTC) trials. The remaining patients almost

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always respond to early empirical or microbiologically inspired modifications of initial therapy; the mortality resulting directly from infection during an episode of FN is only 3%. In responding patients, antibiotics should be discontinued after 5–6 afebrile days in order to avoid superinfection by resistant pathogens, namely fungi.

In patients who do not respond to initial treatment (or to early empirical modifications of it) and remain neutropenic with negative cultures, empirical antifungal therapy is probably indicated. This is particularly true if neutropenia is

very severe and/or if there is any evidence of an infectious focus, either radiologically or clinically; in that respect, an early computed tomography chest scan and bronchoalveolar lavage may be very helpful.

In non-responding patients with positive cultures, adjustment of antimicrobial therapy to the susceptibility of the pathogen is mandatory. If the patient fails to respond to the adapted treatment, the search for a localized infection should be undertaken and the use of granulopoiesis stimulating factors (or granulocyte transfusion) considered.

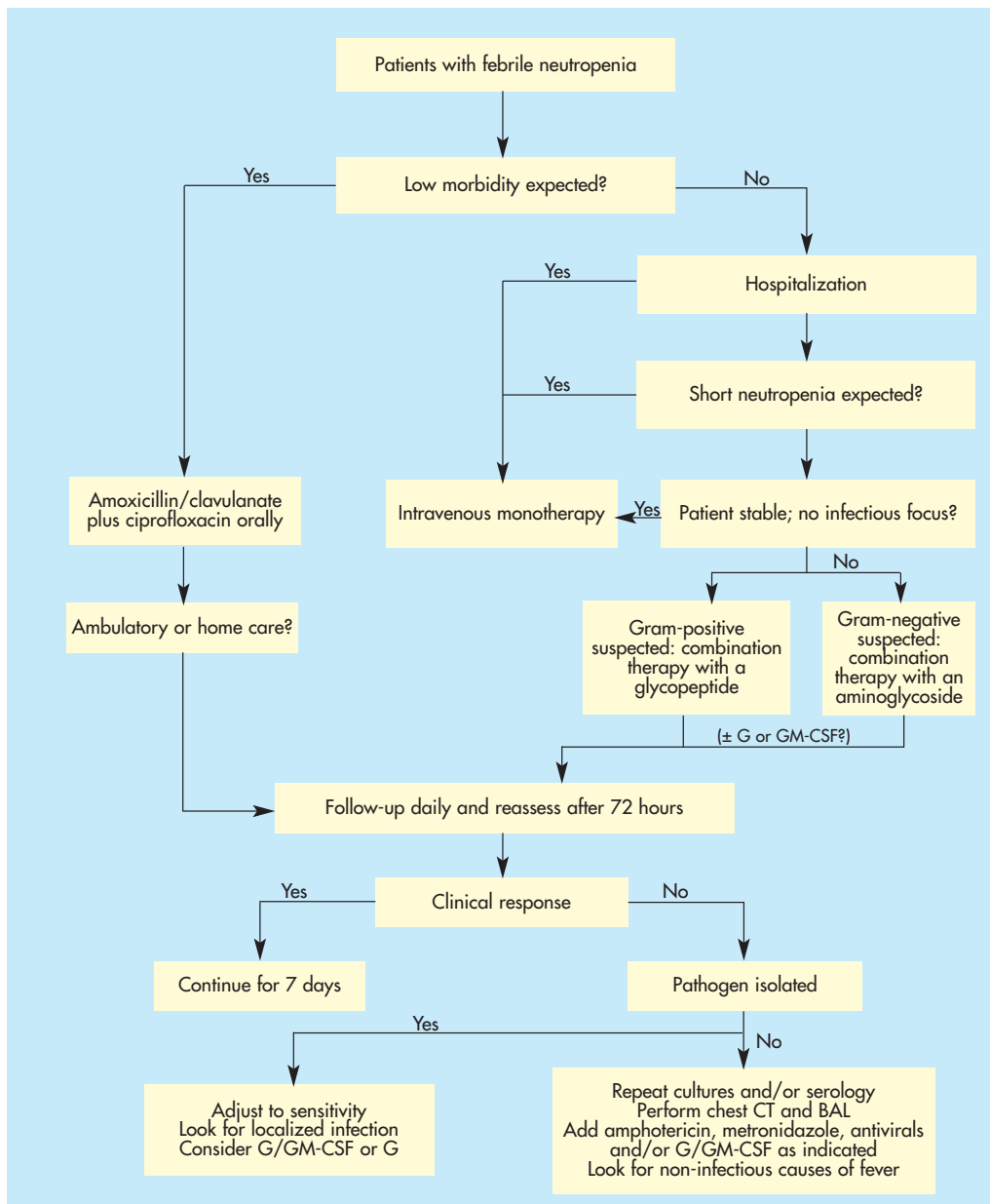


Figure 1. An algorithm for the treatment of febrile neutropenia. BAL= bronchoalveolar lavage; CT = computed tomography; G = granulocyte; GM-CSF = granulocyte-macrophage colony stimulating factor.

CONCLUSIONS

An important recent development in the management of patients with FN has been the identification of a low-risk group suitable for outpatient therapy. In addition, combination therapy with an aminoglycoside is no longer the standard in most patients. The addition of aminoglycosides and/or glycopeptides to broad-spectrum single-agent empirical therapy should be directed by specific clinical signs suggesting Gram-negative or Gram-positive sepsis. Finally, as the granulopoiesis stimulating factors are able to hasten recovery from chemotherapy-induced neutropenia, studies defining their role as an adjunct to empirical antibiotics in the treatment of FN are needed. **HM**

Conflict of interest: none.

- Kern WV, Cometta A, de Bock R et al (1999) Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. *N Engl J Med* **341**: 312–8
- Klastersky J, Paesmans M, Rubenstein EB et al (2000) For the Study Section on Infections, Multinational Association for Supportive Care in Cancer. The Multinational Association for Supportive Care in Cancer Risk Index: a Multinational Scoring System for Identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* **18**(16): 3038–51
- Rubenstein EB, Rolston K, Benjamin RS et al (1993) Outpatient treatment of febrile episodes in low-risk neutropenic patients with cancer. *Cancer* **71**: 3640–6
- Talcott JA, Siegel RD, Finberg R, Goldman L (1992) Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. *J Clin Oncol* **10**: 316–22

KEY POINTS

- The choice of empirical therapy of febrile neutropenia should be adapted according to the risk of developing complications during an episode of febrile neutropenia.
- In patients at low risk of complications, oral therapy with amoxicillin/clavulanate plus ciprofloxacin has been found highly effective — these patients might be treated as ambulatory.
- Intravenous monotherapy for empirical treatment of febrile neutropenia in high-risk patients has become widely accepted; however, in septic patients, namely those with high fever and/or hypotension, combination therapy should remain the rule.