Where do we go from here?

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The initiation of monotherapy with a third- or fourth-generation cephalosporin, or with a carbapenem antibiotic, is now established medical practice for the neutropenic patient who becomes febrile. However, when the duration of neutropenia is prolonged (generally more than a week), additions to, or modifications of, the initial antibiotic regimen are necessary based on the evolving clinical and microbiological course of the patient. The rationale for these modifications of the initial therapy in high-risk neutropenic patients is reviewed along with the prospects for reducing the risk status of the neutropenic patient by bolstering or improving the host’s immunological system and/or the time to haematological recovery.

Keywords: fever, neutropenia, monotherapy, empirical therapy

The broad-spectrum and high bactericidal activity of the third- and fourth-generation cephalosporins and the carbapenems offered the real prospect that a single antibiotic might provide safe, effective and less toxic empirical therapy for febrile neutropenic patients. This promise was forecast with the initial studies by De Pauw et al. in 1983 and has been substantiated since by over 100 randomized clinical trials and several meta-analyses. These clinical trials have demonstrated that monotherapy is as effective as a double or triple combination regimen for the initial management of the neutropenic patient who becomes febrile and thus monotherapy can be viewed as a standard of care. However, for patients with profound and prolonged neutropenia, additions or modifications to the initial monotherapy are necessary to ensure a successful patient outcome. These modifications are best viewed as adjuncts to the overall management, complementing the initial coverage provided by the monotherapy and accommodating the ever-evolving risk status of the patient and the endogenous and exogenous microbial changes that occur with prolonged neutropenia.

The question of what comes after initial monotherapy can be viewed from the perspective of the individual patient as well as that of management principles that will evolve over time. The management of an individual patient is guided by whether a patient is categorized as low or high risk. In general, the factors that determine ‘low-risk’ neutropenia include remission of the underlying cancer, an expected duration of neutropenia of <7 days, the absence of mucositis or other co-morbidities (e.g. hypotension, organ failure) or prophylactic antibiotics. Low-risk patients, who comprise the majority of those who become febrile and neutropenic, can often be treated by monotherapy alone—without additional modifications or changes in therapy. For these patients, even oral therapy with a fluoroquinolone plus ampicillin/clavulanate, or clindamycin, is a viable alternative to parenteral monotherapy.

For the high-risk patient (characterized by neutropenia lasting more than 7 days), a need for additional therapy or modifications of the initial monotherapy are more likely. Patients who present with haemodynamic instability or who have evidence of multiresistant infection require that the initial monotherapy be complemented by the addition of an aminoglycoside and vancomycin. However, in the absence of haemodynamic instability or a defined site of infection, empirical vancomycin is not indicated or recommended. An exception is patients with α-haemolytic or Group A streptococcal infections, especially when associated with myeloablative chemotherapy and the presence of mucositis. In contrast, the need for the addition of an aminoglycoside is more limited unless an organism resistant to the third-generation cephalosporin or carbapenem has been isolated or a life-threatening condition exists.

For patients who remain febrile and neutropenic beyond 7 days, the addition of an antifungal agent (amphotericin B, voriconazole, caspofungin) has proved important in reducing the risks for invasive mycoses and has also become a standard of care and a component of ‘what comes next’ in the management of high-risk febrile neutropenic patients.

Overall, empirical antimicrobial therapy, initiated with monotherapy and then modified based on the patient’s risk status, has become the standard of care and is associated with a survival rate of >95%. To date, these outcomes have been modestly impacted by the adjunctive use of haematopoietic cytokines or...
other immunomodulating agents. While these measures have been effective in optimizing patient management and permitting more dose-intensive regimens to be administered to cancer patients, they are also subject to changes as a consequence of alterations in the host, their microbial flora and developments in cancer treatment. For example, the current success of monotherapy is related, in part, to the breadth and efficacy of the third-generation cephalosporins and carbapenems balanced against the microorganisms responsible for the preponderance of infections in this patient population. Clearly, this can be negatively impacted if the current spectrum of microorganisms now associated with immunocompromised neutropenic patients changes significantly. Most notably, if *Pseudomonas aeruginosa* re-emerged as a dominant pathogen or if the incidence of *Enterobacter* spp., methicillin-resistant *Staphylococcus aureus* or enterococci increased significantly, current monotherapy regimens would almost certainly prove insufficient for the initial management of the febrile neutropenic patient. This balance between the host, the cancer therapy regimen and the endogenous and exogenous microflora could also be altered if the current microorganisms became more resistant to current cephalosporins or carbapenems. In contrast, these negative effects could be countered by the development of broader and more potent antimicrobials—although nothing in the known pipeline suggests that this will occur in the next few years.

Altering the host defence matrix can also impact the efficacy of monotherapy both positively and negatively. Should antineoplastic agents become more selective and less associated with immunosuppression as a side effect, the risk of neutropenia could be reduced, thus reducing the need for empirical antibiotic therapy. Conversely, if regimens became more dose-intensive and patients had greater immunosuppression and a shift towards high-risk status, the success of monotherapy (without additions or modifications) would also be reduced.

Empirical therapy is also a response to the limited ability to diagnose the microbial causes of fever in neutropenic patients. Should more effective and timely diagnostic tools become available—for bacteria, viruses, fungi and protozoa—it would be more possible to utilize antimicrobial therapy more selectively and presumably effectively.

Thus, while empirical antibiotic therapy has been the mainstay of the management of the febrile neutropenic patient for nearly 50 years and initial monotherapy for half of that time, the benefits and liabilities of these regimens may be significantly altered by future changes in the host defence matrix, the endogenous and exogenous microflora and the therapeutic regimens that are employed. Accordingly, risk stratification, coupled with an awareness of the changing landscape that defines modern medicine, will determine what comes next in the management of the febrile neutropenic patient. But for the moment, empirical monotherapy remains a standard of care for the cancer patient with fever and neutropenia.

**Transparency declarations**

None to declare.

**Suggested reading**