Febrile Neutropenia in 2007

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Several recent reports have indicated that not only a shift in the aetiology of infections and resistance patterns in patients with febrile neutropenia, but also important differences between regions and countries. Viridans streptococcal bacteraemias are common among cancer patients being second only to the coagulase-negative staphylococci. However, in certain centres in Europe Gram-negative bacilli have once again become the predominant infecting pathogens,. The problems associated with emerging resistance have been widely documented in the literature. In some institutions methicillin-resistance among coagulase-negative staphylococci has reached very high proportions, and in others the incidence of extended-spectrum beta-lactamase producing Gram-negative bacilli has risen markedly. These shifts in antimicrobial susceptibility are important in guiding the choice of agents for febrile neutropenia. Antibiotic use and prophylaxis have both been associated with changes in susceptibility, and prescribing habits may influence emerging resistance. In this context, the choice of empirical antibiotic therapy and the use of prophylaxis should be driven by a sound understanding of local circumstances.

Initiating empirical broad-spectrum antibacterial therapy has long been the standart practice for febrile neutropenic cancer patients. However, during the last decade it has become evident that patients with febrile neutropenia do not constitute a homogenous group. The risk factors for developing infection and other major complications vary widely in different subsets of patients with cancer. Therefore, a valuable risk assessment of every febrile neutropenic patient is essential in order to define a tailored therapeutic approach. Those patients with hematological malignancies and severe and prolonged neutropenia will fall into the cathegory of "high-risk", while others who were treated with less intensive chemotherapies and who were expected to have a short duration (e.g. less than 7-10 days) of neutropenia and fewer complications during the course of neutropenia will be categorized in the 'low-risk' group. Recently published "The Multinational Association for Supportive Care in Cancer (MASCC)" risk index has been shown to be a valuable tool for identifiying low-risk patients among adult febrile neutropenic cancer patient population. Patients with solid tumors who were treated with conventional chemotherapy and with minimal or no comorbidities (such as mucositis, cellulitis, anorectal infection, pneumonia) will usually be placed into the cathegory of "low-risk". On the other hand, more intensive chemotherapies have been increasingly used in solid tumor patients and some of them will also undergo an autologous hematopoietic stem cell transplantation (AHSCT). This approach will obviously increase the expected duration of neutropenia, the incidence of other comorbidities (e.g. mucositis), and may also affect the hemodynamic and clinical stability of the patient.

Once the patient is stratified in one of the risk groups, several options for empirical treatment exist. Nevertheless, several other factors need to be considered regarding to specific antimicrobial regimen. Among these are local epidemiological pattern of the infecting microorganisms and their

antimicrobial resistance pattern. Recent published data indicate that low-risk patients who are able to swallow can successfully be treated with oral antibiotics. The most frequent used regimen for this indication is a combination of a quinolone derivative (e.g. ciprofloxacin) and amoxicillin/clavulanate. Newer quinolones with enhanced activity against gram-positive pathogens (e.g. moxifloxacin, gatifloxacin) have been currently under evaluation for a monotherapy option. This type of therapy is applicable for both inpatient and outpatient settings. Stringent criteria need to be applied for selecting patients who will be treated in an outpatient program which also requires a strong committment from both patient and healthcare team's side. Another option is to admit the patient to the hospital and treat with parenteral antibiotics until defervescence, and then swich to oral therapy. This provides a viable alternative for patients receiving more intensive chemotherapies for treating cancer with or without AHSCT. Upon switch to an oral regimen the patient could be discharged if his/her clinical condition is permissive. Comparative solid data for such a practice are lacking yet in the literature, however several studies both in IATG/EORTC and in elsewhere are being undertaken on this issue. For the initial parenteral therapy, monotherapy with various beta-lactam antibiotics has been extensively studied comparing with different beta-lactam plus aminoglycoside combinations. The data indicate that monotherapy with a broad-spectrum cephalosporin (e .g. ceftazidime, cefepime) or beta-lactam/beta-lactamase inhibitor combination (e.g. piperacillin/tazobactam) or a carbapanem (i.e. imipenem or meropenem) is as effective as a beta-lactam plus aminoglycoside combination for initial empirical regimen. Specific concerns for ceftazidime use exist since this drug has been held responsible for increased incidence of extended-spectrum beta-lactamase producing klebsiella infections in some institutions. Recently published metaanalyses caused concern about cefepime which was found to cause increased mortality in patients due to unexplained reasons. Parenteral quinolones has been less studied for this indication and the data are inconclusive. Therefore quinolones can not be recommended as the initial parenteral agent.

Glycopeptides should not be incorporated into the initial empirical regimen, until a documented gram-positive bacterial infection is observed. Recent data indicate that empirical addition of these agents is also unnecessary in those patients without defervescence after 60-72 hours of empirical broad-spectrum antibacterial therapy. Actually, glycopeptide use should strongly be discouraged unless the patient has a documented gram-positive bacterial infection or has strong predisposing factors to acquire such infections (e.g. clinically documented vascular catheter infection, colonization with methicillin resistant staphylococci or penicillin resistant pneumococci).

In summary, a risk-based approach in patients with febrile neutropenia could be more cost-effective. Various regimens with different antibiotics are available, but spesific regimens also need to be tailored to local epidemiological factors.

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