Management of febrile neutropenia in the era of bacterial resistance

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Abstract: Managing cancer patients with fever and neutropenia must be considered as a medical emergency since any delay in initiating appropriate empirical antibacterial therapy may result in high rates of mortality and morbidity. Emerging antibacterial resistance in bacterial pathogens infecting febrile neutropenic patients complicates management, and choosing the type of empirical antimicrobial therapy has become a challenge. To further complicate the decision process, not all neutropenic patients are in same category of susceptibility to develop severe infection. While low-risk patients may be treated with oral antibiotics in the outpatient setting, high-risk patients usually need to be admitted to hospital and receive parenteral broad-spectrum antibiotics until the neutrophil levels recover. These strategies have recently been addressed in two international guidelines from the Infectious Diseases Society of America (IDSA) and the European Conference on Infections in Leukaemia (ECIL). This review gives a brief overview of current antimicrobial resistance problems and their effects in febrile neutropenic cancer patients by summarizing the suggestions from the IDSA and ECIL guidelines.

Keywords: bacterial resistance, empirical antibiotic therapy, febrile neutropenia

Introduction

Patients with malignancies receiving intensive chemotherapy have an increased risk of development of neutropenia and febrile episodes [Freifeld *et al.* 2011; Klastersky, 2004]. Although documented infectious etiology is encountered in 20–30% of these febrile neutropenic patients, defervescence is achieved in up to 60% of patients with the use of empirical broad-spectrum antibacterial therapy [Cometta *et al.* 1996; Freifeld *et al.* 2011; Klastersky 2004; Ramphal, 2004]. This observation may indicate that the infection is responsible for the development of fever in most neutropenic cancer patients. While the incidence of gram-negative infections was high in the 1960s and 1970s, increased use of indwelling catheters, early-generation quinolone prophylaxis, and broad-spectrum empirical antigram-negative antibacterial therapy led to an increase in the incidence of gram-positive pathogens in the 1980s and 1990s [Freifeld *et al.* 2011; Ramphal, 2004; Zinner, 1999]. Thereafter, the most common bacterial etiologic agent isolated from blood cultures in most centers was reported to be coagulase-negative staphylococci [Dettenkofer *et al.* 2003; Freifeld *et al.*

2011; Wisplinghoff *et al.* 2003]. On the other hand, recently in some institutions, drug-resistant gram-negative bacteria such as multidrug resistant (MDR) *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, extended-spectrum beta-lactamase (ESBL)-producing gram-negative bacteria, and carbapenemase-producing gram-negative bacteria have become the causative agents of an increasing number of infections. ESBL-producing gram-negative bacteria are often considered to be susceptible only to carbapenems. Furthermore, carbapenemase-producing pathogens are reported to be etiologic agents of infections unresponsive to carbapenems [Aubron *et al.* 2005; Cattaneo *et al.* 2008; Chen *et al.* 2004; Freifeld *et al.* 2011; Gaynes and Edwards, 2005; Gudiol *et al.* 2011, 2012; Hakki *et al.* 2007; Kontoyiannis *et al.* 2009; Oliveira *et al.* 2007].

A significant increase in the prevalence of resistant gram-positive cocci such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) have also been reported and have become the most isolated resistant pathogens in a number of centers [Morris *et al.* 2008; Weinstock *et al.* 2007].

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Although penicillin-resistant viridans streptococci and penicillin-resistant *Streptococcus pneumoniae* (PRSP) are less common, they may also be the causative agents of severe infections [Carratala *et al.* 1998; Freifeld *et al.* 2011; Dettenkofer *et al.* 2003]. While, vancomycin has long been used successfully for the treatment of MRSA infections, the emergence of *Staphylococcus* species with raised vancomycin minimum inhibitory concentrations (MICs) (≥ 2 mg/l) has coincided with reports of treatment failures [Tenover and Moellering, 2007]. Newer agents with activity against resistant gram-positive pathogens, such as daptomycin, linezolid, and tigecycline, are increasingly being used in various clinical settings. However, few data exist regarding their efficacy and safety in neutropenic patients [Averbuch *et al.* 2012; Kontoyiannis *et al.* 2009; Micek, 2007; Mikulska *et al.* 2012].

Owing to the concept of empirical antimicrobial therapy, mortality rates due to febrile neutropenia have decreased. Unfortunately, the use of broad-spectrum antibiotics for empirical therapy has been associated with the risk of selection of resistant pathogens [Harbarth *et al.* 2001; Kontoyiannis *et al.* 2009; Mebis *et al.* 2010]. The administration of broad-spectrum antibacterial agents, prolonged and/or repeated hospitalization, intensive care unit stay, severity of illness, healthcare-associated infection, the presence of a urinary catheter, and older age are considered to be major risk factors for resistant bacterial infections [Averbuch *et al.* 2012; Mikulska *et al.* 2012]. While recommendations for the evaluation and treatment of febrile neutropenic patients are well established, the ever-changing patterns of antibacterial resistance prevent the use of standard regimens in all febrile neutropenic patients. As immediate empirical antibiotic therapy at the onset of fever in neutropenic patients is crucial, current data on the local epidemiology of predominant pathogens and their resistance patterns in the institution should be taken into consideration for appropriate empirical treatment strategies [Freifeld *et al.* 2011; Kontoyiannis *et al.* 2009; Sipsas *et al.* 2005].

Management of febrile neutropenia

At the onset of fever, risk assessment for severe infection and complication should be carried out to determine the administration route of antibiotics, need for hospitalization, and duration of antimicrobial treatment. Low-risk patients can be

identified by using the Multinational Association for Supportive Care in Cancer scoring system. High-risk patients who are not already inpatients should be admitted to hospital to receive intravenous (IV) empirical antibiotic treatment. Patients at low risk can be treated with orally administered agents. The administration of initial doses of empirical antibiotics should be carried out in a clinic or hospital setting [Averbuch *et al.* 2012; Freifeld *et al.* 2011; Klastersky *et al.* 2000, 2006; Klastersky, 2004].

Initial evaluation of febrile neutropenic patients

In neutropenic patients, the inability to develop an adequate inflammatory response leads to the masking of classical signs and symptoms of infection, and also limits the reliability of some diagnostic tests. A detailed physical examination should be carried out and repeated as required to determine any infectious foci. Data on previous documented infections, colonizing microorganisms, and antimicrobial prophylaxis should be carefully noted. Complete blood count, hepatic transaminases, bilirubin levels, electrolytes, serum creatinine, and blood-urea-nitrogen levels must be included in the laboratory workup [Freifeld *et al.* 2011; Kontoyiannis *et al.* 2009].

For microbiological diagnosis, at least two sets of blood cultures must be obtained. In the absence of a central venous catheter (CVC), two blood culture sets must be obtained from separate venipunctures. If a CVC is present, one of these blood-culture sets must be taken from each lumen of the CVC, and the other one from a peripheral vein site, simultaneously [Adamkiewicz *et al.* 1999; DesJardin *et al.* 1999; Freifeld *et al.* 2011; Kontoyiannis *et al.* 2009; Weinstein, 1996]. A differential time to positivity of 120 min between cultures drawn simultaneously through a CVC and peripheral vein site is suggestive of central line-associated bloodstream infection (CLABSI) [Blot *et al.* 1999; Freifeld *et al.* 2011; Raad *et al.* 2004; Seifert *et al.* 2003]. In case of any other suspicious foci of infection, appropriate clinical specimens must be examined for microbiological diagnosis. In patients with respiratory signs or symptoms, the evaluation of chest radiography is recommended [Freifeld *et al.* 2011; Kontoyiannis *et al.* 2009].

In some studies for the prediction of infectious morbidity, serum levels of interleukin-6,

interleukin-8, procalcitonin, and mannose-binding lectin have been proposed as potentially useful biomarkers [Dommert *et al.* 2013; Eisen and Minchinton, 2003; Lehrnbecher *et al.* 2004; Neth *et al.* 2001; Peterslund *et al.* 2001; Phillips *et al.* 2012; Sakr *et al.* 2008; Santolaya *et al.* 1994; Stryjewski *et al.* 2005]. However, further investigations are needed to assess their value in clinical decision making.

Empirical antibiotic therapy in febrile neutropenia

A combination of ciprofloxacin plus amoxicillin-clavulanate is recommended for oral empirical treatment in low-risk patients [Freifeld *et al.* 2011]. Recently, it has been shown that moxifloxacin can also be used successfully for this purpose [Kern *et al.* 2012]. If the patient is already receiving fluoroquinolone prophylaxis, empirical oral therapy with a fluoroquinolone should not be administered. Initial doses of empirical antibiotics, whether given orally or IV, should be administered in a hospital setting. According to the clinical criteria, low-risk patients could receive subsequent doses as outpatients. Continued stay is required if fever persists, or signs and symptoms of worsening infection exist [Freifeld *et al.* 2011].

High-risk patients should be admitted to the hospital and IV treatment with an antipseudomonal beta-lactam agent must be started. Initial empirical therapy might be modified in patients at risk of infection with resistant bacteria such as MRSA, VRE, ESBL-producing gram-negatives, and carbapenemase-producing microorganisms, including *Klebsiella pneumoniae* carbapenemase (KPC). For MRSA, the addition of vancomycin, teicoplanin, linezolid, or daptomycin to the initial empirical therapy should be considered. For VRE, linezolid or daptomycin is recommended. In the case of infections due to ESBL-producing *Enterobacteriaceae*, carbapenems would be the drugs of choice. The use of colistin or tigecycline should be considered in documented infections caused by KPC-producing gram-negative bacteria [Freifeld *et al.* 2011].

For empirical antibacterial treatment in febrile neutropenia, an escalation or de-escalation approach can be used. In escalation strategy, initial therapy targets activity against *Enterobacteriaceae* and *P. aeruginosa*, but ESBL- and carbapenemase-producing gram-negative bacilli and drug-resistant nonfermentatives

remain out of empirical coverage. In the case of development of clinical deterioration or isolation of a resistant pathogen from clinical samples, the spectrum of antibacterial coverage must be broadened, that is, escalated. In de-escalation strategy, the initial regimen covers activity against drug-resistant pathogens from the beginning, and according to the reports of the microbiology laboratory, therapy is de-escalated to an appropriate narrower spectrum of antibiotic coverage. Escalation strategy may be considered for patients followed in a center where MDR pathogens are rarely seen at the onset of febrile neutropenia, and for those without any specific risk factors for resistant bacterial infections. De-escalation strategy may be used for febrile neutropenic patients who have risk factors for resistant bacterial infections, such as a previous infection or known colonization with ESBL-producing gram-negatives, residents of a center where MDR pathogens are common, and also for those presenting with septic shock and pneumonia. The initial regimen in de-escalation strategy may include monotherapy with a carbapenem, or combination therapy with an antipseudomonal beta-lactam agent and an aminoglycoside/quinolone, or combination therapy with colistin and a beta-lactam agent/rifampicin. If risk factors for resistant gram-positive infections are present, early coverage with a glycopeptide or newer agents (e.g. linezolid, daptomycin, tigecycline) with activity against glycopeptide nonsusceptible gram-positive pathogens should be considered. Patients with suspicion of a catheter-related infection, known colonization with MRSA, VRE, and PRSP, hemodynamic instability, severe sepsis, septic shock, the presence of skin and soft tissue infection, and pneumonia are accepted as candidates for additional antibiotics against resistant gram-positive bacteria [Averbuch *et al.* 2012; Mikulska *et al.* 2012].

According to the time-dependent bacterial killing action of beta-lactam antibiotics, prolonged or continuous infusion following a loading dose may be considered as a feasible strategy. In this way, 'time over MIC', defined as the duration of serum concentration of the drug exceeding the MIC of the microorganism, is extended [Abbott and Roberts, 2012; Crandon and Nicolau, 2011]. Even though, this pharmacodynamic approach seems beneficial, its exact role has not been studied in comparative clinical trials.

Modification of antibiotic therapy in febrile neutropenia

In clinically stable febrile neutropenic patients receiving empirical treatment, persistent fever without any suspected focus of infection seldom requires an empirical change in treatment [Freifeld *et al.* 2011]. According to the recent European Conference on Infections in Leukaemia 2012 recommendations, if there is no microbiologically documented infection at 24–72 h, and if the patient is afebrile and clinically stable, discontinuation of empirical antibacterial treatment after 72 h may be considered if the patient is afebrile for the last 48 h or more [Orasch *et al.* 2012]. This suggestion is somewhat different from that proposed in the updated Infectious Diseases Society of America guideline where continuation of the initial empirical treatment until recovery from neutropenia is recommended [Freifeld *et al.* 2011]. We recommend early discontinuation of empirical antibacterial therapy in stable, afebrile neutropenic patients while they are closely observed in hospital. Such practice will be useful in preventing collateral damage caused by broad-spectrum antibacterial therapy. In the presence of clinically or microbiologically documented infection, the duration of targeted treatment must be decided according to the specific infectious condition. In the case of CLABSI, if the etiological agents are *S. aureus*, *P. aeruginosa*, fungi, or mycobacteria, catheter removal is recommended together with systemically administered antibiotics for at least 14 days. In patients with port pocket site infection, endocarditis, septic thrombosis, sepsis, tunnel infection, or persistence of bloodstream infection even after 72 h of appropriate antibiotic treatment, catheter removal is also recommended [Dugdale and Ramsey, 1990; Fowler *et al.* 1998; Freifeld *et al.* 2011; Hanna *et al.* 2004; Nguyen *et al.* 1995; Raad *et al.* 2004]. The duration of treatment must be longer (4–6 weeks) for complicated CLABSI, which may be related to the presence of endocarditis, deep tissue infection, septic thrombosis, and persistent bacteremia or fungemia 72 h after catheter removal despite appropriate antimicrobials [Freifeld *et al.* 2011].

If the initial regimen includes an agent active against aerobic gram-positive cocci, this may be stopped after a 2-day period if no evidence of a gram-positive infection can be documented [Freifeld *et al.* 2011].

Low-risk patients receiving their orally or IV-administered empirical treatment in hospital may change to a simplified regimen if they are clinically stable. Switching their antibiotic regimen from IV to oral may be considered if there is not any doubt about gastrointestinal absorption. Patients transferred to the outpatient setting must be followed up daily. If fever persists or returns within 48 h of outpatient setting, they should be re-admitted to the hospital and enrolled as high-risk patients [Freifeld *et al.* 2011].

In hemodynamically unstable febrile neutropenic patients receiving standard regimens, the antimicrobial coverage should be broadened to be active against resistant gram-negative, gram-positive, and anaerobic bacteria and fungi. Empirical antifungal treatment is considered in high-risk patients receiving appropriate broad-spectrum antibacterial therapy for 4–7 days and who have persistent fever without any defined source of infection [Freifeld *et al.* 2011].

Administration of antibiotic prophylaxis

Antibacterial prophylaxis with a fluoroquinolone is recommended for high-risk patients with anticipated neutropenic periods lasting at least for 7 days. The prophylaxis should be discontinued with recovery from neutropenia. Before administering fluoroquinolone prophylaxis, local epidemiological data must be taken into consideration, and if given, close monitoring for the emergence of quinolone resistance in bacterial pathogens should be provided [Freifeld *et al.* 2011; Gyssens *et al.* 2012; Tomblyn *et al.* 2009]. The use of quinolones has been associated with an increase in infections due to quinolone-resistant and/or ESBL-producing *Escherichia coli*, MRSA, and *Clostridium difficile* [Freifeld *et al.* 2011; Kern *et al.* 2005; MacDougall *et al.* 2005; Muto *et al.* 2005; Park *et al.* 2012; Pépin *et al.* 2005].

Infection prevention and control measures in neutropenic patients

Appropriate hand-hygiene practices are considered the most effective way to prevent patients from exposure to pathogens in the healthcare setting [Boyce and Pittet, 2002; Freifeld *et al.* 2011; Tomblyn *et al.* 2009]. Isolation procedures according to the specific condition and standard precautions should be carried out. Fresh or dried flowers and plants should be prohibited in the rooms of neutropenic patients. All CVCs must

be inserted using maximal sterile barrier precautions [Freifeld *et al.* 2011; Raad *et al.* 1994; Tomblyn *et al.* 2009]. Preferably, the CLABSI prevention bundle, including hand hygiene, maximal barrier precautions, cutaneous antisepsis with chlorhexidine, avoiding femoral sites as insertion routes, and removing CVCs as soon as no need exists, should be considered [Freifeld *et al.* 2011; Pronovost *et al.* 2006; Tomblyn *et al.* 2009].

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Conflict of interest statement

None declared.

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