Editorials

Infectious Complications of Chemotherapy-Induced Neutropenia: Don't Throw the Baby Out with the Bathwater

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Most drugs used for anti-neoplastic chemotherapy have a marginal therapeutic index: their ability to kill tumor cells does not skip normal cell populations, in particular those of the mucosal surfaces and bone marrow. Myelosuppression is the most serious consequence of anti-neoplastic chemotherapy, because the resulting neutropenia is associated with a high rate of infectious complications that are often severe and life-threatening. Fever is the most consistent manifestation of systemic infection in neutropenic patients. The chemotherapeutic regimens commonly associated with the development of febrile neutropenia are those producing myelosuppression lasting more than one week, such as the induction protocols for acute leukemias and the conditioning regimens used in bone marrow transplantation. At least one-half of neutropenic patients who become febrile have an established or occult infection, and at least one-fifth of patients with neutrophil counts of < 100 cells/mm^3 have bacteremia [1]. However, it has been well documented that negative cultures do not exclude infection [2]. The mortality from infection in the neutropenic cancer patient remains substantial (between 5% and 10%) despite patient awareness and the empiric approach to antibiotic treatment [3]. Consequently, the appearance of fever in a neutropenic patient is considered a medical emergency and requires immediate attention.

The organisms responsible for infections associated with neutropenia are most often the patient's own bacteria. The primary source of pathogens is the alimentary tract, where cancer chemotherapy-induced mucosal damage allows invasion of opportunistic organisms. Similarly, skin damaged by invasive procedures, e.g., with vascular access devices, is another portal of entry for infectious organisms. As the duration of hospital stay extends, cross-infection with nosocomial pathogens becomes increasingly dominant. In the early years chemotherapy-induced febrile neutropenia was associated mostly with Gram-negative septicemia, which was often caused by *Escherichia coli*, *Klebsiella* spp, *Enterobacter* spp. and *Pseudomonas aeruginosa*. More recently, an increasing incidence of Gram-positive septicemia was noted in some centers due to widespread use of prophylactic antibiotics such as fluoroquinolones, the most common isolates being *Staphylococcus aureus*, coagulase-negative staphylococci, and streptococci.

Attempts to reduce the infectious complications of chemotherapy-induced neutropenia have included empiric antimicrobial therapy [4] and prophylactic antibiotics [5]. The concept of empiric therapy consists of prompt administration of broad-spectrum antibiotics as soon as fever develops in the neutropenic patient, before the results of cultures are available. The choice of the antibiotic regimen has to be guided therefore by indirect information on the prevailing bacterial pathogens associated with neutropenic fever. These, as we have seen, have changed with time but can also vary in place. Most importantly, the local antimicrobial resistance pattern must also be considered.

Until the 1980s, combination antibiotic therapy (consisting usually of a beta-lactam and an aminoglycoside) was the rule [6]. However, despite the proven efficacy of combination therapy, the potential of monotherapy for the empiric management of febrile neutropenic patients is attractive because of its lack of toxicity, ease of administration and lower cost. Several studies have documented the efficacy of ceftazidime, cefepime, carbapenem or piperacillin/tazobactam monotherapy [7]. Despite the increase in Gram-positive bacteremia, several clinical trials have demonstrated that including vancomycin in the initial management of febrile neutropenic patients did not provide a survival advantage [8]. Moreover, because of the emergence of vancomycin-resistant enterococci associated with an excessive use of vancomycin, this agent should be used very cautiously.

In this issue of *IMAJ*, Paul et al. [9] report their findings on bloodstream isolates from neutropenic patients in a single medical center over more than a decade. The most common organisms were E. *coli* (18.9% of isolates in adult patients), P*seudomonas aeruginosa* (16.7%), and *Klebsiella pneumoniae* (11%). Gram-negative bacteria predominated throughout the study period and the ratio of Gram-negative to Gram-positive bacteremia increased from 1.7 to 2.3. Among children, on the other hand, the ratio of Gram-negative to Gram-positive bacteremia reversed from 1.2 to 0.7, due to the increasing prevalence of coagulase-negative staphylococcal bacteremia. Another factor that had impact on

the prevalence of different pathogens was the length of hospital stay prior to bacteremia. The prevalence of E. *coli* decreased with time in hospital while the rates of P*seudomonas aeruginosa*, *Klebsiella pneumonia*e, E*nterobacter* spp., A*cinetobacter* spp., E*nterococcus* spp. and C*andida* spp. increased. Not surprisingly, the duration of hospitalization also had repercussions on the susceptibility of the isolates: resistance to the broad-spectrum antimicrobial agent used for empiric monotherapy in the authors' center was observed in > 40% of Gram-negative bacteria when bacteremia was acquired after more than 14 days in hospital. Are these findings center-specific or in other words, can they be generalized for use in other institutions?

Greenberg and colleagues [10] investigated the microbiological spectrum and susceptibility patterns of pathogens causing bacteremia in pediatric febrile neutropenic patients. Their retrospective study was conducted at the Soroka Medical Center in Beer Sheva and covered the period 1998 to 2002. The most common organisms were: *Klebsiella* spp. 15.2%, coagulase-negative staphylococci 11.4%, P*seudomonas* spp. 10.6%, S*treptococcus* spp. 9.8%, E*nterobacter* spp 9.1%, and E. *coli* 8.3%. A trend toward an increase over time in recovery rates of Gram-positive organisms was observed. In the study by Paul and team [9] the distribution of blood isolates in pediatric patients during the same period was different, with coagulase-negative staphylococci (26.6%) and viridans streptococci (12.9%) being the most prevalent, followed by E. *coli* and P. *aeruginosa* (9.7% each). More importantly, the resistance rates in the two centers differed noticeably. Whereas in Soroka the resistance to ceftazidime, pipracillin-tazobactam and ciprofloxacin was approximately 5–10%, in Schneider Children's Hospital it was approximately 15% to ciprofloxacin and 30% to the other two agents.

The geographic diversity in the prevalence of different pathogens and particularly in their susceptibility pattern is exemplified by the following reports. At a medical center in Taiwan [11] where routine antibacterial prophylaxis was not used, bacteremia in febrile neutropenic adult patients between 1999 and 2002 was caused mostly by Gram-negative rods, accounting for 78.2% of isolates. E. *coli* was responsible for 27.5% of Gram-negative isolates; other isolates included K. *pneumoniae* (19.3%), P. *aeruginosa* (11%), and E*nterobacter cloacae* (10.1%). Staphylococci, mostly methicillin-resistant S*taph. aureus*, were responsible for approximately 70% of Gram-positive isolates. Quite surprisingly, P. *aeruginosa* isolates were the most sensitive Gram-negative organisms while E. *cloacae* were the most resistant. In a prospective multicenter study conducted in Norway over 2 years, bacteremia was documented in 34% of neutropenic fever episodes [12]. Overall, 40% of the episodes were caused by Gram-positive organisms, 41% by Gram-negative organisms and 19% were polymicrobial. The most frequently isolated bacteria were E. *coli* (25.6%), streptococci (15.6%), coagulase-negative staphylococci (12.4%) and *Klebsiella* spp. (7.4%). None of the Gram-negative isolates was resistant to gentamicin, meropenem, ceftazidime or ciprofloxacin. Only five coagulase-negative staphylococci isolates were resistant to both penicillin G and aminoglycoside.

Hence, to achieve best results empiric antimicrobial therapy should be tailored individually for each neutropenic patient, taking into account not only the local distribution of bacterial pathogens and their susceptibility pattern, but also the duration of the patient's stay in hospital, the aggressiveness of the chemotherapeutic protocol used and the resultant depth and duration of neutropenia, the degree of skin damage, and whether antibiotic prophylaxis was used. Only a few surveys on the microbiology of neutropenic fever in Israel have been published. Yet, it is not known whether more information would have benefitted other facilities. Not only should each medical center treating febrile neutropenic patients gather and analyze its own data, but such surveys should be repeated periodically to detect any changes in the antimicrobial resistance.

Initial attempts of antibiotic prophylaxis in neutropenic patients used non-absorbable antimicrobials (such as vancomycin, polymyxin, aminoglycosides) or cotrimoxazole. Although results were encouraging, the tolerability of these agents was low. The use of cotrimoxazole was also associated with a high incidence of allergic skin reactions and a mild myelosuppressive effect. More recently, several studies have demonstrated the efficacy of fluoroquinolones in preventing fever in neutropenic patients. More specifically, fluoroquinolones have reduced morbidity from Gram-negative bacteria but not from Gram-positive bacteria. Moreover, there was no impact on infection-related mortality. When compared to earlier regimens, ciprofloxacin was better only in preventing Gram-negative infections. The addition to the fluoroquinolone regimen of a second antibiotic with anti-Gram-positive activity reduced the incidence of Gram-positive infections but likewise had no impact on the morbidity and mortality [3]. Prophylactic levofloxacin had no protective effect against the risk of severe infection or death. Although the use of levofloxacin prophylaxis led to a decrease in the overall rate of documented bacterial infection, there was also a substantial increase in the rate of documented infections with resistant organisms [13,14]. One can conclude that prophylactic antibiotics can reduce the occurrence of febrile episodes in neutropenic patients but they do not affect the disease outcome. Also, the emergence of resistance among Gram-negative organisms in association with the use of fluoroquinolones cannot be ignored. Because of the concern about the spread of resistance to antibiotics and the marginal clinical benefit, the routine use of antimicrobial prophylaxis is not recommended [1,15]. These experts advocate considering the administration of a quinolone plus penicillin or cotrimoxazole during critical periods only for patients with profound and prolonged neutropenia [1,15]. In their update published in this issue of IMAJ, Gafter-Gvili et al. [16] adopted a more liberal approach to antibiotic prophylaxis. They recommended prophylaxis with ciprofloxacin or levofloxacin in patients treated for acute leukemia or high dose chemotherapy with stem cell transplantation. Based on the 'modest' results of the study by Cullen et al. [14], Gafter-Gvili and team [16] also advise that prophylaxis be considered for the first cycle of treatment in patients with solid tumors or lymphoma.

Antibiotic use comes at a price, including increased costs, side

effects, susceptibility to enteric infections, and emergence of resistant endogenous organisms. Additional potential consequences of a broadly applied strategy of antimicrobial prophylaxis are difficult to predict. More research is needed to better characterize those patients at highest risk in order to optimize the balance of risks and benefits.

Finally, as Paul and collaborators [9] rightfully pointed out, adherence to infection control recommendations is of prime importance. Scrupulously maintained hand hygiene is the single most important technique for preventing the spread of hospital pathogens, the antimicrobial resistance of which is incessantly increasing.

References

1. Hughes WT, Armstrong D, Bodey GP, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002;34:730–51.
2. Chanock SJ, Pizzo PA. Fever in the neutropenic host. Infect Dis Clin North Am 1996;10:777–96.
3. Young SD, Feld R. Fever associated with chemotherapy-induced neutropenia: a review of current therapeutic approaches. Curr Opin Infect Dis 1998;11:401–9.
4. Schimpff S, Satterlee W, Young VM, Serpick A. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. N Engl J Med 1971;284:1061–5.
5. Gurwith MJ, Brunton JL, Lank BA, Harding GK, Ronald AR. A prospective controlled investigation of prophylactic trimethoprim/sulfamethoxazole in hospitalized granulocytopenic patients. Am J Med 1979;66:248–56.
6. Fainstein V, Bodey GP. Single-agent therapy for infections in neutropenic cancer patients. Am J Med 1985;79(2A):83–8.
7. Klastersky J, Paesmans M. Risk-adapted strategy for the management of febrile neutropenia in cancer patients. Support Care Cancer 2007;15:477–82.
8. Feld R. Vancomycin as part of initial empirical antibiotic therapy for febrile neutropenia in patients with cancer: pros and cons. Clin Infect Dis 1999;29:503–7.
9. Paul M, Gafter-Gvili A, Leibovici L, et al. The epidemiology of bacteremia with febrile neutropenia: experience from a single center, 1988-2004. IMAJ 2007;9:460–2.
10. Greenberg D, Moser A, Yagupsky P, et al. Microbiological spectrum and susceptibility patterns of pathogens causing bacteraemia in paediatric febrile neutropenic oncology patients: comparison between two consecutive time periods with use of different antibiotic treatment protocols. Int J Antimicrob Agents 2005;25:469–73.
11. Wang F-D, Lin M-L. Liu C-Y. Bacteremia in patients with hematological malignancies. Chemotherapy 2005;51:147–53.
12. Sigurdardottir K, Digranes A, Harthug S, et al. A multi-centre prospective study of febrile neutropenia in Norway: microbiological findings and antimicrobial susceptibility. Scand J Infect Dis 2005;37:455–64.
13. Bucaneve G, Micozzi A, Menichetti F, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 2005;353:977–87.
14. Cullen M, Steven N, Billingham L, et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med 2005;353:988–98.
15. Baden LR. Prophylactic antimicrobial agents and the importance of fitness. N Engl J Med 2005;353:1052–4.
16. Gafter-Gvili A, Paul M, Fraser A, Leibovici L. Antibiotic prophylaxis in neutropenic patients. IMAJ 2007;9:460–2.

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