

Outpatient Management of Febrile Neutropenia: Concerns for the Future

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Commentary on “Outpatient Management of Febrile Neutropenia: Time to Revise the Present Treatment Strategy” by Carstensen and Sørensen (page 199).

Drs. Carstensen and Sørensen provide an excellent review of the available literature evaluating the outpatient management of febrile neutropenia. Although it may have been useful for the authors to include studies of patients with hematologic malignancy in their review, they likely would have drawn similar conclusions. Clearly, there is a subgroup of patients with a variety of malignancies that has been shown to do well with oral antibiotics, and this approach has been supported by both the Infectious Diseases Society of America¹ as well as the more recent guidelines developed by the National Comprehensive Cancer Network.² Further, a recent retrospective review of 712 low-risk, solid tumor outpatients presenting to the emergency department with febrile neutropenia showed that outpatient management was as safe and effective as inpatient therapy and significantly less costly.³

The important issue that has not yet been addressed is how applicable this approach will be in the future, given the interplay of several clinical trends, including the use of antibacterial prophylaxis, the emergence of antibiotic-resistant organisms, and the role of *Clostridium difficile* as an important cause of morbidity and mortality in many patient groups.

Clinical Trends

Antibacterial prophylaxis has been used in both patients with solid tumors and patients with hematologic malignancies. Although prophylaxis for low-risk patients is not recommended by re-

cent guidelines,² it certainly does occur. Several single-institution studies showed that use of quinolones as prophylaxis in neutropenic patients was associated with increased antibiotic resistance in Gram-negative bacilli⁴⁻⁶; however, these findings have not been seen uniformly. Because of this uncertainty, one should be wary of using a quinolone for treatment when the same antibacterial class has been used for prophylaxis. This consideration impacts the findings presented by Drs. Carstensen and Sørensen, because the quinolones are central to most oral therapeutic regimens.

Selection of empiric therapy is further complicated by increasing rates of infection with multi-drug-resistant Enterobacteriaceae (eg, *Escherichia coli*, *Klebsiella* sp, *Enterobacter* sp) as well as non-fermentative Gram-negatives (eg, *Pseudomonas* sp, *Stenotrophomonas* sp), for which quinolone susceptibility is varied.⁷ Although not specific to patients with neutropenia, recent susceptibility data from US medical centers demonstrate increasing rates of extended-spectrum cephalosporinase- and carbapenemase-producing organisms, which are often fluoroquinolone-resistant.⁸

In contrast, resistant Gram-positive organisms and their associated morbidity and mortality in the neutropenic host have been well documented.^{7,9} In neutropenic populations, vancomycin-resistant enterococcal (VRE) bacteremia has been associated with a longer duration of bacteremia and higher mortality than vancomycin-susceptible strains,⁹ likely as a result of inadequate empiric therapy. Although methicillin-resistant strains of *Staphylococcus aureus* (MRSA) have not been consistently shown to be more virulent than methicillin-susceptible strains, the commonly used oral antibiotic regimens mentioned would not provide sufficient coverage. Therefore, in localities where the incidence of VRE and MRSA is high, regimens used for oral therapy of neutropenic fever would require adjustment.

Unfortunately, choices among oral agents are few (linezolid [Zyvox]) and do not represent ac-

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ceptable first-line therapy, given the untoward effects of prolonged use. Infection with other Gram-positive pathogens, such as penicillin-resistant *Streptococcus pneumoniae* and viridans group streptococci, has been increasingly reported, as has infection with more unusual vancomycin-resistant organisms such as *Leuconostoc*, *Lactobacillus*, and *Pediococcus*.⁷ Despite these concerns, it is important to note that most febrile episodes in patients with neutropenia will not have a documented microbiologic etiology. Assessing the importance of antibiotic-resistant strains in this clinical setting is therefore difficult.

In addition to the challenges of resistant organisms, the emergence of *C difficile* as a potential pathogen is yet another problem. There are surprisingly few reports of outcomes associated with *C difficile*-associated diarrhea (CDAD) in neutropenic patients. Among 200 patients undergoing autologous stem-cell transplantation in a single center, 14 patients developed 15 episodes of CDAD.¹⁰ Five patients were neutropenic at the time of diagnosis, and all received ciprofloxacin with or without ampicillin prophylaxis from the completion of chemotherapy until neutrophil recovery or the presence of fever that required intravenous antimicrobials. This finding is consistent with the results of a retrospective chart review of 371 patients treated in a German leukemia ward between 1991 and 2000, where CDAD was described in 7% of 875 courses of myelosuppressive chemotherapy.¹¹ Interestingly, a more recent study reported a significant increase in Gram-negative bacteremia and CDAD in neutropenic patients receiving prophylaxis with moxifloxacin rather than with levofloxacin.¹² Although none of these authors reported mortality that was directly attributable to CDAD, the emergence of a new toxin-hyperproducing strain of *C difficile* is particularly worrisome, given its association with fluoroquinolone resistance and increased mortality.

In this issue of *The Journal of Supportive Oncology*, Drs. Carstensen and Sørensen have reviewed the important clinical data highlighting the efficacy and safety of oral antibiotic therapy in patients with febrile neutropenia. Notably, half of the studies were published before 2000 and before the burgeoning importance of resistant organisms and the growing clinical impact of *C difficile*. With the recognition that microbial resistance varies from city to city and hospital to hospital, the epidemiol-

ogy of antimicrobial resistance needs to be a consideration in the selection of any antibiotic regimen for any patient group, including for low-risk patients with neutropenic fever. Drs. Carstensen and Sørensen have clearly outlined the advantages and potential disadvantages of oral therapy. Along with the principles of therapy described by the authors, local trends in the epidemiology and microbiology of infections will determine the clinical utility and longevity of this practice.

References

PubMed ID in brackets

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;34:730–751. [11850858]
2. National Comprehensive Cancer Network Clinical practice guidelines in oncology: prevention and treatment of cancer-related infections. Version 1.2008. Available at: http://www.nccn.org/professionals/physician_gls/PDF/infections.pdf. Accessed April 24, 2008.
3. Elting LS, Lu C, Escalante CP, et al. Outcomes and cost of outpatient or inpatient management of 712 patients with febrile neutropenia. *J Clin Oncol* 2008;26:606–611. [18235119]
4. Kern WV, Klöse K, Jellen-Ritter AS, et al. Fluoroquinolone resistance of *Escherichia coli* at a cancer center: epidemiologic evolution and effects of discontinuing prophylactic fluoroquinolone use in neutropenic patients with leukemia. *Eur J Clin Microbiol Infect Dis* 2005;24:111–118. [15714332]
5. Cattaneo C, Quaresmini G, Casari S, et al. Recent changes in bacterial epidemiology and the emergence of fluoroquinolone-resistant *Escherichia coli* among patients with haematological malignancies: results of a prospective study on 823 patients at a single institution. *J Antimicrob Chemother* 2008;61:721–728. [18218645]
6. Reuter S, Kern WV, Sigge A, et al. Impact of fluoroquinolone prophylaxis on reduced infection-related mortality among patients with neutropenia and hematologic malignancies. *Clin Infect Dis* 2005;40:1087–1093. [15791505]
7. Rolston KV. Challenges in the treatment of infections caused by Gram-positive and Gram-negative bacteria in patients with cancer and neutropenia. *Clin Infect Dis* 2005;40:S246–S252. [15768330]
8. Jones RN, Kirby JT, Rhomberg PR. Comparative activity of meropenem in US medical centers (2007): initiating the 2nd decade of MYSTIC program surveillance. *Diagn Microbiol Infect Dis* 2008 Mar 7 [Epub ahead of print]. [18329835]
9. DiazGranados CA, Jernigan JA. Impact of vancomycin resistance on mortality among patients with neutropenia and enterococcal bloodstream infection. *J Infect Dis* 2005;191:588–595. [15655783]
10. Bilgrami S, Feingold JM, Dorsky D, et al. Incidence and outcomes of *Clostridium difficile* infection following autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant* 1999;23:1039–1042. [10373070]
11. Gorschlüter M, Glasmacher A, Hahn C, et al. *Clostridium difficile* in patients with neutropenia. *Clin Infect Dis* 2001;33:786–791. [11512083]
12. von Baum H, Sigge A, Bommer A, et al. Moxifloxacin prophylaxis in neutropenic patients. *J Antimicrob Chemother* 2006;58:891–894. [16880172]

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