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NEW GENERATION CEPHALOSPORINS IN THE EMPIRICAL TREATMENT OF FEBRILE NEUTROPENIA

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Neutropenic patients are at substantial risk of developing life-threatening bacterial infections when they become febrile. The current spectrum of infection in such patients includes gram-positive organisms such as coagulase-negative staphylococci, viridans streptococci, *Enterococcus* spp. (~60-70%); gram-negative bacilli including *E. coli*, *Klebsiella* spp., *P. aeruginosa* (~10-15%); with 10-15% of documented infections being polymicrobial. Consequently, the prompt administration of parenteral, broad-spectrum, empiric antibiotics in maximal therapeutic doses is considered to be the standard management of febrile neutropenia. The choice of specific antibacterial agents depends upon local factors such as frequency of specific pathogens and susceptibility/resistance patterns. However, several treatment strategies have been successfully used in this setting and include: combination antibiotic therapy (with or without vancomycin) and single agent therapy or monotherapy. Monotherapy is generally as effective, and is often less expensive than combination therapy. Agents traditionally used for monotherapy have included extended-spectrum (third generation) cephalosporins such as ceftazidime and cefoperazone, and the carbapenems such as imipenem. The newer (fourth generation) cephalosporins, cefepime and cefpirome, have recently become available and represent newer choices for monotherapy. In a recent survey of susceptibility among 758 gram-negative bacilli at M. D. Anderson Cancer Center, cefepime was associated with a significantly lower incidence of resistance (8%) than ceftazidime (14%), and was comparable to imipenem (9% resistance), Table 1.

Table 1. Resistance among 758 gram-negative bacilli from M. D. Anderson Cancer Center

Agent	% Resistance	Agent	% Resistance
piperacillin/tazobactam	5	ofloxacin	14
meropenem	6	ciprofloxacin	14
cefepime	8	ceftazidime	14
imipenem	9	ticarcillin/clavulanate	14
amikacin	12	tobramycin	24

Similarly, in a multicenter (10 cancer centers) study comparing the activity of broad-spectrum beta-lactams against 1128 gram-positive isolates, cefepi-

me and imipenem were more active than ceftazidime against these organisms, Table 2.

Table 2. Comparative activity of ceftazidime and cefepime against selected gram-positive organisms from cancer patients.

Organism (No.)	Agent	% Resistance
S. aureus (240)	cefepime	5.4
(oxacillin-susceptible)	ceftazidime	10.0
Coagulase-negative (101)	cefepime	3.0
Staph (oxacillin-susceptible)	ceftazidime	5.0
viridans streptococci (62)	cefepime	11.3
	ceftazidime	51.6
Streptococcus pneumoniae (59)	cefepime	10.2
	ceftazidime	37.3
B-haemolytic (44)	cefepime	0.0
Streptococci	ceftazidime	6.8

Thus, the newer cephalosporins may provide an advantage over older agent, potentially reducing the need for empiric vancomycin, amino-glycosides and/or antifungal therapy.

Cefepime monotherapy has been compared to penicillin-aminoglycoside combinations, and to ceftazidime monotherapy in several clinical trials in neutropenic patients. These studies did not show superiority of one regimen over the other and survival at the end of the neutropenic episode, and 30 days later, was ≥90% in each case. In patients receiving cefepime, the addition of an aminoglycoside was required infrequently and these patients required less frequent addition of vancomycin than patients treated with comparator regimens.

In summary, current in-vitro and clinical studies indicate that monotherapy with newer generation cephalosporins such as cefepime is an acceptable option for the initial empiric therapy of febrile neutropenic patients. Individual cancer centers need to continue to monitor their microflora for the emergence of drug-resistant isolates to all agents that are used frequently in this setting.