

Addition of Fluoroquinolone Prophylaxis to a Blood and Marrow Transplant Unit to Reduce Gram-Negative Infections

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Introduction

Patients receiving chemotherapy or stem cell transplantation are at risk of developing severe infectious complications, and those infections remain a particular concern due to Gram-negative bacteria. Following prolonged exposure to ceftazidime, "SPICE" organisms (*Serratia* spp, *Pseudomonas aeruginosa*, indole-positive *Proteus*, *Citrobacter* spp, and *Enterobacter* spp) have demonstrated an inducible beta-lactamase. One strategy to control such Gram-negative bacteria in an institutional setting is the use of antimicrobial prophylaxis incorporating fluoroquinolones. This strategy, however, may select for resistant organisms.

Antibiotic resistance is increasingly a global concern. Consequences include longer hospital stays and increased morbidity, especially for those seriously ill or immunocompromised. Mortality may double when resistant microbes are involved. The Centers for Disease Control and Prevention (CDC) has estimated the annual cost of treating resistant infections at \$14 billion.

This study is a retrospective survey of the SPICE bacteria isolates obtained from patients developing febrile neutropenia in a blood and marrow transplant (BMT) inpatient unit. Its objectives are first to compare the rates of isolation of SPICE bacteria before and after addition of a fluoroquinolone prophylaxis and second, to examine the

effect of fluoroquinolone prophylaxis on the proportion-resistant isolates. *Proteus* isolates were relatively few and were omitted from consideration.

This study is based on a review of all organisms isolated from sterile body sites of patients receiving chemotherapy between 1990 and 2000 in the BMT unit at our institute. The BMT unit serves patients undergoing autologous or allogeneic stem cell transplantation, those receiving chemotherapy prior to collection of peripheral blood stem cells, and patients requiring readmission subsequent to these treatments. Records that did not include the mean inhibitory concentration (MIC) values were excluded.

Methods and Definitions

Between January 1990 and March 1996, the empiric treatment of febrile neutropenia consisted of ceftazidime and vancomycin, initiated at the onset of an elevated temperature. Patients who were allergic to either of these medications were empirically given an equivalent antimicrobial agent. In August 1998, cefepime replaced ceftazidime. Starting in April 1996, a fluoroquinolone, levofloxacin, was used as antimicrobial prophylaxis accompanying the administration of chemotherapy. Trovafloxacin replaced levofloxacin in 1998 for several months before returning to the use of levofloxacin. Additional antimicrobial agents were administered on a case-by-case basis as clinically indicated.

Definitions for antimicrobial resistance followed the current National Committee for Clinical Laboratory Standards guidelines. Resistance to ceftazidime for *P. aeruginosa* is defined as an MIC ≥ 32 $\mu\text{g/mL}$. Intermediate resistance to ceftazidime in the Enterobacteriaceae is defined as an MIC value of 16 $\mu\text{g/mL}$, and full resistance is defined as ≥ 32 $\mu\text{g/mL}$. Accordingly, two additional *Pseudomonas* isolates were scored as resistant. One *Enterobacter* and a single *Serratia* isolate were resistant to ceftazidime on a Kirby-Bauer test but MIC values were not reported. Both were scored as resistant.

As applied to blood isolates, the words "before" and "after" refer to the point at which routine use of fluoro-

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Abbreviations used in this paper: BMT = blood and marrow transplant, SPICE = *Serratia*, *Pseudomonas*, *Citrobacter*, and *Enterobacter*, MIC = mean inhibitory concentration.

Comparison of SPICE Organism Isolation Rates and Proportions Resistant Before and After Addition of a Quinolone to a Cephalosporin Regimen in a Blood and Marrow Transplant Unit

Organism	Resistant + Sensitive = Total		Percent Resistant		Rate per 10,000 Patient Days		Comparison ^c	
	Before	After	Before	After	Before ^a	After ^b	z Value	P Value
<i>Enterobacter</i>	25 + 22 = 47	2 + 6 = 8	53.2%	25.0%	17.7	4.4	3.92	.000
<i>Pseudomonas aeruginosa</i>	3 + 30 = 33	0 + 9 = 9	9.1%	0%	12.4	5.0	2.52	.012
<i>Citrobacter</i>	7 + 3 = 10	1 + 4 = 5	70.0%	20.0%	3.8	2.8	Insufficient data	
<i>Serratia</i>	1 + 4 = 5	0 + 0 = 0	20.0%	0%	1.9	0.0	Insufficient data	
All SPICE organisms	36 + 59 = 95	3 + 19 = 22	37.9%	13.6%	35.7	12.2	4.78	.000

^a 26,624 patient days at risk before quinolone prophylaxis.
^b 18,110 patient days after quinolone prophylaxis.
^c Comparison of incidence of isolates per 10,000 patient days at risk. Proportions resistant appear in the Figure.

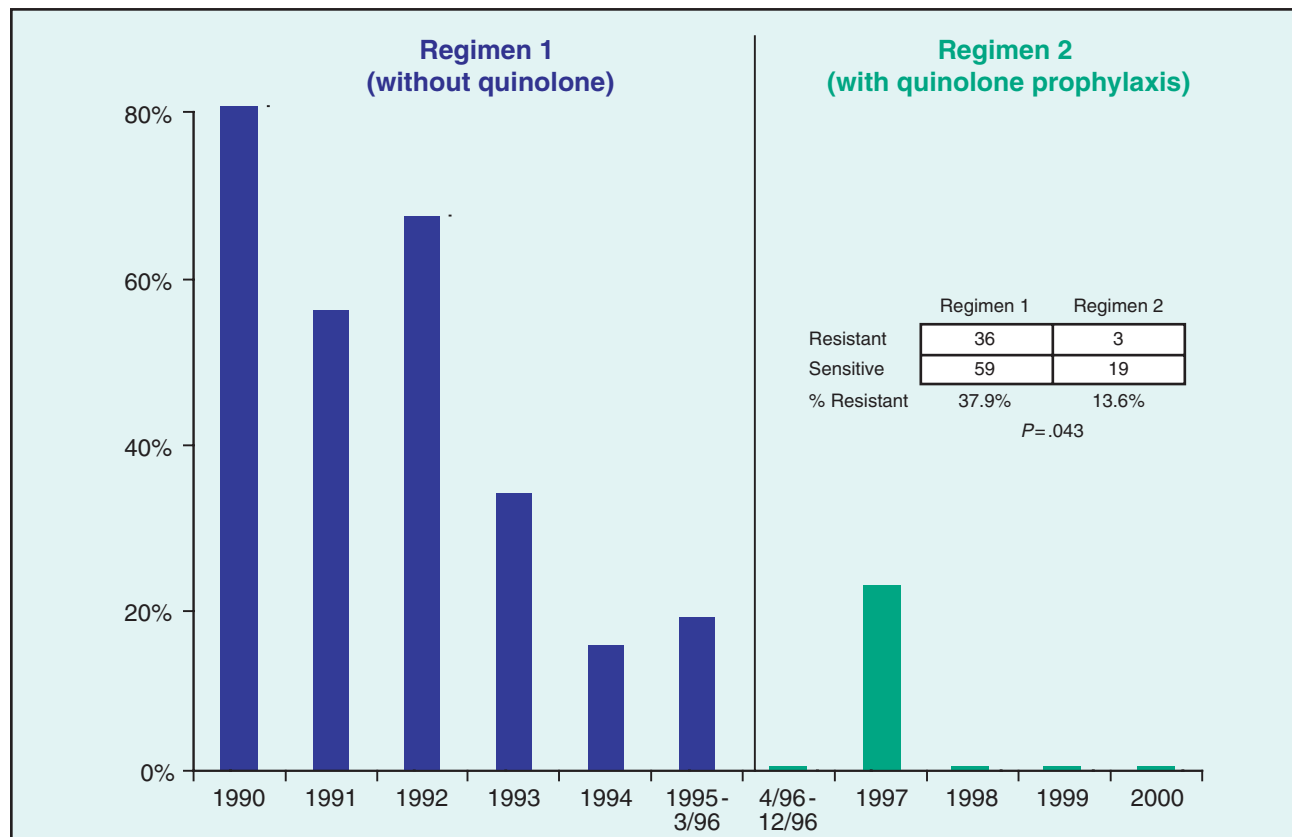
quinolone prophylaxis began (April 1996). Only the first culture was counted as an isolate if the same patient yielded a subsequent isolate within 30 days of the initial culture. Rates of isolation before and after the addition of fluoroquinolone prophylaxis were compared using patient hours at risk as denominators (Table). The effect of the addition of a quinolone was also examined by a Fisher's Exact Test using crude counts of the number of isolates resistant and susceptible (Figure).

Results

SPICE organisms were found among 116 total isolates that were cultured from 112 patients. Seventy-one organisms

were isolated from blood, 26 from urine, 17 from respiratory specimens, and 2 from catheter tips. These isolates included 55 *Enterobacter*, 42 *P aeruginosa*, 15 *Citrobacter*, and 5 *Serratia*. Of the *Enterobacter* isolates, 45 were *E cloacae*, 7 were *E aerogenes*, and 1 each were *E amnigenus*, *E gergoviae*, and *E agglomerans* (now *Pantoea agglomerans*). Among the *Citrobacter* isolates, 13 were *C freundii*, 1 was *C braakii*, and 1 was *C koseri*. All 4 *Serratia* isolates were *S marcescens*.

Isolation rates and percents of isolates resistant are presented in the Table, and the proportions of all isolates resistant appear in the Figure. The incidence of *Enterobacter*, the most common isolate (n = 47) before the addition of fluoroquinolone prophylaxis, fell from 17.7 per



Percent of SPICE organisms resistant to ceftazidime in a bone and marrow transplant population.

10,000 patient days at risk to 4.4 after the addition. The proportion of *Enterobacter* isolates resistant to ceftazidime also fell from 53.2% to 25%, and the incidence of *P. aeruginosa* decreased significantly. Isolates of *Citrobacter* and *Serratia* were too few to be meaningfully evaluated independently and were tallied into the category of "All SPICE Organisms." For that group as a whole, the incidence rate of all species isolates declined by nearly two thirds following the use of fluoroquinolone prophylaxis, from 35.7 to 12.2 per 10,000 patient days. The overall decline in the proportion of isolates resistance, from 37.9% (36/95) to 13.6% (3/22), was also statistically significant (Fisher's Exact statistic = 4.82, $P=0.043$).

Among the isolates with resistance to ceftazidime, 94.7% (36/38) were also resistant to ticarcillin/clavulanate, and 86.8% (33/38) were also resistant to piperacillin. The incidence of *Escherichia coli* was high during the 1993–1995 period (3.8 cases per 100 patients) but later dropped to 0.51 cases per 100 patients between 1996 and 2003.

Discussion

Indiscriminate use of broad-spectrum antibiotics, inappropriate dosages, and substandard nosocomial infection control procedures have all contributed to the global rise of antibiotic resistance. Notably, the prolonged use of vancomycin beyond its period of efficacy has led to the rise of vancomycin-resistant *Enterococcus* (VRE) in some intensive care units.^{1,2}

Although nosocomial Gram-positive infections have increasingly occurred among patients with cancer, Gram-negative infections also remain a threat and are a cause of high morbidity among immune-compromised patients.^{3,5} Cancer patients, with their prolonged hospital stays, numerous invasive procedures, intravascular catheters, and exposure to broad-spectrum antibiotics not only are at increased risk for complicated infections but also create an ideal setting for resistant nosocomial organisms.^{6,7} Of the more than 2 million nosocomial infections each year in the United States, an estimated 50% to 60% are resistant to some type of antimicrobial.⁸ Fluoroquinolones have been proven to be safe and effective in reducing the number of Gram-negative infections in neutropenic patients, but they have not been shown to increase survival.⁹ Fluoroquinolones act on DNA gyrase to prevent replication of bacterial DNA. Resistance has developed through mutations in this enzyme, resulting in a decreased affinity for the fluoroquinolones.¹⁰ Resistance among community-acquired isolates remains minimal but is rising among nosocomial pathogens.¹¹

A number of studies have compared cefepime to ceftazidime in the treatment of febrile neutropenia. Responses and cure rates have been compared both head-to-head or as components of combination therapy. The consensus

is that cefepime is at least as effective as ceftazidime in treating neutropenic patients.^{4,12-14}

P. aeruginosa is an organism that poses a particular threat to the cancer patient. Infection rates have risen in those with acute leukemias.¹⁵⁻¹⁷ Coverage for *P. aeruginosa* should be included in both antimicrobial prophylaxis regimens and in the empiric treatment of suspected infection in immune-compromised patients. The 1997–1999 SENTRY Antimicrobial Surveillance Program classified multidrug-resistant strains of *P. aeruginosa* that lack susceptibility to piperacillin, ceftazidime, imipenem, and gentamicin.¹⁶ One of the challenges in managing *P. aeruginosa* infections is an inherent resistance mechanism, one preexisting in the genome and not induced by external stimuli. Its multiplicity of resistance mechanisms may render this microbe less amenable to control by antibiotic cycling.¹⁸ Among the quinolones, ciprofloxacin is still the most active against *P. aeruginosa*. Nevertheless, a European study conducted in 1995–1996 reported that 22% of respiratory isolates were resistant to this antibiotic.¹⁹

Enterobacter species, especially *E. cloacae*, have also emerged as a significant cause of nosocomial infections and can express an extended spectrum beta-lactamase. Resistance to ceftazidime, first identified in 1982,²⁰ has since been strongly linked with previous ceftazidime exposure.⁵ As with *P. aeruginosa*, plasmid-mediated resistance has also been attributed in part to clonal spread in *Enterobacter* species.¹⁷ In a pediatric hospital in the Netherlands,¹⁸ two major clones of *Enterobacter* were responsible for 36% of all colonization. Another 35% of isolates consisted of unique strains. Furthermore, most of the major clones were isolated within surgical and neonatal intensive care units. Thus, hospital infection control procedures appear to be as important as is the selective use of broad-spectrum antibiotics. As with *P. aeruginosa*, *Enterobacter* species are most sensitive to cefepime and the carbapenems.¹¹ Nevertheless, resistance to imipenem, conferred by the NmCA gene, is beginning to emerge. Classic beta-lactamase inhibitors such as clavulanic acid and tazobactam can inhibit this enzyme. The IMP-1 gene, however, expresses a gene product that confers resistance to imipenem and is not sensitive to either clavulanic acid or tazobactam.¹⁹ *Enterobacter* species do not appear to express the multiresistance mechanisms characteristic of *P. aeruginosa*.

Despite increasing antibiotic resistance nationally and globally, the incidence of resistant SPICE bacteria decreased significantly between 1990 and 2000 in the BMT unit of our institute since incorporating fluoroquinolones as antimicrobial prophylaxis. Levaquin prophylaxis has continued as of mid-2004 and has continued to suppress the appearance of SPICE organisms. In contrast, some centers have reported the emergence of fluoroquinolone-resistant Gram-negative bacilli, especially *P. aeruginosa*, in patients given fluoroquinolone prophylaxis.²¹ Although the decline in incidence and rate of

resistance organisms for *Pseudomonas* were less marked than that for *Enterobacter*, our results are nevertheless gratifying.

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