Letters

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Emerging Gram-Negative Antibiotic Resistance: Daunting Challenges, Declining Sensitivities, and Dire Consequences

We write to respond to Dr Siegel's review[1] on the curse of antibiotic resistance among Gram-negative bacilli. In nonacademic, nonresearch health-care centers in rural and remote locations, his recommended strategy of comprehensive pharmacologic and infection-control measures to slow down the development of resistance to carbapenems might not be realistic. Nevertheless, clinicians might at least be motivated toward a better response to multiple-drug resistance if they have local antibiograms based on analysis of their local multiple-drug-resistant organisms. During the past 5 years we conducted such an exercise at our tertiary-care hospital in Delhi, India, which we believe has been helpful. Though clinicians initially had concerns, they have been guided toward more appropriate empirical antibiotic therapy. The in vitro susceptibility of multiple-drug-resistant isolates to otherwise unanticipated antibiotic formulation was realistic for subsequent therapeutic options.

In October 2002 we started culture surveillance for nosocomial infection, identified by a cut-off of 2–3-days between hospitalization and a positive culture.[2] Our initial data set was from October 2002 to March 2003. Subsequent data were for the 1-year period between April 2003 and March 2004. During the last quarter of 2004, promising antimicrobials against the local isolates were chosen from 28 antimicrobials. The cut-off susceptibility value was $\geq 75\%$ for oral and injected antibiotics.[3] As of October 2005, isolates from hospitalized patients in intensive care or with serious infections were also tested for susceptibility to aztreonam, meropenem, piperacillin-tazobactam, and cefepime.

Nosocomial infection susceptibility during 2002 through 2005 and 2006 for amoxicillin-clavulanic acid, amikacin, ciprofloxacin, and ofloxacin was statistically similar. The fourth-year trends in relation to the initial 3-year interval indicated a rise in the ratio of isolates susceptible to amoxicillin-clavulanic acid, amikacin and ofloxacin, but a concurrent decline in susceptibility to ciprofloxacin (Table 1). Later, the 2005-2006 period and 2006-2007 period susceptibility for aztreonam, meropenem, piperacillin-tazobactam, cefepime was comparable, but with a declining proportion of the susceptible isolates (Table 2).

In nosocomial isolates we found multiple-drug resistance to several categories of antimicrobial, including β-lactam/β-lactamase inhibitors, aminoglycosides, quinolones, cephalosporins, monobactam, and carbapenem. During 2002 there was one multiple-drug-resistant *Escherichia coli* (from urine), resistant to amikacin, ciprofloxacin, and ofloxacin but susceptible to amoxicillin-clavulanic acid and nitrofurantoin. During 2003, one multiple-drug-resistant *Pseudomonas aeruginosa* (from pulmonary tissue) was resistant to amoxicillin-clavulanic acid, amikacin, and ciprofloxacin, and was susceptible only to ofloxacin. During 2004 there was one *P. aeruginosa* (from lung) that was resistant to amoxicillin-clavulanic acid, amikacin, and ciprofloxacin but susceptible to pefloxacin, ofloxacin, netilmicin, ceftazidime, and ampicillin-sulbactam. During 2004 there were 2 multiple-drug-resistant *E. coli* from urine: one was resistant to amikacin, ciprofloxacin, and ofloxacin but susceptible only to amoxicillin-clavulanic acid; the other was resistant to amikacin, ciprofloxacin, and ofloxacin but susceptible to amoxicillin-clavulanic acid, ampicillin-sulbactam, and nitrofurantoin.

There were 2 multiple-drug-resistant species from pulmonary tissues in 2006. One *E. coli* was resistant to aztreonam, cefepime, amikacin, ofloxacin, but susceptible to meropenem, piperacillin-tazobactam, and amoxicillin-clavulanic acid. One *Klebsiella pneumoniae* was resistant to cefepime, amikacin, aztreonam, piperacillin-tazobactam, and amoxicillin-clavulanic acid but susceptible to meropenem and ofloxacin.

During 2007 there were 2 multiple-drug-resistant species. One *P. aeruginosa* (from purulent material) was resistant to meropenem, piperacillin-tazobactam, amoxicillin-clavulanic acid, and amikacin but susceptible to cefepime, aztreonam, ciprofloxacin, and ceftazidime. And one *Proteus* species (from urine) was resistant to aztreonam, meropenem, piperacillin-tazobactam, cefepime, amikacin, and amoxicillin-clavulanic acid but susceptible to nitrofurantoin and teicoplanin.

Unit-based antibiograms and combination antibiograms[4] would be synergistic to international, national, or regional surveillance data. Moreover, rapid polymerase-chain-reaction identification or immediate placement of E-test strips on clinical materials[4] would not be feasible all the time. Obviously, clinicians should be urged to avoid "tradition-based" antibiotic regimens, and instead should receive frequent updates on the broad-spectrum antibiotics in local use, to guide their antibiotics selections for treating multiple-drug-resistant infections.

Even without comprehensive antibiograms, the nosocomial Gram-negative bacilli antibiograms could help clinicians select empirical antibiotic therapy[1] and "fine-tune" the local antibiotics treatment and de-escalation strategies.[1,4] That should emerge as a rational approach to address an otherwise poor armamentarium against Gram-negative antibiotic resistance.[1]

Subhash C Arya PhD
Nirmala Agarwal FRCOG
Shekhar Agarwal MCh
Sant Parmanand Hospital
Delhi, India

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Table 1. Trends in Antibiotic Susceptibility of Nosocomial Isolates and Selected Antimicrobials: 2002 to 2006*

		Susceptible Isolates/Total Isolates (*n* and %)			
Isolate	Period	Amoxicillin-Clavulanic Acid	Amikacin	Ciprofloxacin	Ofloxacin
Escherichia coli	2002 to 2005	18/24 (75)	7/10 (70)	11/26 (42)	12/26 (46)
	2005 to 2006	3/4 (75)	2/3 (67)	1/5 (20)	4/5 (80)
Klebsiella	2002 to 2005	8/9 (89)	4/6 (67)	2/8 (25)	5/8 (63)
	2005 to 2006	12/14 (86)	10/14 (71)	7/14 (50)	10/14 (71)
Proteus	2002 to 2005	0/3 (0)	2/3 (67)	1/4 (25)	3/4 (75)
	2005 to 2006	1/1 (100)	0/1 (0)	0/1 (0)	0/1 (0)
Pseudomonas	2002 to 2005	2/8 (25)	2/6 (33)	5/9 (56)	7/9 (77)
	2005 to 2006	0/2 (0)	2/2 (100)	1/2 (50)	1/2 (50)
Cumulative	2002 to 2005	28/44 (64)	15/25 (60)	19/47 (40)	27/47 (57)
	2005 to 2006	16/21 (76)	14/20 (70)	9/22 (22)	15/22 (68)

* Data were analyzed for changes in susceptibility rate with Fisher's exact test and chi-square test for linear trends. None of the differences (except ciprofloxacin) were significant at $P \leq .05$.

Table 2. Trends in Broader-Spectrum Antibiotics of Nosocomial Isolates: 2005 to 2007*

		Susceptible Isolates/Total (*n* and %)			
Isolate	Period	Aztreonam	Meropenem	Piperacillin-Tazobactam	Cefepime
Escherichia coli	2005 to 2006	3/5 (60)	4/4 (100)	5/5 (100)	1/4 (25)
	2006 to 2007	2/5 (40)	5/5 (100)	4/5 (80)	1/5 (20)
Klebsiella	2005 to 2006	10/14 (41)	14/14 (100)	13/14 (93)	8/14 (57)
	2006 to 2007	6/16 (27)	12/16 (77)	14/16 (88)	5/15 (33)
Proteus	2005 to 2006	0/1 (0)	1/1 (100)	1/1 (100)	1/1 (100)
	2006 to 2007	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)
Pseudomonas	2005 to 2006	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)
	2006 to 2007	4/8 (80)	4/5 (80)	5/5 (100)	2/5 (40)
Cumulative	2005 to 2006	15/22 (68)	21/21 (100)	21/22 (95)	12/21 (57)
	2006 to 2007	14/28 (50)	23/28 (82)	25/28 (89)	10/27 (37)

* Data were analyzed for changes in susceptibility rate with Fisher's exact test and chi-square test for linear trends. None of the differences were significant at $P \leq .05$.

The author responds:

Local susceptibility testing and production of an antibiogram of the local community is ideal to guide initial empirical therapy and therapy for patients who fail initial antibiotic treatment, while awaiting in vitro susceptibility results. A locally produced antibiogram of local organisms is the most useful because it better reflects the organisms and resistance patterns in the population served than can national guidelines. Each hospital and hospital unit has different resistance patterns, and clinicians who are aware of the local patterns are more likely to choose the best empirical antibiotic, and to pick more appropriate antibiotics if the initial antibiotics fail.

In rural areas with limited resources the knowledge of local resistance patterns may be important because less expensive antibiotics may be effective if resistance to those agents is locally uncommon. Only knowledge of the local antibiotic resistance patterns will permit those choices to be made safely. Important changes in local resistance patterns, detected via surveillance, will guide shifts to antibiotics that will remain effective and inexpensive for the population served.

Robert E Siegel MD
Intensive Care Unit
James J Peters Veterans Affairs
Medical Center
Bronx, New York

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