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Resistance of gram-negative organisms to extended-spectrum cephalosporin and fluoroquinolone antibiotics, 1990-2002: results of the Antimicrobial Resistance Management (ARM) program

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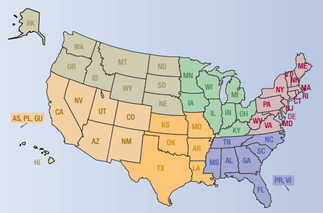
What is the Antimicrobial Resistance Management (ARM) Program?

PURPOSE

- The Antimicrobial Resistance Management (ARM) Program is an ongoing study to document trends in antimicrobial susceptibility patterns in inpatient and outpatient isolates and to identify relationships between antibiotic use and resistance rates
- Hospitals can delineate if and when antimicrobial resistance occurs
  - Allows strategic intervention
  - Provides data for local, regional, national benchmarks
  - Has potential to reduce costs of antibiotics associated with inappropriate use
- A total of 285 institutions have enrolled as of November 13, 2003
  - 229 (80.4%) nonteaching
  - 55 (19.3%) teaching
- For the purposes of comparison, US hospitals are grouped in 6 geographic regions (see map, below)



- The number of hospitals included from each region is as follows:
  - North Central: 50 (17.5%)
  - Northeast: 70 (24.6%)
  - Northwest: 7 (2.5%)
  - South Central: 52 (18.2%)
  - Southeast: 86 (30.2%)
  - Southwest: 20 (7.0%)

DATA COLLECTION

- Each hospital provides a minimum of 3 years of antibiogram or sensitivity report data
- Individual antibiotics and organisms are captured in the database
  - 48 antibiotics
  - 19 organisms
- A Web-based analysis tool allows comparisons between antibiotic use and resistance rates for any number of parameters
  - One year with another year
  - Groups of years to other groups of years
  - Hospital to hospital
  - Hospital to hospital system
  - Hospital to state
  - Within a state
  - Hospital to region
  - Hospital to national
  - State to state
  - State to region
  - State to national
  - Region to national

Abstract

RATIONALE: Evidence suggests an increasing association between fluoroquinolone resistance and extended-spectrum beta-lactamase (ESBL) production, limiting the role of these antibiotics against ESBL producers, represented by Escherichia coli, Klebsiella pneumoniae, *and* Proteus mirabilis.

OBJECTIVE: The ongoing ARM program is designed to document resistance patterns in inpatient and outpatient isolates; to date, more than 17 million isolates from 251 US hospitals have been entered into a surveillance database.

METHODS: Using a Web-based analysis tool, antibiograms and sensitivity reports of E coli, K pneumoniae, *and* P mirabilis *isolates were reviewed for resistance to extended-spectrum cephalosporin (cefotaxime, ceftriaxone, cefepime) and fluoroquinolone (ciprofloxacin, levofloxacin) antibiotics. Comparative susceptibility between cephalosporins is used as a surrogate marker for the presence of ESBLs.*

RESULTS: E coli, P mirabilis, *and* K pneumoniae *isolates were more resistant to fluoroquinolones than to extended-spectrum cephalosporins. For* E coli, *resistance was 3.2% to ciprofloxacin (n=444,947), 5.4% to levofloxacin (n=201,532), and 0.8% to cefotaxime (n=107,394), ceftriaxone (n=464,931), and cefepime (n=81,980), respectively.* P mirabilis *isolate resistance was 12.5% to ciprofloxacin (n=83,186), 12.2% to levofloxacin (n=35,277), 1.0% to cefotaxime (n=18,802), 0.7% to ceftriaxone (n=83,652), and 2.3% to cefepime (n=13,968). For* K pneumoniae, *resistance was 4.6% to ciprofloxacin (n=144,698), 4.5% to levofloxacin (n=57,462), 1.9% to cefotaxime (n=33,189), 2.0% to ceftriaxone (n=145,328), and 1.9% to cefepime (n=25,503).*

CONCLUSION: A greater percentage of gram-negative isolates are resistant to fluoroquinolone than to extended-spectrum cephalosporin antibiotics.

IMPLICATIONS: These results suggest low levels of ESBL activity are occurring and that fluoroquinolone resistance among gram-negative aerobes requires continued monitoring.

Rationale and Objective

- Extended-spectrum beta-lactamase (ESBL)-producing enzymes can mediate resistance to extended-spectrum antibiotics, causing infectious outbreaks
- The most common ESBL-producing organisms include *E coli* and *K pneumoniae*, both causes of serious nosocomial and ICU gram-negative infections[1]; other isolates of Enterobacteriaceae, such as *P mirabilis*, also produce ESBLs
- Recent evidence suggests increasing frequency of an association between fluoroquinolone resistance and ESBL production, greatly limiting the role of this class of antibiotic against ESBL producers[2]
- The ARM program includes a surveillance database designed to document national and regional resistance patterns in inpatient and outpatients isolates from US institutions

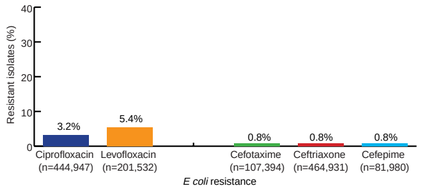
Methods

- Antibiograms and sensitivity reports of *E coli*, *K pneumoniae*, and *P mirabilis* isolates in the ARM program surveillance database were reviewed for resistance to the third-generation cephalosporins, cefotaxime and ceftriaxone; the fourth-generation cephalosporin cefepime; and the fluoroquinolones, ciprofloxacin and levofloxacin
- The presence of ESBLs was determined using comparative susceptibility between cephalosporins as a surrogate marker
- Data were reported both collectively for the years 1990 through 2002 and individually beginning in 1997, which was selected to reflect initial collection of isolates tested against levofloxacin and cefepime

Results

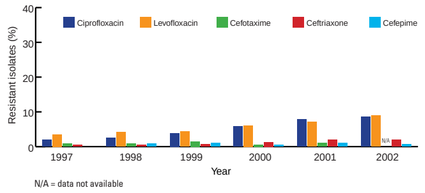
- Sensitivity rates for cefotaxime and ceftriaxone isolates in the ARM program database prior to January 2002, when the NCCLS adopted an MIC of ≥ 4 μg/mL for both agents, are artificially suppressed
- Low rates of *E coli* isolate resistance to the cephalosporins were observed; however, resistance was 3.2% to ciprofloxacin and 5.4% to levofloxacin (Figure 1)

Figure 1. National* E coli *isolate resistance to the fluoroquinolones and extended-spectrum cephalosporin antibiotics, 1990-2002



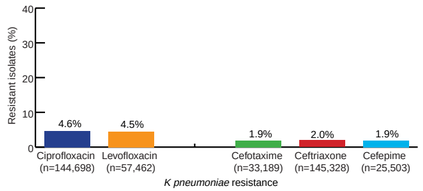
- When examined by year, resistance to ciprofloxacin and levofloxacin was observed to increase steadily between 1997 and 2002 (Figure 2)

Figure 2. National* E coli *isolate resistance to the fluoroquinolones and extended-spectrum cephalosporin antibiotics by year, 1997-2002



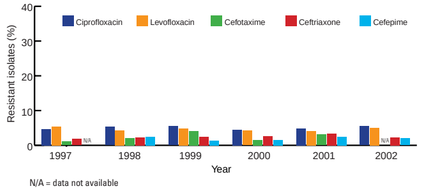
- A similar trend was observed for *K pneumoniae* isolates, with the cephalosporins demonstrating low rates of resistance and the fluoroquinolones having a higher resistance rate (Figure 3)

Figure 3. National* K pneumoniae *isolate resistance to the fluoroquinolones and extended-spectrum cephalosporin antibiotics, 1990-2002



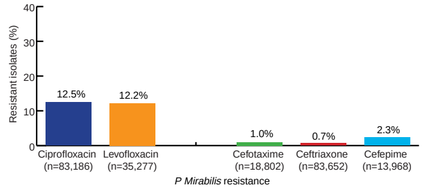
- For individual years, *K pneumoniae* isolates were more resistant to the fluoroquinolone antibiotics than to the cephalosporins (Figure 4)

Figure 4. National* K pneumoniae *isolate resistance to the fluoroquinolones and extended-spectrum cephalosporin antibiotics by year, 1997-2002



- For *P mirabilis*, resistance remained lower to the cephalosporins than to the fluoroquinolones; however, compared with *E coli* and *K pneumoniae*, *P mirabilis* demonstrated an even greater resistance to both ciprofloxacin (12.5%) and levofloxacin (12.2%) (Figure 5)

Figure 5. National* P mirabilis *isolate resistance to the fluoroquinolones and extended-spectrum cephalosporin antibiotics, 1990-2002



- *P mirabilis* isolate resistance to the fluoroquinolones surpassed 10% for ciprofloxacin in 1998 and 20% for both ciprofloxacin and levofloxacin by 2002 (Figure 6)
- When examined regionally, this resistance was most notable in South Central and Southeast (Table 1)

Figure 6. National* P mirabilis *isolate resistance to the fluoroquinolones and extended-spectrum cephalosporin antibiotics by year, 1997-2002

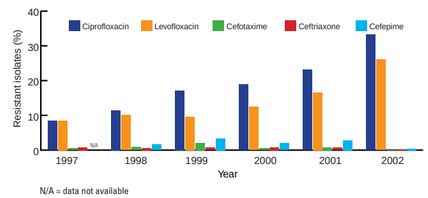


Table 1. Regional* E coli, K pneumoniae, *and* P mirabilis *isolate resistance to the fluoroquinolones and extended-spectrum cephalosporin antibiotics, 1990-2002

Antibiotic	Organism	Region: North Central Resistant (%)	Northeast Resistant (%)	South Central Resistant (%)	Southeast Resistant (%)	Southwest Resistant (%)
Ciprofloxacin	*E coli*	1.3	3.3	3.0	3.9	8.0
	K pneumoniae	5.3	4.5	4.4	4.5	1.3
	P mirabilis	7.3	9.7	**32.9**	**13.5**	6.6
Levofloxacin	*E coli*	3.2	5.2	3.1	6.1	5.7
	K pneumoniae	2.7	3.9	3.7	4.8	8.4
	P mirabilis	10.0	9.8	**23.6**	**11.9**	5.8
Cefotaxime	*E coli*	0.7	0.7	0.9	0.9	N/A
	K pneumoniae	3.4	1.5	1.9	1.5	N/A
	P mirabilis	1.1	0.8	0.4	1.0	N/A
Ceftriaxone	*E coli*	0.6	0.8	0.7	0.8	1.3
	K pneumoniae	1.8	1.4	2.4	2.6	1.1
	P mirabilis	0.6	0.9	1.1	0.6	0.2
Cefepime	*E coli*	0.2	0.4	0.4	1.1	0.7
	K pneumoniae	2.2	1.7	0.7	2.1	1.1
	P mirabilis	1.5	1.6	1.6	2.7	0

N/A = data not available

Conclusion

- National and regional differences in *E coli*, *K pneumoniae*, and *P mirabilis* resistance were detected to cephalosporin and fluoroquinolone antibiotics, suggesting low levels of ESBL activity are occurring; these differences were associated with an anticipated class/subclass effect

Implications

- The increasing resistance observed with ESBL-producing organisms to classes of antibiotics including the fluoroquinolones emphasize the necessity for institutions to improve the ability of their clinical laboratories to detect ESBLs and increase accuracy among their sensitivity reporting systems to assure the most appropriate antimicrobial therapy is selected

References

1. Nathisuwan S, Burgess DS, Lewis JS II. Extended-spectrum ß-lactamases: epidemiology, detection, and treatments. *Pharmacotherapy.* 2001;21(8):920-928.
2. Paterson DL. Recommendation for treatment of severe infections caused by Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs). *Clin Microbiol Infect.* 2000;6:460-463.

Acknowledgments

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