735
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Prevalence and Antimicrobial Susceptibility Profiles of Leading Nosocomial Pneumonia Pathogens: The Ten Year Report from the European SENTRY Antimicrobial Surveillance Program

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AMENDED ABSTRACT*

Objectives: To present a 10-year summary of bacterial pathogens (prevalence and antimicrobial susceptibility [S] trends; SENTRY Antimicrobial Surveillance Program) recovered from European patients hospitalized with pneumonia (HAP). The emergence of resistance (R) among pathogens responsible for HAP is changing approaches to empiric therapy, with increasing dependence on carbapenems (CARB), fluoroquinolones (FQ), and beta-lactamase inhibitor combinations.

Methods: Non-duplicate, clinically-significant pneumonia isolates (10,780) were collected from 25 medical centers in Europe participating in the SENTRY Program from 1997-2006. Identifications were confirmed by the central monitoring laboratory and all isolates were S tested using CLSI methods and interpretive criteria (M100-S17) against commonly used antimicrobial agents used for the empiric or directed therapy of HAP.

Results: Ranking European HAP pathogens between the years 1997-2006 included *S. aureus* (SA) > *P. aeruginosa* (PSA) > *Klebsiella* spp. (KSP) > *E. coli* (EC) > *Enterobacter* (ESP) > *Acinetobacter* (ASP) > *Serratia* spp. > *S. maltophilia*. MRSA rates have remained essentially unchanged during the study, although dramatic differences were noted between nations. R-emergence is most notable among Gram-negative bacilli, especially ASP, where R increases have been seen in all sampling periods for CARB, cephalosporins, FQ and aminoglycosides. Modest increases in R have also been detected with PSA (imipenem [IPM], FQ), KSP (ceftazidime [CAZ], FQ, amikacin [AMK]), EC (FQ), and ESP (CAZ, FQ). ESBL-phenotype rates for KSP have more than doubled (>27%) since the start of the Program and are also of concern among EC (9.7%). IPM-R isolates are sporadically detected among KSP and ESP, usually due to the presence of metallo-carbapenemases (VIM-1; Italy, Greece and Turkey).

Organism (R pattern)	% Inhibited at CLSI Breakpoints 1997-1999	2000-2002	2004-2006
S. aureus (SA; 2,442)			
Methicillin-R (MRSA)	37.3	39.6	38.3
P. aeruginosa (PSA; 2,367)			
IPM-NS[a]	23.6	25.1	29.3
CAZ-R	15.2	21.1	19.3
LEV-R	21.2	25.1	28.6
AMK-R	8.7	8.2	7.5
Klebsiella spp. (KSP; 952)			
IPM-NS[a]	0.0	0.0	0.4
CAZ-R	10.2 (13.6)[b]	12.4 (19.4)[b]	17.0 (27.1)[b]
LEV-R	2.4	2.3	12.6
AMK-R	1.0	2.6	5.4
E. coli (EC; 846)			
CAZ-R	1.7 (6.8)	3.1 (8.2)	3.6 (9.7)
LEV-R	4.0	7.4	17.9
Enterobacter spp. (ESP; 745)			
IPM-NS[a]	0.5	0.3	1.1
CAZ-R	21.9	24.5	30.7
LEV-R	7.1	7.8	17.0
Acinetobacter (ASP; 566)			
IPM-NS[a]	33.3	20.9	47.5
CAZ-R	37.8	59.6	69.1
LEV-R	45.2	51.7	68.3
AMK-R	45.9	53.1	62.2

a. NS = non-susceptible.
b. Number in parentheses reflects the ESBL-phenotype rate (MIC values >=2 mg/L).

Conclusions: The SENTRY Program has documented emerging HAP pathogens and changing susceptibility profiles within European medical canters for 10 years. During this time, dramatic changes have been noted with declining S among widely used classes including the cephalosporins (Enterobacteriaceae [ENT]), CARB (PSA), and FQ (ENT, PSA and ASP); marked declines in S to all tested agents were noted with ASP. Changing patient demographics, antimicrobial usage and recognition of R genotypes with highly mobile genetic elements (class 1 integrons) within hospital environments have altered antibiograms, resulting in continued R emergence among HAP pathogens.

*Updated to reflect changes in the number of tested isolates.

INTRODUCTION

Pneumonia accounts for nearly 15% of all hospital-associated infections and ranks first in the intensive care units, where it is often associated with high fatality rates. Early recognition of disease and prompt empiric antimicrobial therapy are cornerstones of patient management to minimize morbidity and mortality. Increasingly, resistance among the commonly occurring pathogens including *Staphylococcus aureus* (oxacillin resistance), *Pseudomonas aeruginosa* and *Acinetobacter* spp. (multidrug resistance), and extended-spectrum ß-lactamase-(ESBL) producing Enterobacteriaceae, has been reported following increased reliance upon third- and fourth-generation cephalosporins, ß-lactam/ß-lactamase inhibitor combinations, carbapenems and fluoroquinolones.

In the absence of rapid diagnostic results, local data on the frequency of occurrence and susceptibility profiles of these pathogens are often used to guide empiric antimicrobial therapy. Regional surveillance data is also helpful in determining resistance rates among common bacterial pathogens on a larger scale. Numerous studies have documented significant differences in pathogen occurrence and rates of antimicrobial resistance between countries and continents, necessitating careful consideration of surveillance information in the preparation of therapeutic guidelines.

The SENTRY Antimicrobial Surveillance Program has monitored regional trends in pathogen occurrence and susceptibility profiles since 1997. In this investigation, we review data from Europe, Turkey and Israel during the first 10 years of the SENTRY Program (1997 - 2006) to characterize regional trends in bacterial occurrence and susceptibility profiles among the common causes of pneumonia in hospitalized patients.

MATERIALS AND METHODS

Bacterial Strain Collection. A total of 10,780 non-duplicate consecutive clinical isolates were submitted from ≥25 medical centers each year located in Europe, Turkey and Israel as part of the international SENTRY Program (1997 - 2006). All isolates were collected from lower respiratory tract sites and determined to be significant by local criteria as the probable cause of pneumonia. The distribution of ranking species (number of strains; % of total) for three surveyed intervals (1997-1999, 2000-2002, and 2004-2006) is included as Table 1.

Susceptibility Test Methods. All strains were tested by the reference broth microdilution method in Mueller-Hinton broth against a variety of antimicrobial agents representing the most common classes and examples of drugs used in the empiric or directed treatment of the indicated pathogen. Interpretation of MIC results was in accordance with Clinical and Laboratory Standards Institute (CLSI) criteria. Enterobacteriaceae with elevated MIC values (≥ 2 mg/L) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as extended-spectrum ß-lactamase-producing phenotypes. Quality control (QC) strains utilized included *Escherichia coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853 and *S. aureus* ATCC 29213 among others; all QC results were within CLSI specified ranges.

RESULTS

- Pneumonia pathogens (10,780 isolates) recovered from European patients between the years 1997-2006 included *S. aureus* (22.7%) > *P. aeruginosa* (22.0%) > *Klebsiella* spp. (8.8%) > *E. coli* (7.8%) > *Enterobacter* (6.9%) > *Acinetobacter* (5.3%) > *Serratia* spp. (2.9%) > *S. maltophilia* (2.6%; Table 1).
- A trend towards increasing prevalence of *S. aureus* was apparent between intervals, along with a decrease in *P. aeruginosa* prevalence (Table 1).
- Over all years of the study MRSA rates have increased slightly (Table 2); marked differences were also noted between nations (Turkey [67.9%] > United Kingdom [59.4%] > Italy [40.0%] > France [33.8%] > Spain [25.7%] > Germany [14.3%]; data not shown).
- Substantial increases in resistance were detected among Enterobacteriaceae, especially for *Klebsiella* spp. (ceftazidime [10.2-17.1%], levofloxacin [2.4-12.6%], amikacin [1.0-5.4%]), *E. coli* (ceftriaxone [1.1-7.2%], levofloxacin [4.0-17.9%]), and for *Enterobacter* spp. (ceftazidime [21.9-30.7%], levofloxacin [7.1-17.0%]; Table 2).
- ESBL-phenotype rates for *Klebsiella* spp. have more than doubled (16.0 to 30.7%) since the start of the SENTRY Program and are also of concern among *E. coli* (6.8 to 10.4%) and *Enterobacter* spp. (9.4 to 12.6%; Tables 2 and 3).
- Carbapenem-resistant isolates are sporadically detected among *Klebsiella* spp. and *Enterobacter* spp., usually caused by the presence of metallo-carbapenemases (VIM-1 enzymes; Italy, Greece and Turkey).
- Resistance emergence was most notable among *Acinetobacter* spp., where increases were observed in all sampling periods for imipenem (range, 16.4 to 43.9%), ceftazidime (26.7 to 46.8%), levofloxacin (45.2 to 68.3%) and amikacin (45.2 to 68.3%; Table 2).
- Modest increases in resistances were also detected among *P. aeruginosa*, especially with imipenem (range 13.4 to 16.1%) and levofloxacin (21.2 to 28.6%; Table 2).

Table 1. Changes occurring in the ranking of common hospital-acquired pneumonia pathogens in Europe, Turkey and Israel (SENTRY Program; 1997 - 2006).

Overall ranking of pathogens (total tested; %)	Ranking of species/groups by designated intervals (no tested) 1997-1999	2000-2002	2004-2006
1 *S. aureus* (2,442; 22.7)	2 (526)	1 (1,240)	1 (676)
2. *P. aeruginosa* (2,367; 22.0)	1 (572)	2 (1,235)	2 (560)
3. *Klebsiella* spp. (952; 8.8)	3 (206)	3 (469)	4 (277)
4. *E. coli* (846; 7.8)	5 (177)	4 (390)	3 (279)
5. *Enterobacter* spp. (745; 6.9)	4 (196)	5 (372)	5 (177)
6. *Acinetobacter* spp. (566; 5.3)	6 (135)	6 (292)	6 (139)
7. *Serratia* spp. (309; 2.9)	7 (91)	7 (134)	7-8 (84)
8. *S. maltophilia* (284; 2.6)	8 (76)	8 (124)	7-8 (84)

Table 2. Resistance (R)[a] profiles among key pathogens causing nosocomial pneumonia from patients hospitalized in Europe, Turkey and Israel (1997 - 2006).

Organism (no. tested/ antimicrobial agent)	1997-1999 MIC$_{50}$	% R	2000-2002 MIC$_{50}$	% R	2004-2006 MIC$_{50}$	% R
S. aureus (2,442)	(526)		(1,240)		(676)	
Oxacillin	0.5	37.3	0.5	39.6	0.5	38.3
Erythromycin	0.5	43.3	0.5	42.3	0.25	38.3
Clindamycin	0.12	34.4	≤0.06	25.7	0.12	20.4
Gentamicin	≤2	25.7	≤2	23.9	≤2	14.3
Ciprofloxacin	0.25	40.1	0.5	40.6	0.5	44.0
Linezolid	2	0.0	2	0.0	2	0.0
Vancomycin	1	0.0	1	0.0	1	0.0
P. aeruginosa (2,367)	(572)		(1,235)		(560)	
Ceftazidime	2	15.2	4	21.1	4	19.3
Cefepime	4	9.4	4	12.6	4	10.9
Piperacillin/tazobactam	4	13.6	8	17.9	8	20.5
Imipenem	1	15.9	1	13.4	1	16.1
Amikacin	4	8.7	4	8.2	4	7.5
Levofloxacin	≤0.5	21.2	1	25.1	1	28.6
Klebsiella spp. (952)	(206)		(469)		(277)	
Ceftriaxone	≤0.25	7.8 (16.0)[b]	≤0.25	7.0 (21.3)[b]	≤0.25	16.2 (30.7)[b]
Ceftazidime	≤1	10.2 (13.6)[b]	≤1	12.4 (19.4)[b]	≤1	17.0 (27.1)[b]
Cefepime	≤0.12	4.4	≤0.12	3.6	≤0.12	8.7
Piperacillin/tazobactam	2	5.8	2	9.4	4	16.6
Imipenem	0.25	0.0	≤0.12	0.0	≤0.12	0.0
Amikacin	2	1.0	1	2.6	2	5.4
Levofloxacin	≤0.5	2.4	≤0.5	2.3	≤0.5	12.6
E. coli (846)	(177)		(390)		(279)	
Ampicillin	>16	52.5	>16	52.6	>16	58.1
Ceftriaxone	≤0.25	1.1 (4.5)[b]	≤0.25	2.6 (5.4)[b]	≤0.25	7.2 (9.7)[b]
Ceftazidime	≤1	1.7 (6.8)[b]	≤1	3.1 (8.2)[b]	≤1	3.6 (9.7)[b]
Cefepime	≤0.12	1.7	≤0.12	2.1	≤0.12	3.9
Piperacillin/tazobactam	1	1.1	2	4.4	2	6.1
Imipenem	0.25	0.0	≤0.12	0.0	0.25	0.0
Amikacin	2	0.0	2	0.5	2	0.4
Levofloxacin	≤0.5	4.0	≤0.5	7.4	≤0.5	17.9
Enterobacter spp. (745)	(196)		(372)		(177)	
Ceftazidime	≤1	21.9	≤1	24.5	≤1	30.7
Cefepime	≤0.12	2.0 (9.7)[c]	≤0.12	0.3 (9.4)[c]	≤0.12	1.7 (12.6)[c]
Piperacillin/tazobactam	2	5.1	2	10.2	4	10.8
Imipenem	0.5	0.0	0.5	0.0	0.5	0.6[d]
Amikacin	2	2.6	2	1.3	2	1.7
Levofloxacin	≤0.5	7.1	≤0.5	7.8	≤0.5	17.0
Acinetobacter spp. (566)	(135)		(292)		(139)	
Ampicillin/sulbactam	-	-	-	-	16	47.5
Ceftazidime	16	37.8	>16	59.6	>16	69.1
Cefepime	8	26.7	16	45.2	16	46.8
Piperacillin/tazobactam	32	42.2	>64	58.1	>64	69.1
Imipenem	1	25.9	1	16.4	4	43.9
Amikacin	32	45.9	>32	53.1	>32	62.6
Levofloxacin	4	45.2	>4	51.7	>4	68.3
Serratia spp. (309)	(91)		(134)		(84)	
Ceftriaxone	≤0.25	6.6	≤0.25	6.7	≤0.25	2.4
Ceftazidime	≤1	3.3	≤1	4.5	≤1	1.2
Cefepime	≤0.12	0.0	≤0.12	2.2	≤0.12	1.2
Piperacillin/tazobactam	1	4.4	2	2.2	2	4.8
Imipenem	0.5	0.0	0.5	0.0	0.5	0.0
Amikacin	2	2.2	2	7.5	2	1.2
Levofloxacin	≤0.5	1.1	0.12	6.0	≤0.5	1.2

a. Percent resistant was based upon CLSI recommended breakpoints (M100-S17); - = not tested.
b. ESBL rates based upon CLSI recommendations (M100-S17) with MIC values ≥2 mg/L.
c. ESBL rates based upon cefepime MIC values ≥4 mg/L.
d. Documented metallo-ß-lactamase (VIM-1).

Table 3. Longitudinal variability in the frequency of ESBL phenotypes among *E. coli*, *Klebsiella* spp. and *Enterobacter* spp. in Europe, Turkey and Israel (1997 - 2006).

Organism/antimicrobial agent	% ESBL phenotype by year[a] 1997-1999	2000-2002	2004-2006
E. coli (no. tested)	(177)	(390)	(279)
Aztreonam	5.6	7.4	10.4
Ceftazidime	6.8	8.2	9.7
Ceftriaxone	4.5	5.4	9.7
Klebsiella spp. (no. tested)	(206)	(469)	(277)
Aztreonam	16.0	21.5	30.7
Ceftazidime	13.6	19.4	27.1
Ceftriaxone	16.0	21.3	30.7
Enterobacter spp. (no. tested)	(196)	(372)	(177)
Cefepime	9.7[b]	9.4[b]	12.6[b]

a. ESBL rates based upon CLSI recommendations (M100-S17) with MIC values ≥2 mg/L.
b. ESBL rates based upon cefepime MIC values ≥4 mg/L.

CONCLUSIONS

- The SENTRY Program has documented changing susceptibility profiles among pneumonia pathogens within European medical centers for 10 years.
- During this monitored interval, changes have been noted with declining susceptibilities among widely used classes including the cephalosporins (Enterobacteriaceae), carbapenems (*P. aeruginosa*), and fluoroquinolones (Enterobacteriaceae and *P. aeruginosa*).
- Marked declines in susceptibilities to all tested agents were noted with *Acinetobacter* spp., especially so for carbapenems.
- Changing patient demographics, antimicrobial usage and recognition of resistance genotypes with highly mobile genetic elements (class 1 integrons) within hospital environments have altered antibiograms, resulting in continued resistance emergence among the cited pathogens.
- Longitudinal comparisons of susceptibility data are critical in the development of good prescribing practices and in identifying appropriate interventions for infection control and public health policy efforts.

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