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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370,
fax 319.665.3371
ronald-jones@jmilabs.com

Changing Patterns of Antimicrobial Resistances Among Bacterial Isolates Recovered from European Patients Hospitalized with Pneumonia: Report from the SENTRY Antimicrobial Surveillance Program (1998 - 2004)

T FRITSCHE, H SADER, D BIEDENBACH, J STREIT, R JONES
JMI Laboratories, North Liberty, IA, USA

SENTRY ANTIMICROBIAL SURVEILLANCE

ABSTRACT

Objectives: To characterize changes in the frequency of occurrence of bacterial pathogens responsible for pneumonia in hospitalized patients in Europe for the years 1998-2004 and examine select antimicrobial susceptibilities (S) for predominant pathogens. The emergence of resistance (R) among pathogens responsible for pneumonia has resulted in changes to empiric therapy, with increasing reliance upon third- and fourth-generation cephalosporins, beta-lactam/beta-lactamase inhibitor combinations, carbapenems and fluoroquinolones.
Methods: Participating European medical centres (10-31/year) in the SENTRY Program referred 50 consecutive, non-duplicate pathogens (8,419 isolates) from lower respiratory tract sites determined to be significant by local criteria as the probable cause of pneumonia. All identified isolates were tested for S by the broth microdilution method [NCCLS M7-A6, 2003] and results interpreted using CLSI [M100-S15; 2005] breakpoint criteria.
Results: Rank order of principle pathogens and changes in select S are in the Table:

Species and Frequency (1998/2004 %)	Antimicrobial Agent	$MIC_{50/90}$ in mg/L (%S) 1998	2004
P. aeruginosa (PA; 22.3/20.5)	Ceftazidime (CAZ)	2/>16(78.8)	4/>16 (74.2)
	Imipenem (IMI)	2/>8 (74.0)	1/>8 (70.0)
	Ciprofloxacin (CIP)	0.25/>2 (78.8)	0.25/>2 (63.1)
S. aureus (SA; 19.9/23.0)	Oxacillin (OX)	0.5/>2 (62.3)	0.5/>2 (59.3)
	Gentamicin	0.5/>8 (75.0)	<=2/>8 (82.3)
	Ciprofloxacin	0.25/>2 (65.0)	1/>2 (51.4)
Enterobacter spp. (ESP; 9.2/6.3)	Ceftazidime	0.5/>16 (73.3)	<=1/>16 (65.7)
	Ciprofloxacin	<=0.03/>2 (84.2)	<=0.03/>2 (88.1)
Klebsiella spp. (KSP; 8.2/9.8)	Ceftriaxone (CRO)	<=0.25/32 (85.2)	<=0.25/>32 (78.8)
	Ciprofloxacin	<=0.03/0.25 (96.3)	<=0.03/>2 (79.8)
E. coli (EC; 7.4/9.7)	Ceftriaxone	<=0.25/0.5 (96.9)	<=0.25/<=0.25 (92.2)
	Ciprofloxacin	<=0.03/0.12 (96.9)	<=0.03/>2 (79.6)
S. pneumoniae (SPN; 5.3/4.9)	Penicillin (PEN)	<=0.03/2 (72.9)	<=0.03/2 (69.2)
	Erythromycin (ERY)	<=0.25/>8 (71.4)	<=0.25/>8 (71.2)

The composition of the six top-ranked pathogens did not change over the study interval; the rank order did, however, with PA, SA, ESP, KSP and EC being predominant in 1998 and SA, PA, KSP, EC and ESP in 2004. Decreasing S were apparent with most key organism/antimicrobial combinations, including OX and CIP among SA; CRO, CAZ and CIP among Enterobacteriaceae; and CAZ, IMI and CIP among PA. PEN and ERY S among SPN decreased until 2000 (66.7 and 49.0%, respectively), increased significantly in 2001 (84.9% S), and returned to near-1998 levels in 2004. ESBL-phenotypes (CRO or CAZ or aztreonam MIC >= 2mg/L) remained essentially unchanged among EC between 1998 and 2004 (8.2% and 8.7%, respectively), whereas among KSP increases were more substantial (16.7% and 26.9%). Metallo-beta-lactamase-producing PA were identified during the study from Italy (2000-2001; 10 isolates, clonally-related; VIM-1), Germany (2002; one isolate; GIM-1) and Greece (2004; two isolates; VIM).
Conclusions: Although temporary R declines were seen among some European pneumonia pathogens, all showed increasing R to most class agents during the study period. The increase in ESBL among Enterobacteriaceae, and R among PA to most agents except polymyxin B, are especially worrisome. Continued longitudinal comparisons of emerging pathogens and changing susceptibility profiles are critical elements in guiding empiric therapies and epidemiologic interventions.

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 the pathogen occurrence and the susceptibility profiles among species producing infections of the bloodstream, respiratory tract, skin and soft tissue, urinary tract and other sites since 1997. In this investigation, we review data from Europe, Turkey and Israel during the years of 1998 - 2004 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 8,419 non-duplicate consecutive clinical isolates were submitted from 10-31 medical centers located in Europe, Turkey and Israel as part of the international SENTRY Program (1998 - 2004). 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 all surveyed years was: *P. aeruginosa* (1,889; 22.4%); *S. aureus* (1,828; 21.7%); *Klebsiella* spp. (735; 8.7%); *Escherichia coli* (620; 7.4%); *Enterobacter* spp. (589; 7.0%); *Streptococcus pneumoniae* (467; 5.5%); *Haemophilus influenzae* (459; 5.4%); *Acinetobacter* spp . (441; 5.2%); *Stenotrophomonas maltophilia* (217; 2.6%); *Serratia marcescens* (203; 2.4%); and others (971; 11.5%).

Susceptibility Test Methods. All strains were tested by the reference broth microdilution method in Mueller-Hinton broth (with 5% lysed horse blood added for testing of streptococci and Haemophilus Test Medium for testing of *H. influenzae*) 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 CLSI criteria. Enterobacteriaceae with elevated MICs (≥ 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 *E. coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853, *H. influenzae* ATCC 49247, *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619 and *Enterococcus faecalis* ATCC 29212; all QC results were within CLSI specified ranges.

RESULTS

- The composition of the six top-ranked pathogens did not change over the study interval; the rank order did, however, with *P. aeruginosa, S. aureus, Enterobacter* spp., *Klebsiella* spp. and *E. coli* being predominant in 1998 and *S. aureus, P. aeruginosa, Klebsiella* spp., *E. coli* and *Enterobacter* spp. in 2004 (Table 1).
- Increasing resistances were apparent with most key organism/antimicrobial combinations, including oxacillin and ciprofloxacin among *S. aureus*; ceftriaxone, ceftazidime and ciprofloxacin among Enterobacteriaceae; and ceftazidime, cefepime and ciprofloxacin among *P. aeruginosa* (Table 1).
- Penicillin and erythromycin resistances among *S. pneumoniae* increased until 2000 (17.6 and 51.0%, respectively), decreased significantly in 2002 (to 10.1 and 23.9%), and returned to near-1998 levels in 2004 (13.5 and 28.8%; Table 2).
- Over the sampled years MLS_B-resistance was higher for strains exhibiting a ribosomal target modification phenotype (57 to 88% and 53 to 82% of *S. aureus* and *S. pneumoniae*, respectively; Table 3).
- ESBL-phenotypes remained essentially unchanged among *E. coli* between 1998 and 2004 (8.2 and 8.7%, respectively), whereas ESBL-like isolates among *Klebsiella* spp. increased substantially (16.7% and 26.9%; Table 4).
- Metallo-ß-lactamase-producing *P. aeruginosa* were identified during the study from Italy (2000 - 2001; 10 isolates, clonally-related; VIM-1), Germany (2002; one isolate; GIM-1) and Greece (2004; two isolates; VIM).
- Resistances among *Acinetobacter* spp. were especially notable to all ß-lactam agents (including carbapenems), aminoglycosides and fluoroquinolones (Table 2).
- The large majority of *P. aeruginosa* and *Acinetobacter* spp. remained susceptible to polymyxin B (98.2 and 95.5%, respectively) with the vast majority of MIC values at ≤ 2 mg/L; data not shown.

Table 1. Longitudinal changes occurring in the ranking of common pathogens in patients hospitalized with pneumonia in Europe, Turkey and Israel (1998 - 2004).

Organism (total tested; %)	Prevalence (%) of ranked species/groups by year (no tested): 1998	1999	2000	2001	2002	2004
	(1,309)	(536)	(1,377)	(2,077)	(2,064)	(1,056)
P. aeruginosa (1,889; 22.4)	22.3	26.9	26.6	22.3	19.7	20.5
S. aureus (1,828; 21.7)	19.8	15.7	17.4	22.3	26.0	23.0
Klebsiella spp. (735; 8.7)	8.2	10.0	10.2	8.8	7.0	9.8
E. coli (620; 7.4)	7.4	5.6	7.0	7.3	6.9	9.7
Enterobacter spp. (589; 7.0)	9.2	5.6	6.6	6.5	7.0	6.3
S. pneumoniae (467; 5.5)	5.3	5.6	3.7	6.0	6.7	4.9
H. influenzae (459; 5.4)	4.3	5.4	4.5	5.1	7.8	4.0
Acinetobacter spp. (441; 5.2)	4.6	7.8	8.5	4.3	4.1	4.4
S. maltophilia (217; 2.6)	2.9	4.1	2.5	2.1	2.2	3.1
S. marcescens (203; 2.4)	3.2	2.2	3.3	1.8	1.8	2.6

Table 2. Resistance profiles among key pathogens causing nosocomial pneumonia from patients hospitalized in Europe, Turkey and Israel (1998 - 2004).

Organism (no. tested/ antimicrobial agent	MIC_{50} (mg/L)/%Resistant[a,b] 1998	2000	2002	2004
P. aeruginosa (1,889)				
Ceftazidime	2/17.5	4/25.1	2/17.2	4/19.4
Cefepime	2/7.2	4/15.6	4/8.4	4/13.8
Piperacillin/tazobactam	4/13.7	8/18.6	8/17.7	8/24.0
Imipenem	2/17.1	1/17.5	1/11.8	1/17.1
Amikacin	4/9.2	4/11.5	4/5.4	4/9.7
Ciprofloxacin	0.25/17.8	≤0.25/29.5	0.25/23.3	0.25/31.3
S. aureus (1,828)				
Oxacillin	0.5/37.7	1/47.9	0.5/35.1	0.5/40.7
Erythromycin	0.5/43.5	1/48.7	0.5/36.8	0.25/39.1
Clindamycin	0.12/31.5	0.12/32.5	0.12/20.9	0.12/23.9
Gentamicin	0.5/24.2	≤1/39.2	≤2/18.3	≤2/17.7
Ciprofloxacin	0.25/33.5	1/47.9	0.5/36.4	1/48.1
Quinupristin/dalfopristin	0.25/0.4	0.5/1.2	0.25/0.7	0.5/0.4
Vancomycin	1/0.0	1/0.0	1/0.0	1/0.0
Klebsiella spp. (735)				
Ceftriaxone	≤0.25/8.3	≤0.25/9.2	≤0.25/5.6	≤0.25/12.5
Ceftazidime	≤0.12/9.3	≤0.12/19.9	≤1/6.3	≤1/15.4
Cefepime	≤0.12/5.6	≤0.12/3.5	≤0.12/4.2	≤0.12/7.7
Piperacillin/tazobactam	2/5.6	2/12.8	2/7.6	4/20.2
Imipenem	0.25/0.0	0.12/0.0	0.12/0.0	≤0.12/0.0
Ciprofloxacin	≤0.016/2.8	≤0.25/5.7	≤0.03/5.6	≤0.03/14.4
Gentamicin	0.5/14.8	≤1/12.8	≤2/7.7	≤2/15.4
E. coli (620)				
Ampicillin	>16/56.7	16/49.5	8/48.6	>16/54.5
Ceftriaxone	≤0.25/2.1	≤0.25/2.1	≤0.25/3.5	≤0.25/6.8
Ceftazidime	≤0.12/3.1	≤0.12/1.0	≤1/3.5	≤1/3.9
Cefepime	≤0.12/3.1	≤0.12/12.1	≤0.12/2.1	≤0.12/3.9
Piperacillin/tazobactam	2/1.0	1/3.1	2/2.8	2/5.8
Imipenem	0.12/0.0	0.12/0.0	0.12/0.0	≤0.12/0.0
Ciprofloxacin	≤0.016/3.1	≤0.25/6.2	≤0.03/11.3	≤0.03/20.4
Gentamicin	1/7.2	≤1/7.2	≤2/4.9	≤2/8.7
Enterobacter spp. (589)				
Ceftazidime	0.5/25.0	0.5/20.9	≤1/26.2	≤1/22.4
Cefepime	≤0.12/1.7	≤0.12/1.1	≤0.12/0.0	≤0.12/0.0
Piperacillin/tazobactam	2/4.2	2/7.7	4/11.8	4/7.5
Imipenem	0.5/0.0	0.5/0.0	0.5/0.0	0.25/1.5
Ciprofloxacin	≤0.016/12.5	≤0.25/7.7	≤0.03/7.6	≤0.03/10.4
Gentamicin	0.5/2.5	≤1/6.6	≤2/4.1	≤2/9.0
S. pneumoniae (467)				
Penicillin	≤0.03/15.7	0.03/17.6	≤0.016/10.1	≤0.016/13.5
Cefotaxime[c]	0.016/4.3	-/-	-/-	-/-
Ceftriaxone[c]	-/-	≤0.25-3.9	≤0.25/2.9	≤0.25/1.9
Erythromycin	≤0.25/27.1	2/51.0	≤0.06/23.9	≤0.06/28.8
Clindamycin	≤0.06/21.4	≤0.06/27.5	≤0.06/19.6	≤0.06/23.1
Levofloxacin	≤0.5/0.0	1/0.0	1/1.4	1/0.0
Vancomycin	0.5/0.0	0.5/0.0	0.25/0.0	0.25/0.0
Acinetobacter spp. (441)				
Ampicillin/sulbactam	-/-	-/-	-/-	32/53.2
Ceftazidime	8/33.3	>16/65.3	>16/54.1	>16/76.6
Cefepime	4/16.7	16/50.0	16/44.7	>16/57.4
Piperacillin/tazobactam	16/28.3	>64/63.6	>64/52.4	>64/78.7
Imipenem	0.5/18.3	1/11.0	1/15.3	8/48.9
Amikacin	4/35.0	>32/61.9	16/45.9	>32/57.4
Ciprofloxacin	>2/56.7	>2/78.0	>4/64.7	>4/87.2

a. Percent resistant was based upon CLSI recommended breakpoints (M100-S15).
b. - = not tested.
c. Non-meningitis breakpoints (CLSI, M100-S15).

Table 3. Longitudinal variability of the phenotypic resistance rates to MLS_B antimicrobial agents among *S. aureus* and *S. pneumoniae* in Europe, Turkey and Israel (1998 - 2004).

Year (no. tested)	% *S. aureus*/*S. pneumoniae* strains resistant to erythromycin 1998 (113/19)	1999 (34/11)	2000 (117/26)	2001 (211/19)	2002 (196/33)	2004 (95/15)
Erythromycin-resistant/ clindamycin-susceptible (efflux phenotype)[a]	29/21	12/18	33/46	39/47	43/18	40/20
Erythromycin-resistant/ clindamycin-resistant (ermB phenotype)	71/79	88/82	67/54	61/53	57/82	60/80

a. Inducible resistance to clindamycin was not determined.

Table 4. Longitudinal variability in the frequency of ESBL phenotypes among *E. coli* and *Klebsiella* spp. in Europe, Turkey and Israel (1998 - 2004).

Organism/antimicrobial agent	% ESBL phenotype by year[a] 1998	1999	2000	2001	2002	2004
E. coli (no. tested)	(97)	(30)	(97)	(151)	(142)	(103)
Aztreonam	5.2	3.3	10.3	6.6	6.3	7.8
Ceftazidime	8.2	3.3	9.3	8.6	7.1	8.7
Ceftriaxone	6.2	0.0	5.2	6.6	4.2	7.8
Klebsiella spp. (no. tested)	(108)	(54)	(141)	(184)	(144)	(104)
Aztreonam	14.8	25.9	29.1	23.4	11.8	26.9
Ceftazidime	12.0	22.2	24.8	21.7	11.2	23.1
Ceftriaxone	16.7	22.2	27.0	23.4	13.2	26.9

a. ESBL rates were based upon CLSI recommendations (M100-S15) with MIC values ≥ 2 mg/L for ceftazidime or ceftriaxone or aztreonam.

CONCLUSIONS

- Although short-term declines in resistance rates were documented among some pneumonia pathogens (*S. pneumoniae*) from Europe, Turkey and Israel, all major species showed increasing resistance to most class agents during the study period (1998 - 2004).
- The increase in ESBL-producing strains among Enterobacteriaceae, and multidrug resistance among *P. aeruginosa* and *Acinetobacter* spp. (except for polymyxin B), were especially worrisome; elevated rates in many locations appear due to epidemic or endemic clones that can persist in the hospital environment for extended periods of time.
- Continued longitudinal comparisons of emerging pathogens and changing susceptibility profiles are critical elements in guiding future empiric therapies and epidemiologic interventions.

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