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Susceptibility Analysis of Gastroenteritis and Beta-Haemolytic Streptococcal Pathogens Collected During a Decade of SENTRY Antimicrobial Surveillance Program Monitoring in Europe (1997-2006)

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SENTRY ANTIMICROBIAL SURVEILLANCE

AMENDED ABSTRACT

Objectives: To determine the antimicrobial susceptibility (S) of ß-haemolytic streptococci (BHS) and gastroenteritis (GI) pathogens in Europe (EUR) over 10 years. Infections caused by BHS can be relatively mild or severe and invasive due to suppurative sequelae. Although infections caused by GI pathogens are mostly self-limiting (diarrhea), invasive disease such as bacteremia due to *Salmonella* spp. (SAL) or *Aeromonas* spp. (ASP) can be more common among the very young, elderly and immunocompromised persons.

Methods: During 1997-2006, the following pathogens (no.) were collected from SENTRY Program (EUR) objectives and tested for S: ASP (157), *Y. enterocolitica* (YET; 52), *Shigella* spp. (SHIG; 283), SAL (1,526) and BHS (2,553). CLSI broth microdilution test methods and interpretive criteria were utilized with appropriate concurrent quality assurance practices.

Results: ASP/YET isolates were resistant (R) to ampicillin (AMP) but S to penicillin with a beta-lactamase inhibitor (85/>99%), cefuroxime (CXM; 80/95%) and ceftriaxone (CRO), cefepime (FEP), and gentamicin (GENT) at >95%. Tetracycline (TET) and trim/sulfa (T/S) R in ASP was 15%, and nalidixic acid (NA)-R was 28% associated with a high ciprofloxacin (CIP) MIC_{90} to 1 mg/L compared to the wildtype population (≤0.03 mg/L). The AMP-S of SHIG in 2001 (63%) was only 23% in 2003 influenced by Russian epidemic isolates (>95% AMP-R). R to NA was 0% in 2001 but 4.3% in 2003; and TET-R increased >7% during the sampled interval. S among SAL and BHS were compared during the first and the second five year samples. There was a decline in S among SAL during the last five years with AMP-R (24.7%), NA-R (17.4%) and TET-R (20.3%). A significant increase in ESBL phenotypes (2002-2006) followed a clonal *S. typhimurium* (CTX-M-5) outbreak in Russia. We noted a 5-7% decline in S to erythromycin (ERY) among Groups A and B BHS during the second sampled period. ERY-R rates for BHS varied between nations with highest rate in Italy (37%). TET-S was stable between years, but varied among serogroups (A and C/70-80%, G/50% and B/20%). All BHS were S to linezolid, vancomycin, quin/dalfo and were very S to levofloxacin and penicillin.

	Year (no.)			
	1997-2001(664)		2002-2006 (862)	
Salmonella spp./Antimicrobial	%S[a]	%R[a]	%S[a]	%R[a]
Ampicillin	77.4	21.8	74.6	24.7
Cefuroxime	69.6	0.2	53.1	2.7
Ceftriaxone	100.0	0.0 (0.2)[b]	98.1	1.9 (2.7)[b]
Cefepime	100.0	0.0	98.4	0.3
Nalidixic Acid	85.4	14.6	82.6	17.4
Ciprofloxacin	99.9	0.1 (13.7)[c]	99.7	0.1 (16.1)[c]
Tetracycline	76.8	22.0	78.7	20.3
Trim/Sulfa	93.8	6.2	93.6	6.4
Gentamicin	98.3	1.4	97.1	1.3

a. Criteria as published by the CLSI (M100-S16).
b. % of strains with ESBL screen-positive (MIC ≥2 mg/L for CRO).
c. % strains with elevated CIP MIC (≥0.12 mg/L).

Conclusions: GI pathogens and BHS contribute a significant amount of morbidity in EUR and worldwide. Antimicrobial surveillance of these species in EUR shows a trend toward declining S to several drug classes and continued monitoring is necessary to track the R profiles of these important bacterial species.

INTRODUCTION

The SENTRY Antimicrobial Surveillance Program has monitored ß-haemolytic streptococci from various sources of infection, mainly bloodstream and skin and soft tissue infections, and gastroenteritis pathogens from stool and bloodstream cultures during a ten year period (1997-2006). Combined, these bacterial pathogens are among leading causes of morbidity and mortality worldwide. This study documents the antimicrobial susceptibility of these pathogens isolated from medical centers in Europe, Israel and Turkey.

ß-haemolytic streptococci are causative agents of diverse acute and chronic infectious diseases and must be monitored for antimicrobial susceptibility to determine if current prescribing practices are appropriate for a particular patient population, medical center or geographic region. Species within the genus groups of *Salmonella*, *Shigella*, *Aeromonas* and *Yersinia* are mainly considered to be pathogens associated with gastroenteritis. Although most causes of gastroenteritis are self-limited and do not require antimicrobial treatment, some at-risk patients and those with extraintestinal infections should be treated with appropriate agents. Antimicrobial susceptibility may differ from one geographic region to another and can also differ markedly within a genus group. For example, *Salmonella enterica* serovar Typhimurium definitive type 104 (DT104) is a multidrug-resistant pathogen that has become prevalent in Europe and North America but is less commonly isolated in other regions. In this study, we evaluated trends in prevalence and susceptibility rates for ß-haemolytic streptococci and gastroenteritis pathogens for the European region as part of the SENTRY Program.

MATERIALS AND METHODS

Forty-one medical centers in the European Union, Israel, Turkey and Russia collected 2,553 patient isolates of ß-haemolytic streptococci as part of the SENTRY Antimicrobial Surveillance Program from infection sites including bloodstream, skin and soft tissue and upper-respiratory tract since the inception of the program in 1997. Pathogens associated with gastroenteritis were collected mainly from bloodstream infections in this region with an increased emphasis on isolate collection during 2001 and 2003 from both bloodstream and stool cultures resulting in a total of 2,018 strains from thirty-eight medical centers. Isolates were forwarded to a central laboratory for identification confirmation and antimicrobial susceptibility testing using validated broth microdilution panels (TREK Diagnostics, OH, USA) according to the CLSI methods and interpretive criteria (M7-A7, 2006; M100-S17, 2007). *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and *Streptococcus pneumoniae* ATCC 49619 were concurrently tested for quality assurance.

RESULTS

- The resistance rates to ampicillin were similar for *Salmonella* spp. from stool (23.7%) and blood culture (27.5%) isolates collected in European medical centers (Table 1). Stool culture isolates were, however, more resistant to ampicillin in Israel (26.9%), Turkey (19.0%) and Russia (21.3%) compared to blood culture isolates (6.9-11.1%).
- Ceftriaxone, ciprofloxacin and trimethoprim/sulfamethoxazole had excellent activity (>92%, susceptible) against *Salmonella* spp. isolates from all monitored countries. Strains with elevated nalidixic acid MIC values (≥16 mg/L) were common in Europe, Israel and Turkey (7.2-36.4%). ESBL phenotypes were rare with one ongoing outbreak of CTX-M5 isolates noted in Russia (Table 1).
- Table 2 shows that over 50% of *Shigella* spp. isolated in European countries and 93.4% in Turkey were susceptible to ampicillin with much lower susceptibility rates noted in Israel and Russia (4.7-11.8%). All strains remained susceptible to ciprofloxacin while resistance to trimethoprim/sulfamethoxazole was high (63.8 to 100.0%).
- Among *Aeromonas* spp. (Table 2), resistance to piperacillin (7.0%) and pipercillin/tazobactam (13.9%) was much lower than to ticarcillin (83.7%) and ticarcillin/clavulanate (44.2%). Other tested ß-lactams, aminoglycosides and fluoroquinolones had good activity against this group (>95% susceptibility). All tested agents showed activity (>90%) against *Y. enterocolitica* except for ampicillin and amoxicillin/clavulanate (Table 2).
- Table 4 shows that all strains of ß-haemolytic streptococci were susceptible to linezolid, vancomycin and quinupristin/dalfopristin. Few strains were non-susceptible to chloramphenicol, levofloxacin or penicillin.

Table 1. Susceptibility percentages of *Salmonella* spp. isolated from blood and stool cultures collected during the SENTRY Antimicrobial Surveillance Program in Europe, Israel, Turkey and Russia (1997-2006).

	Blood		Stool	
Country/Antimicrobial agent	% Susceptible[a]	% Resistant[a]	% Susceptible[a]	% Resistant[a]
European Union[b]	408 strains		732 strains	
Ampicillin	71.6	27.5	75.9	23.7
Ceftriaxone	100.0	0.0 (0.5)[c]	99.9	0.1 (0.1)
Ciprofloxacin	99.9	0.0 (19.9)[d]	99.5	0.2 (18.9)
Trimethoprim/sulfamethoxazole	92.2	7.8	94.2	5.8
Israel	22 strains		26 strains	
Ampicillin	95.2	4.8	73.1	26.9
Ceftriaxone	100.0	0.0 (0.0)	100.0	0.0 (0.0)
Ciprofloxacin	100.0	0.0 (36.4)	96.2	3.8 (19.2)
Trimethoprim/sulfamethoxazole	95.5	4.5	92.3	7.7
Turkey	29 strains		84 strains	
Ampicillin	93.1	6.9	81.0	19.0
Ceftriaxone	100.0	0.0 (0.0)	100.0	0.0 (0.0)
Ciprofloxacin	100.0	0.0 (13.8)	100.0	0.0 (7.2)
Trimethoprim/sulfamethoxazole	100.0	0.0	100.0	0.0
Russia	9 strains		216 strains	
Ampicillin	88.9	11.1	77.8	21.3
Ceftriaxone	100.0	0.0 (0.0)	93.1	6.9 (6.9)
Ciprofloxacin	100.0	0.0 (0.0)	100.0	0.0 (6.0)
Trimethoprim/sulfamethoxazole	100.0	0.0	92.3	7.7

a. Susceptibility percentages based upon the CLSI recommendations for routinely reported antimicrobial agents for *Salmonella* spp. only (CLSI, M100-S17).
b. Includes the following countries, Belgium, France, Germany, Greece, Ireland, Italy, Spain, Portugal, Poland, Sweden, Switzerland, the Netherlands and the United Kingdom.
c. Percentage in parentheses indicates isolates with an ESBL phenotype according to the CLSI criteria (M100-S17).
d. Percentage in parentheses indicates isolates with nalidixic acid MIC values ≥16 mg/L and possible first step QRDR mutations.

- Susceptibility to erythromycin decreased among Group A and B streptococci between 1997-2001 (85-89%) and 2002-2006 (80-83%). Among all ß-haemolytic streptococci, erythromycin resistance was highest in Italy (36.9%) and higher in France, Belgium and Spain (21-30%) compared to other monitored countries (data not shown).

Table 2. Antimicrobial susceptibility of *Shigella* spp. isolates from European medical centers during surveillance of gastroenteritis pathogens in 2001 and 2003 (SENTRY Antimicrobial Surveillance Program).

	MIC (mg/L)				
Country (no. tested)/ Antimicrobial agent	50%	90%	Range	% Susceptible[a]	% Resistant[a]
European Union (63)[b]					
Ampicillin	4	>16	≤2->16	54.0	44.4
Amoxicillin/clavulanate	8	16	≤2-16	-[c]	-
Cefuroxime	4	8	1-8	-	-
Ceftriaxone	≤0.25	≤0.25	≤0.25	-	-
Nalidixic acid	2	4	1->32	-	-
Ciprofloxacin	≤0.03	≤0.03	≤0.03-1	100.0	0.0
Tetracycline	>8	>8	≤4->8	-	-
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5->2	28.6	71.4
Israel (17)					
Ampicillin	>16	>16	≤2->16	11.8	88.2
Amoxicillin/clavulanate	8	16	≤2->16	-	-
Cefuroxime	4	8	1->16	-	-
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	-	-
Nalidixic acid	2	2	1->32	-	-
Ciprofloxacin	≤0.03	≤0.03	≤0.03-0.25	100.0	0.0
Tetracycline	≤4	>8	≤4->8	-	-
Trimethoprim/sulfamethoxazole	>2	>2	>2	0.0	100.0
Russia (127)					
Ampicillin	>16	>16	≤2->16	4.7	95.3
Amoxicillin/clavulanate	16	16	≤2->16	-	-
Cefuroxime	2	4	2-8	-	-
Ceftriaxone	≤0.25	≤0.25	≤0.25-1	-	-
Nalidixic acid	1	2	1-8	-	-
Ciprofloxacin	≤0.03	≤0.03	≤0.03	100.0	0.0
Tetracycline	>8	>8	≤2->8	-	-
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5->2	36.2	63.8
Turkey (76)					
Ampicillin	≤2	4	≤2->16	93.4	6.6
Amoxicillin/clavulanate	4	4	≤2-16	-	-
Cefuroxime	2	4	≤0.12->16	-	-
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	-	-
Nalidixic acid	2	2	1-4	-	-
Ciprofloxacin	≤0.03	≤0.03	≤0.03	100.0	0.0
Tetracycline	>8	>8	≤4->8	-	-
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5->2	19.7	80.3

a. Criteria as published by the CLSI (M100-S17).
b. Included the following countries: Belgium (6 strains), France (19), Germany (3), Ireland (1), Italy (6), Spain (19) and the United Kingdom (9).
c. - = susceptibility not to be routinely reported for *Shigella* spp.

Table 3. Antimicrobial susceptibility profiles of *Aeromonas* spp. and *Y. enterocolitica* collected from medical centers in Europe, Israel and Turkey as part of the SENTRY Program (1997-2006).

	MIC (mg/L)				
Organism (no. tested)	50%	90%	Range	% Susceptible[a]	% Resistant[a]
Aeromonas spp. (157)					
Piperacillin	≤4	32	≤8->64	84.7	7.0
Piperacillin/tazobactam	4	>64	≤0.5-64	65.6	13.9
Ticarcillin	>128	>128	≤16->128	4.8	83.7
Ticarcillin/clavulanate	64	>128	≤16->128	22.4	44.2
Ceftazidime	≤2	≤2	≤2->16	98.7	1.3
Cefepime	≤0.12	0.25	≤0.12->16	99.4	0.6
Aztreonam	≤0.12	0.25	≤0.12->16	98.7	1.3
Imipenem	≤0.5	2	≤0.5->8	95.5	2.5
Amikacin	≤4	8	0.5->32	99.4	0.6
Gentamicin	≤2	≤2	≤2->8	97.5	2.5
Tobramycin	1	4	≤0.12->16	94.9	3.8
Ciprofloxacin	≤0.25	0.5	≤0.25->4	97.5	1.2
Tetracycline	≤4	>8	≤4->8	77.7	15.9
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	85.3	14.7
Y. enterocolitica (52)					
Ampicillin	>16	>16	8->16	1.9	84.6
Amoxicillin/clavulanate	8	16	1->16	69.2	7.7
Piperacillin	≤8	≤8	≤8-32	98.0	0.0
Piperacillin/tazobactam	≤0.5	1	≤0.5-2	100.0	0.0
Cefoxitin	4	8	2->32	90.4	5.7
Ceftazidime	≤2	≤2	≤2	100.0	0.0
Cefepime	≤0.12	≤0.12	≤0.12-0.5	100.0	0.0
Aztreonam	0.5	1	≤0.12-2	100.0	0.0
Imipenem	≤0.5	≤0.5	≤0.5	100.0	0.0
Amikacin	≤4	≤4	≤4-8	100.0	0.0
Gentamicin	≤2	≤2	≤2	100.0	0.0
Tobramycin	1	1	0.5-2	100.0	0.0
Ciprofloxacin	≤0.25	≤0.25	≤0.25-0.5	100.0	0.0
Tetracycline	≤4	≤4	≤4->8	92.3	3.8
Trimethoprim/sulfamethoxazole	≤0.5	2	≤0.5->2	98.1	1.9

a. Criteria as published by the CLSI (M100-S17).

Table 4. Antimicrobial susceptibility profiles of 2,553 isolates of ß-haemolytic streptococci from Europe, Israel and Turkey during two sample periods: results from the SENTRY Antimicrobial Surveillance Program (1997-2006).

	1997-2001 (% Susceptible)[a]					2002-2006 (% Susceptible)[a]				
Antimicrobial agents	BSA	BSB	BSC	BSG	BSF	BSA	BSB	BSC	BSG	BSF
Penicillin	100.0	99.2	100.0	99.2	92.3	100.0	100.0	100.0	100.0	100.0
Erythromycin	85.3	89.1	90.1	79.2	92.3	80.1	82.6	90.2	84.7	60.0
Clindamycin	95.8	92.5	93.3	88.2	100.0	94.6	91.6	95.1	93.4	80.0
Levofloxacin	99.9	100.0	100.0	100.0	100.0	99.8	99.8	100.0	98.4	100.0
Tetracycline	73.4	21.4	68.3	48.3	84.6	83.8	20.4	70.7	48.9	60.0
Chloramphenicol	96.8	97.4	100.0	100.0	100.0	97.1	99.2	100.0	100.0	100.0
Quinupristin/dalfopristin	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Linezolid	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Vancomycin	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

a. Criteria as published by the CLSI (M100-S17).

CONCLUSIONS

- *Salmonella* spp. isolates collected from patient bloodstream infections in Europe were more resistant to ampicillin compared to isolates collected in Israel, Turkey and Russia.
- Although fluoroquinolone resistance remains very rare among gastroenteritis pathogens, high levels of nalidixic acid resistance among the *Salmonella* spp. isolates indicate pre-existing mutations in the QRDR.
- Significant resistance to ampicillin and trimethoprim/sulfamethoxazole was noted among *Shigella* spp. isolates in this study. In contrast, *Aeromonas* spp. and *Y. enterocolitica* were susceptible to many of the tested agents, including cephalosporins, aminoglycosides and fluoroquinolones.
- ß-haemolytic streptococci remain susceptible to many antimicrobial agents although significant variability in macrolide resistance was noted between countries.

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