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Susceptibility to Telithromycin in 1,011 *Streptococcus pyogenes* Isolates from 10 Central and Eastern European Countries

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Among 1,011 recently isolated *Streptococcus pyogenes* isolates from 10 Central and Eastern European centers, the MICs at which 50% of isolates are inhibited (MIC_{50}s) and the MIC_{90}s were as follows: for telithromycin, 0.03 and 0.06 μg/ml, respectively; for erythromycin, azithromycin, and clarithromycin, 0.06 to 0.125 and 1 to 8 μg/ml, respectively; and for clindamycin, 0.125 and 0.125 μg/ml, respectively. Erythromycin resistance occurred in 12.3% of strains. *Erm*(A) [subclass *erm*(TR)] was most commonly encountered (60.5%), followed by *mef*(A) (23.4%) and *erm*(B) (14.5%). At <0.5 μg/ml, telithromycin was active against 98.5% of the strains tested.

Streptococcus pyogenes strains continue to be penicillin susceptible, but erythromycin resistance has increasingly been reported. A recent Canadian study (10) has documented that 2.1% of *S. pyogenes* strains collected in 1997 were macrolide resistant. Significant rates of erythromycin resistance have been reported in many countries including Finland, Sweden, Spain, France, and Italy (1, 3, 6, 8, 11, 12, 16, 18, 20, 21, 24). In the United States, it has been assumed that the rate of erythromycin resistance is low (14, 15). However, a recent study has reported erythromycin resistance rates of 32% among isolates from specimens from patients with invasive disease and 9% among isolates from cultures of throat swab specimens isolated between 1994 and 1995 in the San Francisco, California, area (25).

For *S. pyogenes* isolates from most areas tested, macrolide resistance is mediated by the *mef*(A) gene (23), making the isolates resistant to 14- and 15-membered-ring macrolides but susceptible to 16-membered-ring macrolides and clindamycin. *Erm*(A) [subclass *erm*(TR)] has also been described (21); strains containing *erm*(A) are usually inducibly resistant to 14- and 15-membered-ring macrolides but are susceptible to 16-membered-ring macrolides and lincosamides. The *erm*(B) gene has also been described, with strains that contain this gene being resistant to macrolides and lincosamide (6, 10, 11, 16).

Telithromycin is a ketolide (9, 13, 19) with low MICs for erythromycin-susceptible and -resistant *S. pyogenes* strains except those carrying *erm*(B). To understand macrolide susceptibility in areas where high rates of drug-resistant pneumococci have been described, Central and Eastern Europe (2), we tested the activities of telithromycin, erythromycin, azithromycin, clarithromycin, and clindamycin against 1,011 isolates of *S. pyogenes*. Levofloxacin was tested as the representative fluoroquinolone.

Strains were consecutively obtained from clinical isolates recovered during 1999 and 2000 and were screened by the bacitracin disk method. Organisms were frozen at all collection sites except Warsaw (where swabs in Amies transport medium were used) and were transported on dry ice to Hershey Medical Center, where they were stored frozen in double-strength skim milk (Difco Laboratories, Detroit, Mich.) at −70°C until use. The identities of the organisms were confirmed by colonial morphology, bacitracin testing, beta-hemolysis, and, in some cases (e.g., Romanian urine isolates), serogrouping.

MICs were determined by the agar dilution methods used in our laboratory on Mueller-Hinton agar (BBL Microbiology Systems, Cockeysville, Md.) with 5% sheep blood (9, 19); the plates were incubated in air (5). The breakpoints were those approved by the National Committee for Clinical Laboratory Standards for *S. pneumoniae* (17) for all drugs except telithromycin, for which breakpoints of 0.5 and 2.0 μg/ml were used. Macrolide-resistant strains were tested by PCR for the presence of *erm*(B), *mef*(A), and *erm*(A) genes as described previously (21–23). Clindamycin MICs were not high for some erythromycin-resistant strains that were positive for the *erm*(B) or the *erm*(A) gene (4, 7, 23). These and all other erythromycin-resistant strains were screened for the presence of inducible resistance by double-disk diffusion (5).

Patient ages varied between <2 and >60 years, with the age group with the highest rate of infection being children ages 2 to 10 years in all countries except Romania (where most organisms were detected in those ages 11 to 20 years). Among all 1,011 *S. pyogenes* isolates tested, 826 (81.7%) were isolated from throat swab cultures, 119 (11.8%) were isolated from

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TABLE 1. MIC_{50}s and MIC_{90}s for the *S. pyogenes* tested by agar dilution

Country	MIC_{50}/MIC_{90} (μg/ml)						
	Penicillin G	Telithromycin	Erythromycin	Azithromycin	Clarithromycin	Clindamycin	Levofloxacin
Slovak Republic	0.016/0.016	0.06/0.5	0.125/8.0	0.25/8.0	0.06/8.0	0.125/0.25	0.5/2.0
Romania	≤0.008/0.016	0.03/0.06	0.06/0.125	0.125/0.25	0.06/0.125	0.125/0.125	1.0/1.0
Hungary	0.016/0.016	0.06/0.06	0.06/0.125	0.125/0.25	0.06/0.06	0.125/0.125	1.0/2.0
Lithunania	0.016/0.016	0.03/0.06	0.06/0.125	0.25/0.25	0.06/0.06	0.125/0.125	1.0/2.0
Slovenia	0.016/0.016	0.03/0.06	0.06/2.0	0.125/16.0	0.06/2.0	0.125/0.125	0.5/1.0
Czech Republic	0.016/0.016	0.06/0.125	0.125/0.125	0.125/0.25	0.06/0.125	0.125/0.125	1.0/2.0
Latvia	0.016/0.016	0.03/0.06	0.06/0.125	0.125/0.5	0.06/0.125	0.125/0.25	0.5/1.0
Bulgaria	0.016/0.016	0.03/0.06	0.06/2.0	0.25/8.0	0.06/1.0	0.125/0.25	0.5/1.0
Poland	≤0.008/0.016	0.03/0.06	0.06/2.0	0.125/8.0	0.03/1.0	0.125/0.125	0.5/1.0
Croatia	0.016/0.016	0.03/0.125	0.06/8.0	0.125/16.0	0.06/4.0	0.125/0.25	1.0/2.0
All strains	0.016/0.016	0.03/0.06	0.06/2.0	0.125/8.0	0.06/1.0	0.125/0.125	1.0/2.0

wounds or pus, and 32 (3.1%) were isolated from blood. In Romania 20 strains were urine isolates. No further information was available for those 20 strains. Isolates were predominantly recovered from throat swab cultures in each country except Lithuania, where *S. pyogenes* was recovered predominantly from pus and wounds.

Overall, the telithromycin MICs at which 50% of isolates are inhibited (MIC_{50}s) and MIC_{90}s were 0.03 and 0.06 μg/ml, respectively (Table 1). The MIC_{90}s for the other drugs tested were as follows: erythromycin, 2 μg/ml; azithromycin, 8 μg/ml; clarithromycin, 1 μg/ml; and clindamycin, 0.125 μg/ml. Macrolide MIC_{90}s were the highest for isolates from Croatia and the Slovak Republic: ≥4 μg/ml for erythromycin, clarithromycin, and azithromycin. All strains were penicillin G susceptible (MICs, ≤0.03 μg/ml). The levofloxacin MIC_{90} was 2 μg/ml.

The overall rates of susceptibility to telithromycin at 0.5 and 2 μg/ml were 98.5 and 98.9%, respectively (Table 2). For the macrolides and azalides, isolates from Hungary had the highest susceptibility rates (94.8%) and isolates from Croatia and Bulgaria had the lowest susceptibility rates (approximately 82%). All *S. pyogenes* isolates from Slovenia were susceptible to clindamycin, while the lowest susceptibility rate was for isolates from Bulgaria (90.6%). All isolates from Bulgaria, the Czech Republic, Latvia, Poland, and Slovenia were susceptible to levofloxacin. The highest prevalence of levofloxacin-intermediate *S. pyogenes* was found in Lithuania (10.2%).

The incidence of macrolide-resistant strains and the mechanisms of resistance are shown in Table 3. The prevalence of macrolide-resistant *S. pyogenes* was <10% in the Czech Republic (7.7%), Hungary (5.2%), Latvia (9.0%), and Romania (9.7%). One hundred twenty-four strains (12.3%) were macrolide resistant, and *erm*(A) was found in 75 (60.5%) strains. Twenty-nine strains (23.4%) had *mef*(A); the largest number of *mef*(A) strains was found in the Slovak Republic, with 9 of 17 (52.9%) macrolide-resistant strains having *mef*(A), while no strains with *mef*(A) were found in the Czech Republic, Latvia, Lithuania, Poland, or Slovenia. Eighteen resistant strains (14.5%) had *erm*(B) and were found in Croatia, Hungary, Poland, Romania, and the Slovak Republic. The largest number of isolates with *erm*(B) was found in Croatia, with 6 of 18 (33.3%) macrolide-resistant strains having *erm*(B).

The correlation between the MIC distribution and the mechanism of resistance in *S. pyogenes* is shown in Table 4. The MIC_{50} and the MIC_{90} of telithromycin for *erm*(A) strains were 0.06 and 0.06 μg/ml, respectively. Most *erm*(B) strains (11) had constitutive resistance, and the MIC_{90}s of all macrolides were >64 μg/ml for these strains; six strains from Croatia with *erm*(B) genes had inducible resistance, with azithromycin, cla-

TABLE 2. Rates of susceptibility to *S. pyogenes*

Country	% Susceptible					
	Telithromycin[a]	Erythromycin	Azithromycin	Clarithromycin	Clindamycin	Levofloxacin
Slovak Republic	96.0/97.0	83.3	82.3	84.3	96.0	97.0
Romania	99.0/99.0	90.2	90.2	90.2	99.0	99.0
Hungary	97.9/98.9	94.8	94.8	94.8	97.9	97.9
Lithunania	100/100	89.8	89.8	89.8	96.9	89.8
Slovenia	100/100	87.2	86.2	87.2	100	100
Czech Republic	100/100	92.3	92.3	92.3	98.0	100
Latvia	100/100	91.0	91.0	91.0	98.0	100
Bulgaria	100/100	82.2	82.2	82.2	90.6	100
Poland	95.9/95.9	83.6	83.6	83.6	93.8	100
Croatia	95.9/97.9	81.8	81.8	82.8	95.9	94.9
All strains	98.5/98.9	87.7	87.5	87.8	97.3	98.0

[a] For telithromycin, values are for breakpoints for telithromycin susceptibility at ≤0.5/≤2.0 μg/ml.

TABLE 3. Incidence of macrolide resistance and mechanisms of resistance for isolates from 10 centers

Country	No. (%) of macrolide-resistant *S. pyogenes* strains	No. of strains with the following gene:			
		Erm(B)	*Erm*(A)	*Mef*(A)	Other
Slovak Republic	17 (16.7)	4	3	9	1
Romania	10 (9.7)	1	1	8	0
Hungary	5 (5.2)	2	2	1	0
Lithunania	10 (10.1)	0	10	0	0
Slovenia	13 (12.7)	0	13	0	0
Czech Republic	8 (7.7)	0	8	0	0
Latvia	9 (9.0)	0	9	0	0
Bulgaria	18 (16.8)	0	12	6	0
Poland	16 (16.3)	5	11	0	0
Croatia	18 (18.2)	6	6	5	1
Total	124 (12.3)	18	75	29	2

TABLE 4. MIC distribution by mechanism of resistance in *S. pyogenes*

Drug resistance gene[a]	MIC (μg/ml)		
	Range	50%	90%
Telithromycin			
erm(B)^C (*n* =12)	0.125–>64	16	>64
erm(B)^I (*n* = 6)	0.125–4	2	
erm(A)^C (*n* = 3)	0.03–0.125	0.06	
erm(A)^I (*n* = 72)	0.004–0.125	0.06	0.06
mef(A) (*n* = 29)	0.25–0.5	0.5	0.5
Others (*n* = 2)	0.125	0.125	
Total (*n* = 124)	0.004–>64	0.06	16
Azithromycin			
erm(B)^C (*n* = 12)	>64	>64	>64
erm(B)^I (*n* = 6)	>64	>64	
erm(A)^C (*n* = 3)	4–>64	>64	
erm(A)^I (*n* = 72)	4–>64	16	64
mef(A) (*n* = 29)	4–16	8	8
Others (*n* = 2)	2–8	8	
Total (*n* = 124)	2–>64	16	>64
Erythromycin			
erm(B)^C (*n* = 12)	64–>64	>64	>64
erm(B)^I (*n* = 6)	>64	>64	
erm(A)^C (*n* = 3)	2–>64	64	
erm(A)^I (*n* = 72)	1–>64	4	8
mef(A) (*n* = 29)	4–16	8	16
Others (*n* = 2)	0.125–0.5	0.5	
Total (*n* = 124)	0.125–>64	4	>64
Clarithromycin			
erm(B)^C (*n* = 12)	16–>64	>64	>64
erm(B)^I (*n* = 6)	>64	>64	
erm(A)^C (*n* = 3)	0.5–32	16	
erm(A)^I (*n* = 72)	1–>64	2	4
mef(A) (*n* = 29)	2–8	4	8
Others (*n* = 2)	0.125–0.25	0.25	
Total (*n* = 124)	0.125–>64	2	>64
Clindamycin			
erm(B)^C (*n* = 12)	8–>64	>64	>64
erm(B)^I (*n* = 6)	0.125–0.25	0.25	
erm(A)^C (*n* = 3)	2–>64	>64	
erm(A)^I (*n* = 72)	0.06–1	0.25	0.5
mef(A) (*n* = 29)	0.06–0.25	0.125	0.125
Others (*n* = 2)	0.06–2	2	
Total (*n* = 124)	0.06–>64	0.125	>64

[a] I, inducible; C, constitutive.

rithromycin, and erythromycin MIC_{50}s of >64 μg/ml, while the clindamycin MIC_{50} was 0.25 μg/ml and the telithromycin MIC_{50} was 2 μg/ml. The MIC_{90} of telithromycin for strains with *mef*(A) was 0.5 μg/ml. For two strains from Croatia and the Slovak Republic, the erythromycin MICs were lower (0.125 and 0.5 μg/ml, respectively), but the azithromycin MICs were high (2 and 8 μg/ml, respectively) and the strains had no discernible macrolide resistance mechanisms.

Taking into consideration the heterogeneity of sample origins, the prevalence of macrolide-resistant *S. pyogenes* strains was 12.3%, varying from 5.2 to 18.2%. Most erythromycin-resistant *S. pyogenes* strains had *erm*(A) and most had inducible resistance. These strains were cross resistant to azithromycin, erythromycin, and clarithromycin. All strains with *mef*(A) were clindamycin susceptible (6, 10, 16). No strain had more than one macrolide resistance mechanism. Two strains from Croatia and the Slovak Republic (Tables 3 and 4), for which azithromycin MICs were higher (2 to 8 μg/ml) but for which erythromycin MICs were lower (0.125 to 0.5 μg/ml), did not have the *erm*(A), *erm*(B), or *mef*(E) gene (23); we are working to determine their mechanisms of resistance. Telithromycin MICs were lower (0.004 to 0.5 μg/ml) than those of macrolides and azalides (0.5 to >64 μg/ml) for *S. pyogenes* strains with *erm*(A) or *mef*(A); however, the telithromycin MIC_{50} and MIC_{90} were higher (16 and >64 μg/ml, respectively) for *erm*(B) strains (5).

In summary, telithromycin had excellent in vitro activity against *S. pyogenes* isolates with the exception of isolates with *erm*(B). However, the presence of *erm*(B) is not a common mechanism of resistance in *S. pyogenes* strains from most countries. The prevalence of erythromycin resistance in Croatia, Poland, and the Slovak Republic was higher than that in other countries. Our findings point to the potential use of telithromycin in the treatment of *S. pyogenes* infections.

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