Macrolide Treatment Failure in Streptococcal Pharyngitis Resulting in Acute Rheumatic Fever

abstract

Macrolide resistance (MR) in group A *Streptococcus* (GAS) has been well documented in several countries and has become clinically significant since the large increases in macrolide usage during the 1970s. Macrolides are recommended as an alternative therapy for GAS pharyngitis, the most common cause of bacterial pharyngitis. Macrolide resistance has been associated with certain *emm* types, a sequence-based typing system of the hypervariable region of the GAS M-protein gene. Clinical failure of macrolide treatment of GAS infections can be associated with complications including acute rheumatic fever and rheumatic heart disease, the leading cause of acquired heart disease in children worldwide. Here we report 2 pediatric cases of MR and/or treatment failure in the treatment of GAS pharyngitis with the subsequent development of acute rheumatic fever. We also review the literature on worldwide MR rates, molecular classifications, and *emm* types, primarily associated with GAS pharyngeal isolates between the years of 2000 and 2010. The use of macrolides in the management of GAS pharyngitis should be limited to patients with significant penicillin allergy. *Pediatrics* 2012;129: e798–e802

AUTHORS: Latania K. Logan, MD,[a] James B. McAuley, MD, MPH,[a] and Stanford T. Shulman, MD[b]

[a]*Section of Pediatric Infectious Diseases, Department of Pediatrics, Rush University Medical Center, Rush Medical College, Chicago, Illinois; and* [b]*Division of Infectious Diseases, Department of Pediatrics, Children's Memorial Hospital, Northwestern University Feinberg School of Medicine, Chicago, Illinois*

KEY WORDS

macrolides, anti-bacterial agents, child, pediatrics, *Streptococcus pyogenes*, streptococcal infections, pharyngitis, drug resistance, bacterial drug resistance, rheumatic fever, phenotype, genotype, bacterial antigens

ABBREVIATIONS

ARF—acute rheumatic fever
GAS—group A *streptococcus*
MLS—macrolide-lincosamide-streptogramin antibiotics
MR—macrolide resistance
RADT—rapid antigen-detection test
RHD—rheumatic heart disease

Drs Logan, McAuley, and Shulman have made substantive intellectual contributions to the study including substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article, and/or revising it critically. All authors have approved the final version of the publication.

www.pediatrics.org/cgi/doi/10.1542/peds.2011-1198

doi:10.1542/peds.2011-1198

Accepted for publication Oct 25, 2011

Address correspondence to Latania K. Logan, MD, Rush University Medical Center, 1653 W Congress Parkway, 736 Murdock, Chicago, IL 60612. E-mail: latania_logan@rush.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

FUNDING: No external funding.

Group A *Streptococcus* (GAS), also known as *Streptococcus pyogenes*, is one of the most common pathogenic bacteria in children and causes a broad range of infections and disease states. Common infections involve the skin and oropharynx; however, suppurative and systemic infections, necrotizing fasciitis, toxic shock syndrome, and immune-mediated illnesses such as acute rheumatic fever (ARF), rheumatic heart disease (RHD), and poststreptococcal glomerulonephritis can be severe and are associated with significant morbidity and mortality.[1] GAS is the most common cause of acute bacterial pharyngitis, accounting for ~30% of episodes of pharyngitis in children, and is most frequently seen in children aged 5 to 11 years.[2] Accurate diagnosis and effective antibiotic treatment of GAS pharyngitis are required to prevent complications such as ARF and RHD.

Standard therapy for GAS pharyngitis is penicillin or amoxicillin. Alternative therapy with significant penicillin allergy is macrolide antibiotics or possibly clindamycin.[3] Macrolide resistance (MR) in GAS remains an increasing worldwide concern. In this report, we present 2 cases of ARF that occurred after presumed macrolide failure for GAS pharyngitis and review the literature on MR associated with clinical GAS isolates during the past decade.

CASE REPORT

Patient 1

In March 2009, an 11-year-old previously healthy white boy presented with fever, rash, joint pain, and swelling. His initial complaints were fever, sore throat, ear pain, and rash. His 6-year-old brother had previously been diagnosed with GAS pharyngitis. The patient was reported to have a significant penicillin allergy. After 7 days of illness, he was empirically treated with azithromycin and diphenhydramine for 10 days. While still taking azithromycin and ~2 weeks after initial symptoms, he developed fever, ankle pain, and swelling. The pain and swelling migrated at varying times to his knees and elbows, requiring the use of a wheelchair during a family vacation. Upon return home 18 days after the initial illness, he had a positive GAS rapid antigen-detection test (RADT) from his pharynx, and azithromycin was continued. Upon presentation to our hospital at 21 days after initial symptom onset, he was afebrile with normal vital signs. On examination, he had notable features of a faded, evanescent, erythematous patchy rash on upper and lower extremities and splotchy truncal rash. He had pain and swelling of his left ankle, and bilateral second to fourth metacarpal phalangeal joints. He did not have a regurgitant murmur.

His leukocyte count was 10 630/mm^3, hemoglobin 10.6 g/dL, hematocrit 30%, platelet count 409 000/mm^3, erythrocyte sedimentation rate 51 mm/h (normal 0–20 mm/h), C-reactive protein 5.8 mg/dL (normal, 0.00–0.8 mg/dL), antistreptolysin O titer 700 IU/mL (normal 0–200 IU/mL), and antideoxyribonuclease b titer of 1920 U/mL (normal, 0–170 U/mL). The results of an echocardiogram, electrocardiogram, and chest radiograph were normal. A throat culture revealed an erythromycin-resistant, clindamycin-sensitive strain of GAS. He was treated with clindamycin and aspirin. He showed prompt resolution of his arthritis with resolution of the rash within 2 weeks and no recurrence. The results of a repeat throat culture were negative, and he received erythromycin as secondary prophylaxis.

Patient 2

In September 2009, a 13-year-old Hispanic girl with a history of vitelliform macular dystrophy (Best disease) presented with history of fever of 4 to 5 days, joint pain, and swelling. Approximately 3 weeks before presentation, she was diagnosed with GAS pharyngitis by RADT and received a 10-day course of azithromycin of unknown dose. She did not have a penicillin allergy. She subsequently developed migratory pain and swelling in her ankles and knees at varying times over 3 days. She was only able to crawl upstairs because of severe pain. She was self-medicating with ibuprofen. Upon presentation, she was afebrile, her heart rate was 112 beats per minute, and her vital signs were normal otherwise. On examination, she had pain and swelling in her left ankle and a small 0.5 × 0.3 cm tender nodule on the palmar surface of her right first digit. She did not have a rash or appreciable cardiac murmur, and her chest was clear to auscultation.

The leukocyte count was 16 400/mm^3, hemoglobin 10.5g/dL, hematocrit 33.9%, platelet count 387 000/mm^3, erythrocyte sedimentation rate 120 mm/h, C-reactive protein 23.0 mg/dL (normal, 0.00–1.0 mg/dL), and antistreptolysin O titer >800 IU/mL. No throat culture was obtained. Electrocardiogram and chest radiograph results were normal. Echocardiogram revealed mild tricuspid and trivial mitral valve regurgitation. She was treated with prednisone, and given penicillin VK for ARF treatment and secondary prophylaxis. An echocardiogram 1 year after presentation was unchanged.

DISCUSSION

GAS pharyngitis is a self-limited illness; however, it can be associated with suppurative tonsillopharyngeal complications or nonsuppurative immune-mediated complications such as ARF, RHD, and poststreptococcal glomerulonephritis. RHD is the most common cause of acquired heart disease in children worldwide and can be prevented with effective treatment of GAS pharyngitis.[1,2]

The diagnosis of ARF is based on the Jones criteria, originally described by T. Duckett Jones in 1944 and most recently revised in 1992.[4] Major criteria include migratory polyarthritis, carditis, subcutaneous nodules, chorea, and erythema marginatum, and minor criteria include fever, elevated acute-phase reactants, arthralgia, and prolonged PR interval on electrocardiography. Diagnosis requires 2 major criteria or 1 major criterion and 2 minor criteria, together with supporting evidence of an antecedent GAS infection, such as a positive throat culture, RADT, or rising or elevated antistreptococcal antibody titers.[2,4] Throat cultures for GAS are positive at presentation in only ~25% of ARF patients.[4]

The latent period between GAS pharyngitis and ARF is usually ≥10 days.[4] Arthritis is seen in ~75% of patients with ARF.[3] We believed that our patient 1 had migratory polyarthritis, fever, and elevated acute-phase reactants and antibody titers; his rash was thought to be related to his illness, but not characteristic of erythema marginatum. In patient 2, the cardiac findings were probably physiologic. We believed that her subcutaneous nodule and migratory polyarthritis represented major ARF criteria. A pharyngeal MR GAS strain was recovered in patient 1, but presumed in patient 2. It is unclear when acquisition of these strains occurred. Whether an unrecognized episode of GAS pharyngitis before these presentations contributed to their development of ARF is uncertain.

Standard management of GAS pharyngitis is 10 days of oral penicillin VK or intramuscular benzathine penicillin G. Amoxicillin is often used for increased palatability and compliance. Penicillin therapy is effective and inexpensive, although there are rare reports of ARF despite therapy.[5] Alternative therapy for those with severe penicillin allergy is macrolide or azalide antibiotics, which include erythromycin, clarithromycin, and azithromycin. The recommended azithromycin dose in GAS pharyngitis is 12 mg/kg per day (maximum 500 mg/day) for 5 days.[3] In nonanaphylactic cases of penicillin allergy, a first-generation cephalosporin may be used.[2,3,6] The diagnosis of GAS pharyngitis is most commonly made by RADT, a specific and inexpensive diagnostic method performed routinely in the outpatient setting.

Although there has never been a penicillin-resistant GAS clinical isolate, MR strains of GAS have been described since the 1950s; increasing resistance during the 1970s was correlated with a massive increase in macrolide consumption in some countries.[7] Clindamycin resistance also occurs in GAS.[8] MR in GAS is mainly attributed to 2 principle mechanisms, an active efflux pump (M phenotype) related to enzymes encoded for by *mef* genes, and ribosomal target site modification by methylation (*erm* genes), which causes coresistance to macrolide, lincosamide, and streptogramin (MLS) antibiotics (MLS phenotype).[7,9] MLS resistance is expressed constitutively (MLS_c) or inducibly (MLS_i). M and MLS phenotypes are distinguished by using double-disk diffusion testing (D-test) evaluating clindamycin (lincosamide) susceptibility in the presence of erythromycin resistance.[10]

We reviewed data recently published between 2000 and 2011 for worldwide prevalence of MR, phenotypic and genotypic characterization of macrolide-resistant GAS isolates, and macrolide-resistant *emm* types, with a focus on multicenter studies involving pharyngeal isolates in children (Table 1). There was a wide spectrum in rates of GAS MR, from 1.1% in Cyprus to as high as 97.9% in Chinese children. Dominant phenotypes and genotypes associated with MR were highly variable by country or region as were *emm* types, a sequence-based typing system based on the N-terminus hypervariable region of the M-protein gene widely used for epidemiological classification of strains.[11] Several reports noted wide fluctuations in molecular classifications and *emm* types occurring annually and/or seasonally.

In the United States, single-center studies have revealed MR rates as high as 48% during a single season.[12,13] In addition, prospective multicenter US surveillance studies have shown increasing resistance rates from 3% to 8.7% between 2000 and 2003 to as high as 12% to 15% at the same centers in 2007.[14–16] The increase in worldwide rates has been attributed to several factors, including horizontal gene transfer and spread of dominant resistance clones, overconsumption of macrolide antibiotics, and temporal variation in the distribution of *emm* types.[17–20]

Although prospective clinical trials have demonstrated successful treatment of GAS pharyngitis with short-course macrolide therapy, macrolides should be used with caution, unless there is an indication of severe penicillin allergy, such as a type I hypersensitivity reaction, because of circulating MR GAS strains.[21–25] In addition, short-course macrolide therapy can be associated with late bacteriologic recurrence,[21] and although there has not been a significant recent increase in the number of ARF cases in the United States, complications of GAS infection associated with MR and treatment failure including ARF as in our cases have been rarely described.[26–28]

CONCLUSIONS

Group A Streptococcal pharyngitis is a common illness in the pediatric population. Penicillin or amoxicillin remain the standard therapy. In nonanaphylactic cases of penicillin allergy,

TABLE 1 Worldwide Prevalence of GAS MR, Resistance Characterization, and Resistant *emm* Types, 2000–2010

Study	Country/ Region	Study Years Included	Multicenter	Source of Isolate	Overall Rate of MR, % (range)	Dominant Phenotype (%)	Dominant Genotype (%)	Predominant MR *emm* Types
Rubinstein et al[29] (2005)	Argentina	2000–2003	Y	Pharyngeal[a]	2.1 (0.59–5.02)	M (84.6)	*mef*A (84.6)	NA
Katz et al[30] (2003)	Canada	2001	Y	Pharyngeal	14.4	M (91.5)	*mef*A (91.5)	NA
Liang et al[31] (2008)	China	2007	Y	Pharyngeal	97.9	MLS_c (94.5)	*erm*B (90.3)	1, 12
Koliou et al[32] (2007)	Cyprus	2003–2004	N	Pharyngeal	1.1	M (100)	NA	NA
Bingen et al[33] (2004)	France	2002–2003	Y	Pharyngeal	22.4	MLS (71)	*erm*B (69.4)	28
Shackcloth et al[34] (2004)	Great Britain, Ireland	2000–2002	Y	Pharyngeal, ear	2.5	NA	*erm*A (67.6)	NA
Malli et al[35] (2010)	Greece/Central	2007–2009	Y	Pharyngeal, pus	24	MLS_i (83)	*erm*A (83)	4, 77
Mazzariol et al[36] (2007)	Italy	2002–2003	Y	Pharyngeal[a]	25.5	MLS_i (50.3)	*erm*B (36)	NA
Koh et al[37] (2008)	Korea	2004	N	Pharyngeal	9.8	MLS_c (87.5)	*erm*B (90.6)	12, 77
Zavadska et al[38] (2010)	Latvia	2002–2006	N	Pharyngeal, pus	78	MLS (78)	*erm*A and/or B (77)	NA
Silva-Costa et al[39] (2008)	Portugal	2004–2006	Y	Pharyngeal	13.2 (11–17.6)	MLS_c (51.3)	*erm*B (53.2)	28, 4, 11
Pavlovic et al[40] (2010)	Serbia	2006–2008	Y	Pharyngeal	6.8	M (83.8)	*mef*A (83.8)	NA
Dundar et al[41] (2010)	Turkey	2006–2008	N	Pharyngeal[a]	9	MLS_i (100)	*erm*A (100)	NA
Martin et al[13] (2006)	United States	2000–2001	N	Pharyngeal	48	M (100)	*mef*A (NA)	6
Tanz et al[15,16] (2008)	United States	2000–2007	Y	Pharyngeal	4.1 (3.8–4.4)	M (75)	*mef*A (70.3)	75, 12, 4
Green et al[14] (2006)	United States	2002–2003	Y	Pharyngeal	5.2 (3–8.7)	M (68)	*mef*A (NA)	75, 12

N, no; NA, data not available; Y, yes.

[a] Majority of study isolates pharyngeal.

a first-generation cephalosporin may be used. Practitioners should be cautioned to use macrolide antibiotics in the management of GAS infection only in the face of anaphylactic-type penicillin allergy because of increased rates of MR and the potential risk of serious complications such as ARF and RHD without adequate therapy.

REFERENCES

1. Gerber MA. Streptococcus pyogenes (group A streptococcus). In: Long SS, Pickering LK, Prober CG, eds. *Principles and Practice of Pediatric Infectious Diseases*. 3rd (rev reprint) ed. Philadelphia, PA: Churchill Livingston Elsevier; 2009:700–711
2. Jaggi P, Shulman ST. Group A streptococcal infections. *Pediatr Rev*. 2006;27(3):99–105
3. Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation*. 2009;119(11):1541–1551
4. Guidelines for the Diagnosis of Rheumatic Fever. Jones Criteria, 1992 update. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. *JAMA*. 1992;268(15):2069–2073
5. Catanzaro FJ, Rammelkamp CH, Jr, Chamovitz R. Prevention of rheumatic fever by treatment of streptococcal infections. II. Factors responsible for failures. *N Engl J Med*. 1958;259(2):53–57
6. Dajani A, Taubert K, Ferrieri P, Peter G, Shulman S. Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association. *Pediatrics*. 1995;96(4 pt 1):758–764
7. Freeman AF, Shulman ST. Macrolide resistance in group A Streptococcus. *Pediatr Infect Dis J*. 2002;21(12):1158–1160
8. Woods CR. Macrolide-inducible resistance to clindamycin and the D-test. *Pediatr Infect Dis J*. 2009;28(12):1115–1118
9. Leclercq R. Mechanisms of resistance to macrolides and lincosamides: nature of the resistance elements and their clinical implications. *Clin Infect Dis*. 2002;34(4):482–492
10. Sanchez ML, Flint KK, Jones RN. Occurrence of macrolide-lincosamide-streptogramin resistances among staphylococcal clinical isolates at a university medical center. Is false susceptibility to new macrolides and clindamycin a contemporary clinical and in vitro testing problem? *Diagn Microbiol Infect Dis*. 1993;16(3):205–213
11. Beall B, Facklam R, Thompson T. Sequencing emm-specific PCR products for routine and accurate typing of group A streptococci. *J Clin Microbiol*. 1996;34(4):953–958
12. Green M, Martin JM, Barbadora KA, Beall B, Wald ER. Reemergence of macrolide resistance in pharyngeal isolates of group a streptococci in southwestern Pennsylvania. *Antimicrob Agents Chemother*. 2004;48(2):473–476
13. Martin JM, Green M, Barbadora KA, Wald ER. Erythromycin-resistant group A streptococci in schoolchildren in Pittsburgh. *N Engl J Med*. 2002;346(16):1200–1206
14. Green MD, Beall B, Marcon MJ, et al. Multicentre surveillance of the prevalence and molecular epidemiology of macrolide resistance among pharyngeal isolates of group A streptococci in the USA. *J Antimicrob Chemother*. 2006;57(6):1240–1243
15. Tanz RR, Rippe J, Kabat K, et al. National and local variations in group A streptococcal macrolide resistance in North America over 7 years. In: Proceedings from the Pediatric Academic Societies' Annual

Meeting; May 6, 2008; Honolulu, HI. Abstract 6430.3

16. Tanz RR, Shulman ST, Shortridge VD, et al; North American Streptococcal Pharyngitis Surveillance Group. Community-based surveillance in the united states of macrolide-resistant pediatric pharyngeal group A streptococci during 3 respiratory disease seasons. *Clin Infect Dis*. 2004;39(12):1794–1801
17. Oliver MA, García-Delafuente C, Cano ME, Pérez-Hernández F, Martínez-Martínez L, Albertí S. Rapid decrease in the prevalence of macrolide-resistant group A streptococci due to the appearance of two epidemic clones in Cantabria (Spain). *J Antimicrob Chemother*. 2007;60(2):450–452
18. Robinson DA, Sutcliffe JA, Tewodros W, Manoharan A, Bessen DE. Evolution and global dissemination of macrolide-resistant group A streptococci. *Antimicrob Agents Chemother*. 2006;50(9):2903–2911
19. Silva-Costa C, Ramirez M, Melo-Cristino J. Identification of macrolide-resistant clones of Streptococcus pyogenes in Portugal. *Clin Microbiol Infect*. 2006;12(6):513–518
20. Bergman M, Huikko S, Pihlajamäki M, et al; Finnish Study Group for Antimicrobial Resistance (FiRe Network). Effect of macrolide consumption on erythromycin resistance in Streptococcus pyogenes in Finland in 1997-2001. *Clin Infect Dis*. 2004;38(9):1251–1256
21. Altamimi S, Khalil A, Khalaiwi KA, Milner R, Pusic MV, Al Othman MA. Short versus standard duration antibiotic therapy for acute streptococcal pharyngitis in children. *Cochrane Database Syst Rev*. 2009;(1):CD004872
22. Brook I. Azithromycin versus penicillin in acute group A streptococcal tonsillopharyngitis. *Curr Infect Dis Rep*. 2003;5(3):191–193
23. Takker U, Dzyublyk O, Busman T, Notario G. Comparison of 5 days of extended-release clarithromycin versus 10 days of penicillin V for the treatment of streptococcal pharyngitis/tonsillitis: results of a multicenter, double-blind, randomized study in adolescent and adult patients. *Curr Med Res Opin*. 2003;19(5):421–429
24. Cohen R, Reinert P, De La Rocque F, et al. Comparison of two dosages of azithromycin for three days versus penicillin V for ten days in acute group A streptococcal tonsillopharyngitis. *Pediatr Infect Dis J*. 2002;21(4):297–303
25. Jorgensen DM. Single-dose extended-release oral azithromycin vs. 3-day azithromycin for the treatment of group A beta-haemolytic streptococcal pharyngitis/tonsillitis in adults and adolescents: a double-blind, double-dummy study. *Clin Microbiol Infect*. 2009;15(12):1103–1110
26. Lavergne V, Thibault L, Garceau R. Macrolide resistance in streptococcal pharyngitis. *CMAJ*. 2007;177(2):177
27. Sungur C. Acute rheumatic fever despite clarithromycin treatment of beta-hemolytic streptococcal tonsillitis. *Ann Pharmacother*. 1994;28(10):1197–1198
28. Ghirga G, Palazzi C, Ghirga P, Turchetti G, Turchetti A, Colaiacomo M. Inefficacy of a 3-day course of azithromycin in preventing acute rheumatic fever after group A streptococcal infection (scarlet fever) in an 8-year-old child. *J Pediatr*. 1999;134(1):123–124
29. Rubinstein G, Amoroso AM, Bavdaz B, De Bunder S, Blazquez N, Gutkind GO. Low macrolide resistance in Streptococcus pyogenes in Southern Argentina. *Int J Antimicrob Agents*. 2005;25(5):450–452
30. Katz KC, McGeer AJ, Duncan CL, et al. Emergence of macrolide resistance in throat culture isolates of group a streptococci in Ontario, Canada, in 2001. *Antimicrob Agents Chemother*. 2003;47(7):2370–2372
31. Liang Y, Shen X, Huang G, Wang C, Shen Y, Yang Y. Characteristics of Streptococcus pyogenes strains isolated from Chinese children with scarlet fever. *Acta Paediatr*. 2008;97(12):1681–1685
32. Koliou M, Ioannou Y, Efstratiou A, et al. Circulating serotypes and antimicrobial sensitivity of Streptococcus pyogenes isolates from children in Cyprus. *Clin Microbiol Infect*. 2007;13(6):645–647
33. Bingen E, Bidet P, Mihaila-Amrouche L, et al. Emergence of macrolide-resistant Streptococcus pyogenes strains in French children. *Antimicrob Agents Chemother*. 2004;48(9):3559–3562
34. Shackcloth J, Williams L, Farrell DJ. Streptococcus pneumoniae and Streptococcus pyogenes isolated from a paediatric population in Great Britain and Ireland: the in vitro activity of telithromcycin versus comparators. *J Infect*. 2004;48(3):229–235
35. Malli E, Tatsidou E, Damani A, et al. Macrolide-resistant Streptococcus pyogenes in Central Greece: prevalence; mechanism and molecular identification. *Int J Antimicrob Agents*. 2010;35(6):614–615
36. Mazzariol A, Koncan R, Bahar G, Cornaglia G. Susceptibilities of Streptococcus pyogenes and Streptococcus pneumoniae to macrolides and telithromycin: data from an Italian multicenter study. *J Chemother*. 2007;19(5):500–507
37. Koh EH, Kim S, Lee NY. Decrease of erythromycin resistance in group A streptococci by change of emm distribution. *Jpn J Infect Dis*. 2008;61(4):261–263
38. Zavadska D, Bērzina D, Drukalska L, Pugacova N, Miklasevics E, Gardovska D. Macrolide resistance in group A beta haemolytic Streptococcus isolated from outpatient children in Latvia. *APMIS*. 2010;118(5):366–370
39. Silva-Costa C, Pinto FR, Ramirez M, Melo-Cristino J; Portuguese Surveillance Group for the Study of Respiratory Pathogens. Decrease in macrolide resistance and clonal instability among Streptococcus pyogenes in Portugal. *Clin Microbiol Infect*. 2008;14(12):1152–1159
40. Pavlovic L, Grego E, Sipetic-Grujicic S. Prevalence of macrolide resistance in Streptococcus pyogenes collected in Serbia. *Jpn J Infect Dis*. 2010;63(4):275–276
41. Dundar D, Sayan M, Tamer GS. Macrolide and tetracycline resistance and emm type distribution of Streptococcus pyogenes isolates recovered from Turkish patients. *Microb Drug Resist*. 2010;16(4):279–284