Streptococcal Infections in Children: An Update

Prakash K Wari¹, Siddappa F Dandinavar², Raghavendraswami Amoghmath³, Roopali Desai⁴, HR Puneeth⁵

ABSTRACT

Streptococcus is the general term for a diverse group of gram-positive cocci that appear in chains or pairs. The most prevalent of the human streptococcal pathogens are the Lancefield group A *Streptococcus* (GAS). This review article provides an update on group A streptococcal infections with key highlights on classification, presentation, the latest diagnostic criteria, management protocols, and complications.

Background: Group A *Streptococcus* is involved in the pathogenesis of a wide variety of pathologic conditions varying from noninvasive infections such as pharyngitis, erysipelas, scarlet fever, and cellulitis to invasive diseases, such as bacterial sepsis, streptococcal toxic shock syndrome, and necrotizing fasciitis. It is also linked with nonsuppurative and postinfectious immunological sequelae, such as acute rheumatic fever (ARF), poststreptococcal glomerulonephritis (PSGN) and pediatric autoimmune neuropsychiatric disorder associated with *Streptococcus pyogenes* (PANDAS). Globally around 18 million people suffer from GAS-related illnesses.

Conclusion: Group A streptococcal infections have a high prevalence and morbidity across the globe, especially in developing countries. Children older than 3 years have a higher risk of such complications necessitating need for proper diagnosis and treatment.

Keywords: Acute rheumatic fever, Group A *Streptococcus*, *Streptococcal pharyngitis*.

Pediatric Infectious Disease (2019); 10.5005/jp-journals-10081-1211

INTRODUCTION

Streptococcus is a general term for a diverse group of gram-positive cocci which appears in chains or pairs. These can be pathogenic or commensals. The hemolytic property of these cocci can help in differentiating from commensals.

In 1933, Rebecca Lancefield pioneered the classification based on the polysaccharide in the cell wall. This paved the way for polysaccharide antigen classification named by capital letter of alphabets (Lancefield groups A, B, C, etc).

The most prevalent of the human streptococcal pathogens are the Lancefield group A streptococci (GAS).

This review article focuses on group A streptococcal infections only.

Group A *Streptococcus* is involved in the pathogenesis of a wide variety of pathologic conditions varying from noninvasive infections, such as pharyngitis, erysipelas, scarlet fever, and cellulitis to invasive diseases, such as bacterial sepsis, streptococcal toxic shock syndrome, and necrotizing fasciitis.

It is also linked with nonsuppurative and postinfectious immunological sequelae such as acute rheumatic fever (ARF), poststreptococcal glomerulonephritis (PSGN), and pediatric autoimmune neuropsychiatric disorder associated with *Streptococcus pyogenes* (PANDAS).

Although there was a decrease in the prevalence of *S. pyogenes* infections in the middle of the 19th century, there has been a resurgence and increased mortality since 1980s.¹

Globally around 18 million people suffer from GAS-related illnesses. Annually around 1.78 million new cases are added.² Innumerable numbers of people suffer from less severe forms of illnesses caused by GAS, which overburden the health expenditure of the state. The majority of these infections are commonly seen in lower socioeconomic strata, who depend on the government sector for their health needs in India. Infection is more common during winter and spring in temperate climates.

¹⁻⁵Department of Paediatrics, Karnataka Institute of Medical Sciences, Hubli, Karnataka, India

Corresponding Author: Prakash K Wari, Department of Paediatrics, Karnataka Institute of Medical Sciences, Hubli, Karnataka, India, Phone: +91 9448063128, e-mail: pkwari55@gmail.com

How to cite this article: Wari PK, Dandinavar SF, Amoghmath R, et al. Streptococcal Infections in Children: An Update. *Pediatr Inf Dis* 2019;1(3):114–119.

Source of support: Nil

Conflict of interest: None

Transmission

There is no known environmental reservoir or natural animal host of *S. pyogenes*, apart from human beings; and as a result, direct or indirect contact with an infected person is the source of human infection. Transmission is thought to occur primarily by large droplets from respiratory secretions, although spread through contaminated objects and food are also other routes of transmission. Outbreaks may occur in households, schools, military facilities, and other settings in which there is close human-to-human contact.

NONINVASIVE GAS INFECTIONS

Streptococcal Pharyngitis

Acute infection of the pharynx, account for a substantial number of visits to primary care physicians. Group A *Streptococcus* is the most common cause of bacterial pharyngitis (Fig. 1) in children and adolescents. It accounts for 15–30% of all cases of pharyngitis in children between the ages of 5 years and 15 years.³⁻⁶ Lower socioeconomic status and places with overcrowding, such as camps, military barracks have a high incidence.⁷

Clinical Features

Abrupt onset of fever, malaise, throat pain with swallowing, and the presence of swollen tender anterior cervical lymph nodes are typical features. Abdominal pain and vomiting are common, especially in younger children. Cough, rhinorrhea, hoarseness, conjunctival irritation, and diarrhea are conspicuously absent in *Streptococcal pharyngitis*, and their presence is more suggestive of a usual viral etiology. On clinical examination, fever (often $>39^{\circ}\text{C}$), erythema, and edema of the posterior pharynx and tonsils, this may be covered with a patchy white or yellowish exudate. Petechiae may be present on the soft palate; anterior cervical lymph nodes typically are enlarged, firm, and tender. The presence of most or all of these characteristic clinical features is suggestive of, but not specific to, *S. pyogenes* pharyngitis.

Diagnosis is obvious on clinical grounds and investigations are not warranted on routine basis. Diagnosis can be confirmed by rapid antigen detection tests (RADTs) especially in children more than 3 years or with significant illness. Culture may be required if RADT is negative, although clinical features suggestive of GAS is sufficient to treat. However, these modalities of diagnosis will not differentiate a true infection and carrier stage.

Fig. 1: Yellowish white exudates on tonsils and pharynx

Treatment

Rest, hydration and appropriate use of antibiotic are the cornerstone. Without treatment, sore throat usually resolves in 3–6 days, and fever abates within 1 week. Despite the resolution of symptoms, throat cultures often remain positive for several weeks in the absence of antibiotic treatment. However the major concern is to prevent suppurative complications like tonsillar abscess, retropharyngeal abscess and the dreaded nonsuppurative complication like ARF. Hence, we need to treat all cases of GAS pharyngitis with 10 days course of antibiotic to ensure complete eradication of streptococci from throat. Based on their narrow spectrum of activity, infrequency of adverse reactions, and modest cost, penicillin or amoxicillin is the recommended drug of choice for those nonallergic to these agents.

Oral or parenteral penicillin for a period of 10 days is the treatment of choice for GAS pharyngitis.⁷ If compliance is an issue, long acting penicillin (benzathine penicillin) can be given. Alternate antibiotics that can be used are amoxicillin and ampicillin. For penicillin allergy cases, oral cephalosporins (for those who are not anaphylactically sensitive) for 10 days, clindamycin or clarithromycin for 10 days, or azithromycin for 5 days are recommended. Some physicians prefer macrolides like clarithromycin for 10 days or azithromycin for 5 days. However, macrolides are to be kept reserved for other childhood infections and should not be used for treating streptococcal throat infections (Table 1).

SCARLET FEVER

Scarlet fever or scarlatina is GAS upper respiratory infection with typical rashes caused by erythrogenic GAS exotoxins. This can occasionally also be seen with skin and soft tissue infection in individuals who do not have antitoxins. Severe forms are not being seen because of early antibiotic usage. The rash is seen within 24–48 hours after the onset of symptoms, beginning around the neck and upper chest and spreading to the trunk and extremities (Fig. 2). The rash is diffuse, fine papular, erythematous which blanches on pressure. It gives a sandpaper texture to the skin with pinpoint deep red petechiae and “Pastia’s lines” which are deep red, along the skin creases. There is strawberry tongue (Fig. 3) with circumoral pallor as an association. After 3–4 days, the rashes start to fade down with desquamation. Treat the underlying focus (URI or skin/soft tissue infections) which is the nidus for toxin elaboration.

Table 1: Recommended treatment for acute *Streptococcal pharyngitis*⁸

Most patients					
	Weight <27 kg	Weight $\geq$ 27 kg	Route	Duration	
Amoxicillin	50 mg/kg once daily (maximum 1000 mg)	Oral		10 days	
Penicillin V	250 mg bd	500 mg bd	Oral	10 days	
Benzathine penicillin G	600,000 units	1.2 million units	Im	Once	
Benzathine penicillin G + Procaine penicillin G	900,000 units + 300,000 units	900,000 units + 300,000 units	Im	Once	
Penicillin allergic patients					
	Oral dose	Frequency	Duration (days)		
Cephalosporins	Varies with agent chosen		10		
Erythromycin	40 mg/kg/day up to 1000 mg/day	Bd	10		
Clarithromycin	15 mg/kg/day	Bd	10		
Azithromycin	12 mg/kg day 1; 6 mg/kg day 2–6	Od	5		
Clindamycin	20 mg/kg/day up to 1.8 g/day up to 1.8 g/day	Tid	10

Fig. 2: Scarlatiniform rash of scarlet fever

Perianal Dermatitis (Fig. 4)

It is also called perianal cellulitis or perianal streptococcal disease. It is characterized by well demarcated perianal erythema associated with anal pruritus, painful defecation, and occasionally blood streaked stools. Physical examination reveals flat, pink to beefy red perianal erythema with sharp margins extended as far as 2 cm from anus. Lesions may be very tender and particularly when chronic, may fissure, and bleed.

Vaginitis

Skin and Soft Tissue Infections of GAS

Clinical details are described in Table 2 and treatment aspects in Table 3.

Common cause in prepubertal girls, majority have serous discharge with marked erythema. This is associated with irritation of the vulval area and discomfort during walking and urination (Table 2).

Fig. 3: Strawberry tongue of scarlet fever

Fig. 4: Perianal dermatitis

Table 2: Skin and soft tissue infections of GAS

<i>Impetigo</i>	<i>Erysipelas</i>	<i>Cellulitis</i>
<ul style="list-style-type: none"> Common superficial skin infection involving epidermis Two forms: bullous and nonbullous Bullous is more common with <i>Staph. aureus</i> and nonbullous lesions are common with GAS Seen commonly on face and limbs Erythematous papules with vesicles that rupture to leave honey colored exudates with crusting 	<ul style="list-style-type: none"> Deep dermis is involved Raised above the skin and painful with streaks of lymphangitis which are reddish and less purulent. (if purulent, suspect <i>Staph. aureus</i>) It has a sharply defined demarcated edge Most often seen on the face or extremities 	<ul style="list-style-type: none"> Deeper dermis with involvement of soft tissues Erythema and edema with tenderness Systemic symptoms like fever, toxemia can be seen Primary skin lesions like eczema, chicken pox and lacerations can be secondarily infected with GAS presenting as pyoderma/ cellulitis

Treatment (Table 3)**Table 3:** Treatment of skin and soft tissue GAS infections

Condition	Antibiotic	Dosing	Duration (days)
Impetigo	Mupirocin (topical)	Apply two times daily	5
	Retapumulin (topical)	Apply two times daily	5
	Cephalexin (oral)	25–50 mg/kg/day, 7–8 hourly	7
	Clindamycin (oral) (if MRSA is also suspected)	20–30 mg/kg/day, 8 hourly	7
Erysipelas (milder forms)	Amoxicillin (oral)	40–90 mg/day in 2–3 divided doses	5
Cellulitis (milder forms)	Cephalexin (oral)	50 mg/kg/day in 4 divided doses (maximum 500 mg/dose)	5
	Clindamycin (oral)	25–30 mg/kg/day, 8 hourly (maximum 1800 mg/dose)	5

Acute Rheumatic Fever

It is one of the important nonsuppurative sequelae of GAS. Considerable evidences have supported the link between antecedent GAS with ARF. It is a multisystem disorder aptly described as the one that bites the heart and licks the joints. The link is by the

autoimmune response to M-protein of GAS with human connective tissue (molecular mimicry). Strong evidences have shown reduction in the number of ARF cases following antibiotic treatment of GAS pharyngitis. Diagnosis has been made easy with the Jones' criteria which have been updated in 2015⁹ (Table 4).

Acute rheumatic fever commonly occurs in children between 5 and 15 years of age with no sex predilection. Management of ARF focuses on the elimination of GAS with targeted treatment of individual sites of involvement.

Carditis requires to be diagnosed for sure, since the duration of secondary prophylaxis (for the prevention of recurrences) depends on the valvulitis with or without failure. Echocardiogram with Doppler needs to be done serially to pick up subclinical carditis.

Treatment of carditis involves strict bed rest, fluid restriction and management of congestive cardiac failure and aspirin or corticosteroid suppression therapy. The efficacy of immunomodulatory drugs like intravenous immunoglobulins has not been established. Steroids are a more potent suppressive agent than aspirin, act faster and are preferred especially if carditis is associated with congestive cardiac failure. The total duration of therapy is 12 weeks. Aspirin is given at a dose of 90–120 mg/kg/day in four divided doses for 10 weeks and then tapered over the next 2 weeks. Alternatively, prednisolone at 2 mg per kg (maximum 60 mg) is given for 3 weeks and then gradually tapered over next 9 weeks.¹⁰ Naproxen is another nonsteroidal anti-inflammatory drugs (NSAID) proven to be effective and has advantage of avoiding the risk of Reye's syndrome.

Sydenham's chorea, more often seen in females is often self limiting. It is a late manifestation and is seen occurring about 3 months after the onset of rheumatic fever.⁷ It has a self limiting

Table 4: Revised Jones criteria 2015

<i>Initial episode of acute rheumatic fever: two major or one major + two minor criteria</i>		
<i>Recurrent episodes of acute rheumatic fever: two major, one major + two minor or three minor</i>		
<i>Essential criteria: previous evidence of group A beta hemolytic streptococcal (GABHS) infection</i>		
	Low risk population	Moderate/high-risk population
	ARF incidence ≤ 2 per 100,000 school-aged children or all-age RHD prevalence of ≤ 1 per 1000 population year	Children not clearly from a low-risk population
Major criteria:		
Carditis	Clinical and/or subclinical*	Clinical and/or subclinical*
Arthritis	Polyarthritis	Monoarthritis Polyarthritis and/or Polyarthralgia
	Chorea	Chorea
	Erythema marginatum	Erythema marginatum
	Subcutaneous nodules	Subcutaneous nodules
Minor criteria		
Carditis	Prolonged PR interval [†]	Prolonged PR interval [†]
Arthralgia	Polyarthralgia	Monoarthralgia
Fever	$\geq 38.5^{\circ}\text{C}$	$\geq 38^{\circ}\text{C}$
Markers of inflammation	Peak ESR ≥ 60 mm in 1 hour and/or CRP ≥ 3.0 mg/dL	Peak ESR ≥ 30 mm in 1 hour and/or CRP ≥ 3.0 mg/dL

Changes compared with the 1992 revision are highlighted in bold

*Subclinical carditis: seen only on echocardiography without auscultatory findings

†Accounting for age variability and only if carditis NOT counted as a major criteria

ARF, acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RHD, rheumatic heart disease

Table 5: Secondary prophylaxis following an episode of rheumatic fever

Antibiotic	Mode of administration and dose
Benzathine penicillin	Single intra muscular injection every 3–4 weeks*, 12 lack IU for children >30 kg and 6 lack IU for children <30 kg
Penicillin V	250 mg orally twice daily
Erythromycin (for penicillin allergy)	250 mg orally twice daily

*In high prevalence regions, 3-week injections are recommended for prophylaxis in patients >30 kg and every 2 weeks in patients <30 kg

course of 2–6 weeks but drug therapy will become essential in severe cases which includes carbamazepine, valproic acid with short course of steroids.

Children with ARF, because of their genetic susceptibility are at high risk for recurrences. More the number of recurrences more are the valvular damage with long-term morbidity and mortality. Secondary prophylaxis becomes essential and important in such children (Table 5).

Poststreptococcal Glomerulonephritis

Poststreptococcal glomerulonephritis is another nonsuppurative complication following streptococcal infection. On the basis of M protein antigen, (on the cell surface or the fimbriae), more than 250 serotypes are classified. This is done by sequencing the terminal portion of the emm gene of GAS that encodes the M protein. Specific GAS diseases are caused by some M protein serotypes. Serotypes causing pharyngitis do not cause skin infections. Few pharyngeal strains like M type 12 is associated with PSGN but many skin strains like M types: 49, 55, 57, and 60 cause PSGN.

Presentation of PSGN ranges from being asymptomatic to severe symptoms like renal failure and rapidly progressive glomerulonephritis, though the rate of long-term complications is in less than 5%.

Poststreptococcal glomerulonephritis typically occurs in children between 5 years and 12 years and less common below 3 years.

It develops 2 weeks following an antecedent GAS pharyngitis or 2–4 weeks after skin infections. Classically presents as abrupt onset of hematuria (microscopic/macrosopic), hypertension, proteinuria and minimal edema.

Conformation of diagnosis involves demonstrating antecedent streptococcal infections by positive antistreptolysin-O (ASO) or anti-DNAse B antibody titres with low C3 levels. Treatment of PSGN is mainly supportive and directed towards the effects of renal insufficiency and hypertension. This includes fluid and sodium restriction, antihypertensives, and need based dialysis.

Treatment to eradicate GAS infection becomes essential if GAS infection is persisting at the time of diagnosis. This prevents spread of nephritogenic strains of GAS to other susceptible contacts.

Pediatric Autoimmune Neuropsychiatric Disorder Associated with *Streptococcus pyogenes*

Pediatric autoimmune neuropsychiatric disorder associated with *S. pyogenes* is the term proposed for a group of neuropsychiatric disorders, particularly obsessive compulsive behavior with tics and choreiform movements with a possible relationship with

GAS infections. The hypothesis is that preceding GAS infection causes autoimmune response to some of the antigens in the basal ganglia. Many case reports have documented the prevention of recurrences of PANDAS by secondary prophylaxis. Some studies have found decreased incidence of PANDAS following tonsillectomy and adenoidectomy. However, the hypothesis will remain controversial for the want of well controlled studies. Therefore, there are no clear recommendations available for treatment or prophylaxis.

Intravenous immunoglobulin, plasmapheresis and secondary prophylaxis have all been tried as a part of treatment and prevention of recurrences.

INVASIVE GAS INFECTIONS

Invasive GAS infections indicate growth of the GAS organisms in sterile sites such as blood, synovial fluid or CSF. The estimated incidence of invasive GAS infections in children is 2–4 cases per 100,000 per year. The incidence is greatest in children <1 year (4–9 cases per 100,000).^{10–14} The spectrum of invasive GAS infections range from bacterial sepsis to streptococcal toxic shock syndrome (STSS) and necrotizing fasciitis.¹⁵

Acute GAS-related bacteremia has not been covered in this article.

Streptococcal Toxic Shock Syndrome

Streptococcal toxic shock syndrome is defined as GAS infection with hypotension and evidence of multiorgan failure as mentioned below.¹⁶

Clinical Criteria

Hypotension plus 2 or more of the following:

- Renal impairment,
- Coagulopathy,
- Hepatic involvement,
- Adult respiratory distress syndrome,
- Generalized erythematous macular rash, and
- Soft-tissue necrosis.

Definite Case

Clinical criteria plus group A *Streptococcus* from a normally sterile site.

Probable Case

Clinical criteria plus group A *Streptococcus* from a nonsterile site.

In STSS, toxins evoke massive immune response via T cell proliferation. This gets perpetuated with superantigens causing massive release of cytokines (cytokine storm). Streptococcal toxic shock syndrome usually follows skin and soft tissue infections with GAS. The patient presents with fever, toxemia, generalized erythroderma, which progresses rapidly to hypotension with features of multiorgan failure. The associated soft tissue infections like necrotizing fasciitis may require surgical interventions. Antibiotic treatment should cover both GAS and staphylococcal infection because clinically they are not easy to differentiate. Antibiotics should include those which cover penicillinase producing GAS. Clindamycin, to cover superantigen producing GAS. To cover staphylococcal infections, vancomycin can be added.

Intravenous immunoglobulin has been tried as an adjunctive therapy, multiple studies have shown reduction in mortality. However this is not come as a recommendation yet.

Acute Necrotizing Fasciitis

Type 2 acute necrotizing fasciitis (ANF) is a rapidly progressing deep tissue infection caused by GAS alone or in combination with *Staphylococcus aureus* and anaerobes. Usually begins as innocuous lesions with pain, erythema and later progresses rapidly. Infant will be toxic, irritable, and febrile. Examination reveals fever with tachycardia, neutrophilic predominant leukocytosis, elevated creatinine phosphokinase with or without coagulopathy. With progression, the skin becomes discolored to purplish with hemorrhagic and serous bullae. Inflammation progresses in the next few days involving the muscle, which shows areas of necrosis. The inflammation progresses until aggressive surgical debridement is done at the earliest (even before specific diagnosis is awaited). Magnetic resonance imaging will be helpful in the diagnosis. Antibiotic therapy is similar to STSS.

CONCLUSION

Group A streptococcal infections has a high prevalence across the globe. Morbidity related to noninvasive infections are common in developing nations. The nonsuppurative complications like ARF possess a major health burden. Children older than 3 years have a higher risk of such complications, so there is a need for proper diagnosis and treatment. Primary prophylaxis of all cases of pharyngitis is not practically feasible.

Vaccine against GAS has been prioritized by global action plan 2014, though not a reality till today as there is no commercially available vaccine. The major issue is a high diversity of strains of GAS. M-surface protein serotype are strain specific and each is distinct with no cross protection offered (250 M-serotypes). Other antigens used for vaccine formulations are SPE-A, SPE-B, C5a peptide, fibronectin binding protein sfb1 and so on. Drug resistance is another issue which the physicians need to be aware of. One such study in Wisconsin, demonstrated azithromycin resistance in 15% of isolates.² This places emphasis on penicillin being the drug of choice until and unless the patient has penicillin allergy.

Clindamycin should be used as add on with penicillinase resistant antibiotics in STSS and ANF type II.

The revised Jones criteria 2015, should guide us in diagnosis and treatment of ARF/rheumatic heart disease cases. Advantage is in picking up subclinical cases of carditis by repeated echocardiography and Doppler study.

Secondary prophylaxis has been proven to prevent the recurrence of ARF, however this is not so for PANDAS. Some

physicians do practice prophylaxis for repeated exacerbations of PANDAS.

REFERENCES

1. Kilian M. *Streptococcus and Enterococcus*. Greenwood D. Medical Microbiology, A guide to Medical infections, 18th ed., Churchill Livingstone Elsevier: Edinburgh; 2012. p. 183.
2. Dietrich ML, Steele RW. Group A *Streptococcus*. *Pediatr Rev* 2018;39(8):379–391. DOI: 10.1542/pir.2017-0207.
3. Pichichero ME. Group a streptococcal tonsillopharyngitis: cost-effective diagnosis and treatment. *Ann Emerg Med* 1995;25(3):390. DOI: 10.1016/S0196-0644(95)70300-4.
4. Tsevat J, Kotagal UR. Management of sore throats in children: a cost effectiveness analysis. *Arch Pediatr Adolesc Med* 1999;153(7):681. DOI: 10.1001/archpedi.153.7.681.
5. Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the infectious diseases society of America. *Clin Infect Dis* 2012;55(10):e86. DOI: 10.1093/cid/cis629.
6. Kronman MP, Zhou C, Mangione-Smith R. Bacterial prevalence and antimicrobial prescribing trends for acute respiratory tract infections. *Pediatrics* 2014;134(4):e956. DOI: 10.1542/peds.2014-0605.
7. Kumar RK, Tandon R. Rheumatic fever & rheumatic heart disease: the last 50 years. *Indian J Med Res* 2013;137(4):643.
8. Robert R. Acute pharyngitis. Lliegman. ed. *Nelson's Textbook of Pediatrics*, 20th ed., Philadelphia: Elsevier; 2016. p. 2017.
9. Beaton A, Carapetis J. The 2015 revision of the Jones criteria for the diagnosis of acute rheumatic fever: implications for practice in low-income and middle-income countries. *Heart Asia* 2015;7(2):7–11. DOI: 10.1136/heartasia-2015-010648.
10. Laupland KB, Davies HD, Low DE, et al. Invasive group A streptococcal disease in children and association with varicella-zoster virus infection. Ontario group a streptococcal study group. *Pediatrics* 2000;105:E60. DOI: 10.1542/peds.105.5.e60.
11. Tapiainen T, Launonen S, Renko M, et al. Invasive group a streptococcal infections in children: a nationwide survey in Finland. *Pediatr Infect Dis J* 2016;35(2):123. DOI: 10.1097/INF.0000000000000945.
12. <https://www.cdc.gov/abcs/reports-findings/survreports/gas15.html> (accessed on February 15, 2018).
13. Nelson GE, Pondo T, Toews KA, et al. Epidemiology of invasive group a streptococcal infections in the United States, 2005–2012. *Clin Infect Dis* 2016;63(4):478. DOI: 10.1093/cid/ciw248.
14. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCS). ABCs Report: group A *Streptococcus*, 2012. www.cdc.gov/abcs/reports-findings/survreports/gas12.html (accessed on August 06, 2014).
15. Lamagni TL, Neal S, Keshishian C, et al. Severe *Streptococcus pyogenes* infections, United Kingdom, 2003–2004. *Emerg Infect Dis* 2008;14(2):202. DOI: 10.3201/eid1402.070888.
16. Shulman S. Group A *Streptococcus*. Kliegman. ed. *Nelson's Textbook of Pediatrics*, 20th ed., Philadelphia: Elsevier; 2016. p. 1327.