Review / *Derleme*

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Invasive Group A Streptococcus Infections in Children

Çocuklarda İnvaziv Grup A Streptokok Enfeksiyonları

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Abstract

Group A streptococci (GAS) are one of the leading causes of invasive bacterial diseases worldwide, and the incidence of invasive GAS (iGAS) infections has been increasing worldwide for the last 20 years. Epidemiological data in developing countries are very limited, as these infections are only required to be reported in a limited number of European countries. Although group A streptococci are universally susceptible to β-lactam antibiotics, resistance to penicillin alternative treatment regimens (macrolide and lincosamide antibiotics) as well as the emergence of subclinical β-lactam resistence is of concern. Despite the vaccine studies that have been going on for a century, there is no effective vaccine yet.

Keywords: *Streptococcus pyogenes*, children, invasive group A streptococcus infections, antibiotic resistance

Öz

Grup A streptokoklar (GAS) tüm dünyada invaziv bakteriyel hastalıkların önde gelen nedenlerinden biridir ve invaziv GAS (iGAS) enfeksiyonlarının sıklığı son 20 yıldır tüm dünyada artmaktadır. Bu enfeksiyonlar, yalnızca sınırlı sayıda Avrupa ülkesinde bildirimi zorunlu olduğundan, gelişmekte olan ülkelerde epidemiyolojik veriler oldukça sınırlıdır. Grup A streptokoklar evrensel olarak β-laktam antibiyotiklere duyarlı olmasına rağmen penisiline alternatif tedavi rejimlerine (makrolid ve linkozamid antibiyotiklere) direnç ve ayrıca subklinik β-laktam direncinin ortaya çıkması endişe vericidir. Bir asırdır devam eden aşı çalışmalarına rağmen etkili bir aşı henüz bulunmamaktadır.

Anahtar Kelimeler: *Streptococcus pyogenes*, çocuklar, invaziv grup A streptokok enfeksiyonları, antibiyotik direnci

Introduction

Streptococcus pyogenes [Group A *Streptococcus*; (GAS)] is a pathogen that causes asymptomatic infection, pharyngitis, pyoderma, scarlet fever or invasive disease and has the potential to trigger immune sequelae after infection. Recent studies report that the incidence of invasive group A streptococcal (iGAS) infections is increasing globally. Although most of the burden of morbidity and mortality due to group A streptococci is in resource-limited countries, data on GAS incidence and mortality in these countries are very limited. Overall, approximately 20% of patients with iGAS infection die within the first seven days after infection. After 2014, mortality rates of up to 45% have been reported in population-based and multicenter hospital-based studies in both high- and middle-low income countries (1,2).

Microbiology and Pathogenesis

Streptococcus pyogenes is the only member of Lancefield group A and its only known reservoir is human skin and mucous membranes. More than 240 different serotypes or genotypes of group A streptococci have been identified based on M-protein serotype or M-protein gene sequence (*emm* types). In general, *emm* typing is more discriminative than M-protein serotyping. *M/emm* typing is valuable for epidemiologic studies and some M types are associated with specific GAS diseases. M types associated with invasive disease are M1, M3, M6, M12, M18 and M28 (2).

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Group A streptococci utilize a number of virulence factors that allow colonization, dissemination and transmission within the host and disrupt both innate and adaptive immune responses to infection. Some exotoxins released from these organisms bind to class II major histocompatibility molecules such as superantigens, causing excessive T lymphocyte stimulation and excessive release of T cell mediators, proinflammatory cytokines and subsequent shock. Streptococcal pyrogenic exotoxins are related to the pathogenesis of streptococcal toxic shock syndrome (STSS) and severe infections (3).

Epidemiology

The incidence of GAS bacteremia and/or invasive infection in children is reported to be 1-3/100.000 per year, with the incidence highest in children under one year of age (3-5/100.000). In late 2022, the World Health Organization (WHO)/ Europe and the European Center for Disease Prevention and Control reported an increase in the number of cases of iGAS disease. In particular, several European countries (including France, Ireland, the Netherlands, Sweden, Sweden and the United Kingdom) have reported an increase in the number of iGAS disease cases and associated deaths among children under 10 years of age since September 2022. The United Kingdom is the country worst affected by this spike (4). As of December 7, 2022, the UK alone had reported more than 6.600 cases of scarlet fever, as well as 652 iGAS infections in a period of just 12 weeks. In the same period, around 60 deaths were confirmed nationwide, with an average case fatality rate of 9.92%. The highest case mortality rates were observed in the 10-14 age group and in people aged 75 years and older (5). Since group A streptococcal and iGAS infections are notifiable only in a limited number of European countries, WHO stated that it is difficult to assess the general level of circulation of GAS in the European Region. Notification is not mandatory in our country.

Studies suggest that the reason for the sudden increase is not related to a specific or new strain, or to the increase in antibiotic resistance of GAS. The elimination of COVID-19-related global lockdowns, increased social interaction and relaxation of other pandemic measures such as hand hygiene may play a role. During the pandemic, it has been claimed that the low burden of many viral and bacterial pediatric infections and decreased immune stimulation, as well as low vaccination rates, are also important, and that as the lockdown periods are prolonged, the number of susceptible individuals increases and the risk of future epidemics will be high. It has also been reported that a concurrent increase in reports of other respiratory infections, including influenza and respiratory syncytial virus (RSV), may also be responsible. It has also been suggested that COVID-19 infections (both symptomatic and asymptomatic) may have led to immune dysregulation in children, making them susceptible to subsequent infections (5).

In a study evaluating iGAS cases in children under 15 years of age in the 37-48th week of the year in 2022 in England and Wales, where notification of iGAS and scarlet fever is mandatory, it was observed that iGAS isolation from lower respiratory tract samples and viral-coinfection rates increased in November 2022. The most commonly identified respiratory tract viruses were RSV, human metapneumovirus (hMPV) and rhinovirus (6). According to a survey involving seven hospitals in the Netherlands, it has been reported that there has been an increase in pediatric iGAS cases since the beginning of 2022 compared to the pre-COVID-19 period (2018-2019), the most significant increase was in the 0-5 age group, in cases of empyema and necrotizing fasciitis, and mortality was 9% (7).

In a study (20 studies from Canada, Finland, Fiji, France, Ireland, Israel, India, Kenya, Norway, South Africa, South Africa, United Kingdom and the United States) evaluating the incidence, mortality and neurodevelopmental outcomes of iGAS in pregnant women and children under five years of age between January 1, 2000 and June 3, 2020 according to the income levels of the countries, it was reported that there were no data on iGAS in pregnant women in middle-low income countries and very limited data in children. It has been reported that the risk of neonatal fatalities in middle-low income countries is 20 times higher than in high-income countries and studies reporting neurodevelopmental outcomes related to iGAS are absent in both high- and low-middle-income countries (8).

Risk Factors

Although various risk factors have been identified for invasive *S. pyogenes* infection, it is known that approximately 20-30% of cases have no risk factor or predisposing factor. This rate is higher especially in children and 50-80% of children have no identified risk factor. The most common risk factor is trauma, surgery or chronic skin lesions as they provide a gateway for streptococci and have been reported in 17-25% of all cases (9). In regions where scabies and impetigo are common, the incidence of iGAS is high and half of iGAS cases in these regions have skin and soft tissue infections (10).

The relation between iGAS and varicella infection is well known. In a study from southern Israel, it has been observed that the overall annual rate of pediatric GAS bacteremia infections decreased by approximately 50% after varicella vaccine was included in the national vaccination program (11).

Invasive GAS infections, along with influenza and other respiratory viruses, often occur in the winter season. Influenza superinfections with GAS have been shown to occur regularly, associated with high mortality. In a study investigating the extent to which influenza A and B, RSV and rhinovirus

circulation contribute to the incidence and severity of iGAS, it has been reported that up to 40% of all cases of STS can be attributed to influenza A circulation (12). In a study evaluating the impact of SARS-CoV-2 on iGAS infections in children, it was reported that a gradual increase in iGAS disease was observed between 2017-2019, a significant decrease was observed from April 2020, and no association with SARS-CoV-2 was observed in any of the pneumonia cases (13).

In the UK, between 1991 and 2014, a significant increase was observed in the number of patients admitted to hospital for treatment of acute tonsillitis and pharyngitis and in the number of iGAS cases in children aged 14 years and younger with the decreasing number of tonsillectomies with compliance with tonsillectomy guidelines (14).

The role of the pharynx as a gateway for iGAS infections has been demonstrated in animal models, but invasive spread through the throat in humans remains a hypothesis. One study has reported that 2.2% of adult and 19.8% of pediatric cases had pharyngotonsillitis at least four weeks before invasive infection (15). In adult iGAS cases, GAS has been detected in the throat in 22% of 45 patients by molecular method. These findings suggest that hematogenous spread from the nasopharynx may be possible (16).

Particles causing air pollution (diesel exhaust particles) have been shown to increase GAS colonization and bacterial spread in mice and cause more severe lung infection and morbidity (17).

Clinic

Invasive GAS infection is defined as the isolation of *S. pyogenes* from a sterile site or from a non-sterile site in a patient with necrotizing fasciitis or SSTS. Invasive infections include skin and soft tissue infections with bacteremia, necrotizing soft tissue infections, STSS, endocarditis, peritonitis, musculoskeletal infections (septic arthritis and osteomyelitis), lower respiratory tract infections (pneumonia and empyema), bacteremia, abscesses (pelvic or retropharyngeal) and postpartum genital infections (2).

Intracranial GAS infection in children is rare and serious, with few data available. The pathogenesis of intracranial GAS infection is multifactorial and may occur secondary to bacteremia, parameningeal infection, pharyngitis or head trauma. Most intracranial GAS infections occur secondary to intracranial spread of otitis media, mastoiditis or sinusitis (Figure 1). Between 1997 and 2014, 91 (3.5%) of 2.596 children with iGAS identified by the Centers for Disease Control and Prevention's (CDC) laboratory-based Active Bacterial Core surveillance system had intracranial infections. Intracranial infections were most common in winter and in children under one year of age, with the main intracranial infections reported as meningitis (42%), intracranial infection after otitis media, mastoiditis or sinusitis (41%) and ventriculo-peritoneal shunt infection (17%). Case mortality rate was reported as 15% and the most common *emm* types were *emm* 1 and 12, risk factors for intracranial GAS infection were reported as presence of ventriculoperitoneal shunt and middle ear or sinus infection (18).

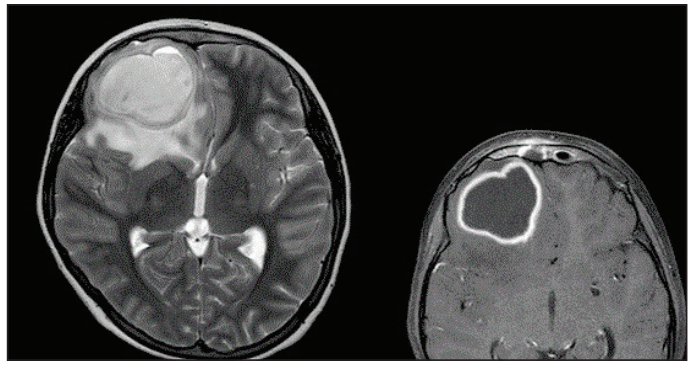

Figure 1. Contrast-enhanced brain MRI of a patient with *S. pyogenes* growth in brain abscess culture revealed right frontal abscess secondary to right frontal sinusitis and osteomyelitis in the anterior and posterior tabula of the right frontal sinus.

Treatment

Treatment of Streptococcal Toxic Shock Syndrome

Management of streptococcal TSS includes treatment of septic shock and associated complications, surgical debridement of the infection, antimicrobial therapy, and intravenous administration of immune globulin. Because streptococcal sepsis causes capillary leak and resistant hypotension, large volumes of intravenous fluids and vasopressors may be required to maintain perfusion. Early aggressive surgical intervention is important in STS with necrotizing soft tissue infection (19).

Initially, since SSTS cannot be differentiated from sepsis due to other pathogens, clindamycin, vancomycin, carbapenem or penicillin + beta-lactamase inhibitor should be started in suspected SSTS. Once streptococcal TSS is proven, treatment consists of a combination of beta-lactam agent and clindamycin (20). *S. pyogenes* is extremely sensitive to bactericidal beta-lactam antibiotics; however, penicillin monotherapy is associated with high morbidity and mortality in GAS infections associated with toxin production (TSS and necrotizing soft tissue infection) (21). Experimental studies have shown treatment failure with penicillin monotherapy when high inoculum is present (22).

Clindamycin and penicillin do not have additive, synergistic or antagonistic effects in vitro. The use of clindamycin is supported by observational studies. In a retrospective study of 1.079 patients with invasive GAS infection, additional clindamycin use has been found to be associated with lower mortality, and this survival advantage has also been seen in patients without shock or necrotizing fasciitis (23).

Advantages of clindamycin;

1) Its efficacy is not affected by inoculum size or bacterial growth phase.

2) Suppresses bacterial toxin production.

3) It has a longer postantibiotic effect.

4) Suppresses the synthesis of penicillin binding proteins (24).

Clindamycin or linezolid (when clindamycin resistance exists) should be continued until clinically and hemodynamically stable for at least 48 to 72 hours, after which penicillin monotherapy may be used. The optimal duration of antibiotics in streptococcal TSS should be tailored to the individual patient's circumstances, including the source of infection and clinical response to treatment. Ceftriaxone or cefazolin is used as an alternative to penicillin in patients with sensitivity to beta-lactam antibiotics (in the absence of anaphylaxis), and vancomycin or daptomycin is used instead of penicillin in patients with anaphylactic reactions (Table 1) (20,25).

Intravenous Immunoglobulin (IVIG)

In patients with streptococcal TSS, 1 g/kg IVIG on day 1, followed by 0.5 g/kg on days 2 and 3 is recommended. This approach is supported by a meta-analysis showing that the use of IVIG has caused a decrease in mortality (Table 1) (26).

Treatment of other iGAS Infections

Penicillin G and clindamycin therapy is recommended for the initial treatment of GAS bacteremia and the optimal duration of antibiotic therapy is uncertain. In patients without shock, organ failure or necrotizing infection, it is recommended to discontinue clindamycin within 48 hours and continue penicillin monotherapy for at least 14 days. In patients with GAS bacteremia (in the absence of shock, organ failure or necrotizing infection), treatment can be completed with an oral agent (penicillin V, amoxicillin, cephalexin, clindamycin) after resolution of bacteremia and systemic manifestations of infection.

Table 1. Medical treatment in Invasive GAS infections

Diagnosis	Antibiotic Treatment[1]	Adjuvant Treatment
Suspicion of streptococcal toxic shock	Clindamycin + vancomycin + carbapenem (or penicillin + beta-lactamase inhibitor)	
Streptococcal toxic shock (definitive diagnosis)	Beta-lactam + clindamycin[2]	IVIG 1 g/kg on day 1, 0.5 g/kg on days 2 and 3
Invasive GAS infection	Penicillin G + clindamycin[2]	IVIG[3]

[1]Ceftriaxone or cefazolin is used as an alternative to penicillin in patients with sensitivity to beta-lactam antibiotics (in the absence of anaphylaxis), and vancomycin or daptomycin is used instead of penicillin in patients with anaphylactic reactions.
[2]Linezolid can be used in clindamycin resistance.
[3]It is not routine in invasive GAS infection but may be given in patients with severe and refractory shock.

In deep-seated iGAS infections, inflammation and toxin-mediated necrosis of tissue and thrombosis of dermal vessels limit antibiotic perfusion, and prompt and aggressive surgical exploration and debridement are mandatory. Urgent surgical consultation should be sought in patients with extreme pain and fever or who are toxic. Surgical examination provides specimens to determine the etiology and allows assessment of the extent of necrosis. The duration of treatment depends on the clinical course and adequacy of surgical debridement; treatment should generally be continued for up to 14 days from the last positive culture obtained during surgical debridement (20).

Nonsteroidal Anti-inflammatory Agents

The role of nonsteroidal anti-inflammatory drugs (NSAIDs) as a risk factor in the development of invasive GAS infection is controversial. In 1985, Brun-Buisson et al. reported a possible association between NSAID use and the development of severe *S. pyogenes* necrotizing fasciitis (27). Aronoff and Bloch, in a meta-analysis of studies published up to 2002 to examine a possible cause/effect relationship, stated that the data did not support a causal role for NSAIDs because most studies lacked appropriate control groups or had other important limitations, but that further studies were needed (28). Subsequently, it has been reported that NSAID use was independently associated with serious secondary complications in children with varicella infection, indicating that NSAID use was independently associated with a threefold increased risk for the development of STS. In experimental muscle injury studies, NSAIDs [especially nonselective cyclo-oxygenase (COX) inhibitors] have been reported to increase the likelihood of GAS-induced necrotizing fasciitis/myonecrosis and bacteremia at the site of injury, and that the use of COX inhibitors reduces the efficacy of antibiotics, including penicillin or clindamycin. It has been reported that NSAIDs may predispose individuals to more severe *S. pyogenes* infections by inhibiting the negative feedback loop that limits TNF-α production, and delay diagnosis and antibiotic treatment by masking the signs and symptoms of developing infections (3).

Antibiotic Resistance in *S. Pyogenes*

Although GAS are universally susceptible to β-lactam antibiotics, resistance to alternative treatment regimens to penicillin (macrolide and lincosamide antibiotics) as well as the emergence of subclinical β-lactam resistance is a major problem. Macrolide, lincosamide and streptogramin B antibiotics have chemically different but similar mechanisms

of action. Bacteria resist these antibiotics by drug inactivation, efflux and ribosomal target modification. In streptococci, efflux is mediated by the mef genes for limited resistance to macrolide (M phenotype). Target modification is controlled by erm-encoded methylases and manifests as constitutive or inducible macrolide-lincosamide-streptogramin B (MLSB) cross-resistance phenotypes. Rare resistance mechanisms include spontaneous mutations in the target sites of 23S rRNA or ribosomal proteins L4 and L22 (29).

One of the first reports on antibiotic resistance reported that 70% of strains causing pharyngitis in Japan in 1979 were resistant to erythromycin. Between 2011 and 2019, the CDC Active Bacterial Core surveillance program reported that iGAS isolates not susceptible to erythromycin and clindamycin increased from 11.9% to 24.7% and from 8.9% to 23.8%, respectively, largely associated with *emm77*, *emm58*, *emm11*, *emm83* and *emm92* strains (30). It was found that resistant isolates were most common and clustered in people who were homeless, imprisoned, drug users and long-term residents of nursing homes. It was reported that 98.4% of the strains isolated from children with tonsillitis and scarlet fever in China in 2014 were resistant to both clindamycin and erythromycin and 90.4% of them showed structural MLSB phenotype. The prevalence of erythromycin-resistant *S. pyogenes* has been shown to be correlated with the consumption of macrolide antibiotics (29).

For severe GAS infections, treatment guidelines of the Infectious Diseases Society of America (IDSA) recommend the combination of clindamycin with penicillin for 10-14 days (31). Clindamycin resistance is associated with treatment failures in patients with severe *S. pyogenes* infection. Oxazolidinones (linezolid, tedizolid), a new class of antibiotics, are protein synthesis inhibitors and can be used in clindamycin resistance. A combination of penicillin and linezolid is recommended for patients with STS due to clindamycin-resistant GAS isolates. In the treatment of myonecrosis due to erythromycin/clindamycin-resistant GAS in adult mice, linezolid and tedizolid have been shown to significantly delay disease progression and/or improve survival (32).

Resistance to Other Antibiotics

Tetracycline resistance in GAS may be associated with macrolide resistance. A retrospective study conducted in Taiwan between 2000 and 2019 found that 12.3%, 99.2% and 13.1% of macrolide-resistant GAS harbor *tet*O, *tet*M and *tet*K genes, respectively. The combination of sulfamethoxazole and trimethoprim is used for the treatment of GAS skin infection, especially in endemic areas. Currently, co-trimoxazole resistance is rarely reported among global GAS isolates. High level resistance to aminoglycosides and fluoroquinolones is rare and resistance to new molecules (such as oxazolidinones, tigecycline and daptomycin) has not been defined (33).

β-Lactam Sensitivity

β-lactams target penicillin-binding proteins (PBPs) to block peptidoglycan cross-linking in metabolically active bacteria, leading to bacterial death. Resistance testing for penicillins or other β-lactams is not recommended for the treatment of GAS infections, as *S. pyogenes* remains susceptible to penicillin, and despite its widespread use, there has been little change in the susceptibility of GAS to penicillin. However, in 2020, the first report of a mutation of the *Pbp2x* cell wall synthesis enzyme was reported in two clinical isolates of *S. pyogenes* in which the ampicillin minimal inhibitory concentration (MIC) was elevated but did not reach resistance levels. Subsequently, whole genome sequence analysis of a large number of GAS reported more than 100 strains carrying *Pbp2x* mutations with high MIC levels against some β-lactam antibiotics, including penicillin, but without reaching resistance levels. It has been reported that penicillin-resistant and tolerant *S. pyogenes* strains have severe physiological defects with extremely poor proliferation rates and large morphological abnormalities, and the probability of development among clinical isolates is low, and the tolerance observed in such mutants is not clinically significant (34).

In our country, studies on antimicrobial resistance in GAS infections are quite limited. Çiftçi et al. investigated penicillin tolerance in 263 GAS isolates isolated from children with tonsillopharyngitis between December 2000 and March 2001 and found no penicillin resistant or tolerant strains (35). Between October 2000 and October 2002, erythromycin resistance was found in 2.6% of 1355 throat swab samples (94.2% children, 5.8% adults) in Ankara, Türkiye (n= 36), of which 17 (47.2%) showed limited resistance to macrolide (M phenotype) and the others showed inducible (16 isolates, 44.4%) or structural (three isolates, 8.3%) MLSB resistance. It was reported that the prevalence of macrolide resistance was low in Ankara and routine antimicrobial susceptibility testing was not required (36). No benzylpenicillin, ceftriaxone, vancomycin, levofloxacin and linezolid resistant strains were found in the isolates of 22 patients (age 3-82 years) with iGAS infection hospitalized between March 2006 and March 2009 at Karadeniz Technical University Faculty of Medicine, 4 (18%) strains were resistant to tetracycline, 3 (13.5) strains were resistant to chloramphenicol, 9 (41%) strains were resistant to tetracycline and 1 (4.5%) strain was moderately susceptible to erythromycin. In the strain, which was moderately susceptible to erythromycin, inducible clindamycin resistance was also detected (37). In a surveillance study conducted between September 2002 and June 2003 in 18 centers in Türkiye, macrolide resistance was found to be 1.3% in 312 *S. pyogenes* respiratory tract isolates, *mef*A gene was detected in three of them and *erm*B gene in one isolate. Moderate levofloxacin resistance was found in one isolate (38). In 2011, moderate resistance to erythromycin was found in 2%, moderate

resistance to clindamycin was 1.1%, moderate resistance to azithromycin was 1.8% and moderate resistance to clarithromycin was 1.8% in GAS isolated from throat cultures in children; 1.3% of the strains were resistant to erythromycin, 2.8% to azithromycin and 1.3% to clarithromycin (39). As can be seen, there are no antibiotic resistance studies on GAS in our country in recent years.

Prevention

Prophylaxis for Contact Persons

GAS is a highly contagious organism. The risk of iGAS disease among household contacts of people with invasive GAS infection is 200-2.000 times higher than in the general population. The approach to post-exposure prophylaxis for the prevention of invasive GAS infection is unclear. The duration and proximity of contact and host factors in contacts should be considered in the decision on prophylaxis. Prophylaxis is recommended for contacts with open wounds, recent surgery or childbirth, concurrent viral infections such as varicella or influenza, or immunodeficiency. HIV and intravenous drug use between 18-45 years of age are independent risk factors. At age 45 and older, diabetes, heart problems, cancer and corticosteroid use are important risk factors. In addition, those aged 65 years and older are at risk due to high mortality from invasive disease. Therefore, prophylaxis in the elderly or people with the aforementioned risk factors makes sense. Chemoprophylaxis is not recommended in schools or kindergartens due to the rarity of secondary cases and the low risk of iGAS infection in children (2).

Antibiotic prophylaxis in contacts varies across countries. In our country, in the information note published by the Ministry of Health General Directorate of Public Health this year, it is recommended to start contact investigation in proven iGAS infection. Contact prophylaxis is recommended for persons aged 75 years and older, pregnant women ≥37 weeks, puerperium (first 28 days postpartum), newborns (up to 28 days), persons with varicella or who have had varicella within two days of last contact with an iGAS case, kindergarten and classmates of the index case in a nursery, kindergarten or school class or in the same school bus when there is a case of another iGAS infection, including iGAS tonsillopharyngitis, in the last 10 days. In addition to the above group, contact prophylaxis is also recommended for those who spent at least 24 hours in the same household with the index case in the seven days before the onset of symptoms of the index case, if the index case is STS. Other close contacts should be warned and informed about the signs and symptoms of GAS infection and should seek medical advice promptly if they develop a febrile illness or any clinical signs of GAS within 30 days. In contact prophylaxis, cephalexin, cefadroxil, cefuroxime axetil, cefdinir, clindamycin, clarithromycin and azithromycin are recommended for those allergic to oral penicillin (25).

Indications for testing for GAS infection in contacts are very limited. It is not recommended except in contacts at high risk for sequelae of GAS infection, such as acute rheumatic fever (ARF). In schools, kindergartens, or other settings where many people are in close contact, the prevalence of GAS pharyngeal carriage in healthy children can reach 25% in the absence of a streptococcal outbreak. Therefore, in-class or more widespread culture practices are generally not necessary (40).

Infection Control

In addition to standard precautions, droplet precautions as well as contact precautions should be taken in patients with iGAS infection associated with soft tissue involvement. Droplet and contact precautions can be discontinued after the first 24 hours of antimicrobial treatment (41).

Vaccine

Despite more than a century of research, an effective GAS vaccine is not yet commercially available. There are historical, scientific, and economic challenges in vaccine studies. The main challenge in vaccine studies is that *S. pyogenes* vaccine antigens contain autoimmune epitopes that can trigger ARA. Massell et al. reported at least two and possibly three cases of ARA due to M protein vaccine in siblings (n= 21 children) of patients with ARA. Following this study, the US Federal Drug Administration (FDA) banned *S. pyogenes* vaccine studies in humans for more than 25 years. Although the ban was lifted in 2005, only four vaccines have since progressed to phase I studies.

Another problem is the complex epidemiology of *S. pyogenes* infections. These include a large number of *emm* types (>240 *emm* types), different anatomical location of infection, epidemiology, disease prevalence and geographical differences in disease burden. Establishing animal models to evaluate protective efficacy against human-only adapted *S. pyogenes* is also a major challenge. Furthermore, economic challenges hamper vaccine studies, as 95% of severe GAS disease occurs in low- and middle-income countries.

In recent years, GAS vaccine research and development efforts have been revitalized. In 2018, WHO declared the global elimination of ARA and rheumatic heart disease as a priority and emphasized the importance of vaccine studies against iGAS infections and increasing trends in antibiotic overuse (33,42).

Conclusion

Until an effective vaccine for group A streptococcus is developed, antibiotics are necessary to treat infection. Although penicillin has been used to treat GAS for over 80 years without resistance, low failure rates and mutations in *pbpx2* are of concern for penicillin insensitivity, and special surveillance is needed as the emergence of penicillin resistance would constitute a public health crisis. Clindamycin and macrolide

resistance is particularly high in some parts of the world. Antibiotic resistance in GAS isolates should be monitored both for the prevention of GAS-related immunologic sequelae and for the safe use of clindamycin in iGAS infections. In our country, reporting of iGAS cases may be mandatory and monitoring antibiotic resistance in GAS isolates will be useful.

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