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Group A *Streptococcus* invasive infection in children: Epidemiologic changes and implications

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ABSTRACT

Group A *Streptococcus* (GAS) can cause a broad array of clinical manifestations and complications. Recently, in post COVID-19 postpandemic months, there has been an increased incidence and severity of invasive infections in the pediatric age group in Spain and other European countries with high morbidity, affecting mostly to young children, associated with seasonal peaks in incidence of viral respiratory pathogens. The increased in incidence and severity has not been associated with predominant GAS strains, but rather to the lack of immunity to both GAS and common viral respiratory infections due to isolation measures to prevent COVID-19. Due to the nonspecific initial clinical manifestations a high index of suspicion is necessary in order to initiate a prompt medical and surgical treatment when necessary to improve the outcome. Prevention strategies are needed as well as continuous microbiological surveillance of iGAS strains.

Keywords: Group A *Streptococcus* infection, infection, invasive, children

INTRODUCTION

Streptococcus pyogenes, also known as group A Streptococcus (GAS), an exclusive human pathogen, can cause a broad range of clinical manifestations and complications, from asymptomatic infections and minor illnesses, such as pharyngitis and impetigo (noninvasive disease), to very severe and deadly infections (invasive diseases) or postinfectious sequelae such as rheumatic heart diseases or poststreptococcal glomerulonephritis [1-3]. Invasive infection (iGAS), defined as laboratory isolation of GAS from any normally sterile site, or isolation of GAS from a non-sterile site in a patient with necrotising fasciitis or streptococcal toxic shock syndrome (STTS) occurs unfrequently, but may lead to sepsis, STSS, complicated pneumonia, meningitis, osteoarticular infections, deep abscesses, or necrotizing fasciitis with potentially fatal outcome [3], requiring a high index of suspicion to start early treatment. During the last decade, increased rates of iGAS disease in children have been reported in many countries [4-6].

EPIDEMIOLOGY

Children may have a higher risk of severe disease. The observed increased rates of infection along with the higher morbidity in the pediatric age group has led to an increase in iGAS notifications in children, particularly in those below 10 years of age [4-7]. Even though during the pandemic years of COVID-19, respiratory infections, including GAS, dramatically decreased due to lockdown, social distancing and the use of masks [8], a recent upsurge has been observed in Europe [5-7]. Early December 2022, the United Kingdom Health Security Agency (UKHSA) published a surveillance report on an unusual incidence of GAS tonsilitis, scarlet fever and simultaneously of iGAS infections with high morbidity and mortality and issued a warning to parents and clinicians about the high iGAS incidence among children [7,9]. Other countries in Europe, including Spain [6], are also reporting similar concerns of increased incidence and severity of GAS infections [6,7,9].

The respiratory tract and skin are the two main portals of entry for iGAS [4]. There are well-known risk factors associated with iGAS. Disease onset and progression can be very rapid, with high fatality rates, especially in young children and elderly, patients with comorbidities (diabetes or cardiovascular disease), immunocompromised, alcohol abuse, intravenous drug users, pregnant women and previous varicella infection [1,10]. Environmental factors such as number of household inhabitants and residential overcrowding have also been associated with iGAS [1]. Concomitant respiratory viral infection might also play a role on the incidence and severity of iGAS, particularly in children. Notably, during the 1918 influenza pandemic, streptococcal superinfections were important causes of death, which besides *Streptococcus pneumoniae* also included GAS [10]. GAS carrier has not consist-

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ently been associated with transmission, although occasional outbreaks with more virulent strains have been reported in children, also in Spain [11,12]. The ability of GAS to transmit quickly and efficiently throughout a closed population during outbreaks may potentially cause an upraise in invasive infection and may indicate a need for intervention to control GAS transmission.

The increased in incidence and severity has not been associated with predominant strains. In the largest study on the microbiology and epidemiology of iGAS disease in Spain, Villalón et al showed that the most prevalent emm types were emm1, emmm89, emm3 and emm4 [13]. In children, the most common emm in Spain type has been emm1 [13,14] in keeping with other European countries [14]. Although it is possible that changes in GAS genome could have led to increased transmissibility or virulence, there has been diversity of strains, and only a minority of cases are attributed to outbreaks [4]. By contrast, the recent upsurge in IGAS in children has been linked to marked seasonal peaks in incidence of respiratory viral pathogens (mostly RSV and influenza), after withdrawing the strict preventive measures against COVID-19 [7]. In addition, the lack of specific immunity to GAS and common viral respiratory tract infections during this isolation period may have predispose young children to higher rates and more severe infections after exposure. Recent studies show that up to 60% of iGAS in children UK had a concomitant viral respiratory tract infection [15].

ETIOPATHOGENESIS

The process of human infection by GAS is complex and multifactorial, involving both host and bacterial factors that contribute to its pathogenesis. Although the surface C-polysaccharide antigens are used to classify *Streptococcus* spp. into Lancefield groups, they have not a major involvement in virulence. By contrast, several virulence factors have been identified in GAS. The major virulence GAS appears to be the surface M protein which is encoded by the *emm* gene with marked immunogenic and virulence properties, including its role in phagocytosis inhibition and adhesion, and promoting a proinflammatory response that may lead to tissue destruction and dissemination. GAS is classified based on the sequence of the 5′ end of the gene encoding the M protein (*emm*). More than 230 *emm* genotypes have so far been identified. As protective antibodies can be generated against the M protein, it represents one of the most characterized vaccine candidates to date.

Other virulence factors of GAS include the hyaluronic capsule, streptolysin O, streptolysin S, streptococcal pyrogenic exotoxins A and B, and NAD glycohydrolase NADase. Bacterial exotoxins act as superantingens to trigger polyclonal T-lymphocyte activation by binding to class II major histocompatibility complex molecules, leading to an excessive release of proinflammatory cytokines and subsequent shock [1,10].

CLINICAL MANIFESTATIONS OF IGAS

iGAS occur predominantly in young children. In a large retrospective study conducted in a referral center in Madrid, the median age at diagnosis was 48 months [15]. Similarly, in a Spanish multicenter retrospective study of SGA bacteremias, most infections occurred in children below 4 years of age, with a median of 24 months [16]. The clinical manifestations of iGAS are varied and include cellulitis and subcutaneous abscesses, ENT abscess, pneumonia, osteoarticular infection, mastoiditis, necrotizing fasciitis, bacteremia and STTS [16]. Initial symptoms include an influenza-like illness prodrome, characterized by fever, chills, confusion, myalgia, nausea, vomiting and diarrhea. It is important to recognize cutaneous lesions that may be the portal of entry, including varicella lesions in settings where varicella vaccine has not been administered [2]. In addition, a suspicious sign at onset may be scarlatiniform rash. More unusual manifestations include meningitis, neonatal infections, peritonitis, gastrointestinal and endovascular infections [2].

Interestingly, in the clustered cases reported by the Spanish multicenter network for analyzing iGAS in Spain (PedGAS-net) in late 2022, there was a shift towards a lower age and presentation with pneumonia and pleural effusion as well as a significant increase in ICU admissions of iGAS compared to prepandemic years [6,17]. The overall mortality in this study was 1.8% [6]. Based on published series, the mortality reported ranged from 0-8% [2], still lower than that observed in adults [4]. Table 1 shows the main characteristics of the Spanish children included in PedGAS-net [6]

Table 1 Main characteristics of cases of iGAS reported in PedGAS-net [6]

	N=220
Demographics	
Gender (female)	95 (43.2%)
Age (months)	41.2 (19.3-81.0)
Syndrome	
Toxic shock syndrome	25 (11.4%)
Pneumonia	66 (30.0%)
Skin and soft tissue infections	so (22.7%)
Bone and joint infection	27 (12.3%)
Primary bloodstream infection	23 (10.5%)
Deep neck infections	22 (10.0%)
Mastoiditis	22 (10.0%)
Complications	1
	0 (4.5%)
Necrotizing fasciitis	21 (9.5%)
Abscess	42 (19.1%)
Pleural effusion	3 (1.4%)
Pneumothorax	14 (6.4%)
Acute kidney failure	
Disseminated intravascular coagulation	9 (4.1%)
Outcomes	
Intensive care admission	89 (40.5%)
Died	4 (1.8%)

IMPLICATIONS FOR TREATMENT AND PREVENTION

Due to the non-specific signs and symptoms of the initial clinical manifestations and the rapid course of iGAS in children a high index of suspicion is mandatory to start early treatment, including prompt and aggressive surgical debridement when necrotizing fasciitis is present [2,10]. Antibiotic therapy remains the mainstone for the treatment of both non-invasive and iGAS infection [10]. GAS remains universally sensitive to β-lactam antibiotics. If penicillin-allergic patients, the use of macrolides should be avoided for empiric therapy for iGAS, since resistance to macrolide frequently result in recurrent infection, treatment failure and poor patient outcomes, and vancomycin is preferred. Linezolid and daptomycin are active *in vitro*, but clinical experience in treating invasive GAS infections is limited [10]. The addition of and antitoxin antibiotic such as clindamycin or linezolid is recommended, particularly if necrotizing fasciitis, STTS, or clinical signs of toxin production by SGA (rash, gastrointestinal signs, hemodinamic instability) [1]. The optimal duration of adjunctive clindamycin is uncertain as data are limited, but at least a minimum duration of 3 to 5 days is recommended [10].

Although resistance to macrolides has been variable in Spain even with local differences in the same city, and frequent in some locations, the overall prevalence is decreasing, but still significant. In the large Spanish surveillance study of almost 2000 iGAS isolates analyzed over a 13-year period, the prevalence of erythromycin resistance was 8.9%, whereas clindamycin resistance remains low, around 4% [13]. As clindamycin resistance is increasing in some settings, clinicians need to order susceptibility testing when using clindamycin for adjunctive treatment. The effect of clindamycin resistance in invasive GAS infections remains unclear. A murine model found that inhibitory concentrations of clindamycin reduced both the size of skin lesions and activity of virulence factors, even in clindamycin-resistant GAS strains [10]. Nevertheless, in these cases linezolid is an option and has become more widely used in clinical practice as an adjunctive agent instead of clindamycin [2,10].

In addition, the use of intravenous polyvalent immunoglobulin must be considered in severe cases of iGAS in order to neutralize exotoxins involved and as immunomodulator of the proinflammatory stage [2].

Prevention of secondary cases is of utmost importance. A major step forward would be to maintain high coverage of varicella vaccine and include universal influenza vaccination in children. The inclusion of influenza vaccine in children in some regions in Spain is a major advance in struggling against the challenge of iGAS in children. The ability of GAS to transmit quickly and efficiently throughout a closed population together with the higher risk of vulnerable patients, including children, as well as such as mother-neonate pairs, highlight the importance of immediate notification and assessment of contacts and targeted prophylaxis should be considered [10]. In addition, continuous microbiological surveillance of iGAS strains should be monitored to determine the characteristics and evolution of circulating clones.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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