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REVIEW

Current insights in invasive group A streptococcal infections in pediatrics

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Abstract A rising incidence of invasive group A *Streptococcus* infections (IGASI) has been noted in children in the past three decades. The relative frequency of the infection types showed marked differences to IGASI in adults, and severity of the disease resulted in a mortality rate usually comprising between 3.6% and 8.3%. The *emm*1-type group A *Streptococcus* (GAS) subclone displaying a particular pattern of virulence factors was widely disseminated and prevalent in children with IGASI while the *emm*3-type GAS subclone appeared as a recent emerging genotype. However, the implication of these hypervirulent clones in the increase of IGASI in children is still controversial. Recent advances in our knowledge on pathogenesis of IGASI underlined that deregulation of virulence factor production, individual susceptibility, as well as exuberant cytokine response are important factors that may account for the severity of the disease in children. Future changes in IGASI epidemiology are awaited from current prospects for a safe and effective vaccine against GAS. IGASI are complex infections associating septic, toxic, and immunological disorders. Treatment has to be effective on both the etiologic agent and its toxins, due to the severity of the disease associated to the spread of highly virulent bacterial clones. More generally, emergence of virulent clones responsible for septic and toxic disease is a matter of concern in pediatric infectiology in the absence of vaccination strategy.

Keywords *Streptococcus pyogenes* · Invasive infection · Children · Incidence · Epidemiology · Mortality · Virulence · Bacterial clones · Individual susceptibility · Immune response · Vaccine

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Introduction

Group A *Streptococcus* (GAS) or *Streptococcus pyogenes* may be encountered in diverse clinical situations in children, from throat carriage whose rate may exceed 20% in populations of school-aged children [74] to a wide array of infections, ranging in severity from mild pharyngitis and skin/soft tissue infections to severe invasive infections. The epidemiology of GAS infections has greatly evolved in the last decades. Although invasive GAS infections (IGASI) remain uncommon in children beside common diseases such as pharyngitis, scarlet fever, and skin infection, an emergence of severe infections is noted since the 1980s [3]. Here, we proposed a review of pediatric data on the changing epidemiology of IGASI together with the results of the IGASI surveillance over a 4-year period in our institution. Particular focus was made on molecular epidemiology of GAS clones responsible for IGASI in children and on recent advances in our IGASI pathogenesis

comprehension regarding regulation of virulence factor production, individual susceptibility, and immune response to the infection as well as in vaccine development.

Changing epidemiology of invasive group A *Streptococcus* infections in children

IGASI frequency in the general population increased worldwide in the past three decades [13, 41, 55, 79]. Pediatric data typically included in the description of the overall population also witnessed an increased incidence in the pediatric population. In Ontario, Canada, the incidence of IGASI increased from 1.1 per 100,000 in 1992 to 2.3 per 100,000 in 1995 [36]. Depending on the patient age and country, IGASI incidence rates were 0.05 to 5.7 per 100,000 in industrialized countries while reaching up to 75 per 100,000 in developing countries and aboriginal population (Table 1) [37, 81]. A higher incidence of IGASI was observed in children under 1 year of age [58, 67, 70]. More generally, an inverse relationship was observed between the IGASI incidence and the children's age (Table 1) [14, 15, 25, 38, 41, 43, 51, 56, 58, 67, 70].

In children, risk factors for IGASI are mainly previous infection with varicella zoster virus and other lesions or diseases of the skin [36, 39], and the use of nonsteroidal antiinflammatory drugs [18]. In addition, severe cases of IGASI concurrent with seasonal or 2009 H1N1 influenza were reported in children [25, 65], suggesting that synergy occurred between viral and GAS infections as described for invasive infections with *Streptococcus pneumoniae* or *Neisseria meningitidis* [44, 60, 65]. Seasonal trends are observed with a high incidence of IGASI in winter and spring [13, 33, 55, 66]. Environmental factors may also be associated with an increased risk of IGASI. Factor et al. suggested that children bring GAS into the home and that crowding influenced the development of IGASI [18]. Prolonged close contact between family members, GAS strain virulence, and host susceptibility were considered as important factors involved in the occurrence of familial IGASI clusters [64]. Outbreak of IGASI may also occur in health care centers [1].

Table 1 Review of invasive group A *Streptococcus* infection incidence rates in children

Reference(s)	Year(s) of study	State and/or country	Incidence per 100,000 children per year (age category)
Davies et al. [14]	1992–1993	Ontario, Canada	1.9[b] (<5 years), 2.4[b] (5–9 years), 0.6[b] (10–19 years)
Laupland et al. [36]	1992–1996	Ontario, Canada	1992, 1.1; 1995, 2.3
Mulla et al. [49]	1996–2000	Florida, USA	0.3[b] (<9 years), 0.2[b] (10–19 years)
Montes et al. [48]	1998–2009	Spain	3.1 (<15 years)
Siljander et al. [66]	1998–2007	Finland	2.5 (<1 year), 1.3 (1–14 years)
O'Loughlin et al. [55][a]	2000–2004	USA	5.3 (<1 year), 3.6 (1 year), 2.6 (2–4 years), 1.4 (5–17 years)
O'Grady et al. [54]	2001–2004	Victoria, Australia	4.3[b] (<5 years), 2.8[b] (5–9 years), 1[b] (10–14 years), 0[b] (15–19 years)
Darenberg et al. [13]	2002–2004	Sweden	2[b] (<5 years), 1[b] (5–9 years), 0.5[b] (10–19 years)
Lamagni et al. [33][a]	2003–2004	11 countries, Europe	0.5 to 5[b] (<5 years), 0.5 to 2[b] (5–9 years), 0 to 4[b] (10–14 years), 0.5 to 3[b] (15–19 years)
Luca-Harari et al. [41]	2003–2004	Denmark	2[b] (<5 years), 1.3[b] (5–9 years), 0.4[b] (10–19 years)
Imöhl et al. [24]	2003–2007	Germany	0.22 (<5 years), 0.11 (6–9 years), 0.05 (6–19 years)
Steer et al. [70]	2005–2007	Fiji	44.9 (<1 year), 2–3[b] (0–4 years), <1[b] (5–14 years)
Le Hello et al. [37]	2006	New Caledonia	75 (<5 years), 27[b] (5–14 years)
Bidet et al. [3], Lepoutre et al. [39]	2007	France	5.7 (<5 years), 1.6[b] (5–9 years), 0.58 (10–19 years)
Whitehead et al. [81]	2008	Queensland	3.5 (total pediatric population), 13.2 (aboriginal population)

[a] In these two studies, the incidence in children under 1 year was the second highest rate after that observed for patients over 65 years

[b] Data extrapolated from published figures

Clinical presentation and severity of invasive group A *Streptococcus* infections in pediatrics

IGASI are defined as the isolation of GAS from a normally sterile site in patients with necrotizing fasciitis (NF), streptococcal toxic shock syndrome (STSS), bacteremia with no identified focus or focal infections with or without bacteremia (e.g. meningitis, pneumonia, septic arthritis). The isolation of GAS from a non-sterile site in the presence of signs of serious illness including STSS, soft-tissue necrosis or meningitis and in the absence of another identified etiology, is considered as an invasive infection [75]. STSS and bacterial cellulitis without isolation of GAS are also recognized as being invasive cases in some countries (USA, Canada) [14].

In children, marked differences in the patterns of IGASI were reported compared to the adult population; particularly, septic arthritis, osteomyelitis, and pleural infection were more frequently observed whilst NF is an uncommon presentation [39]. In the University Hospital of Montpellier, a total of 160 children had a streptococcal infection (pharyngitis excluded) over a 4-year study (2007–2010). Among them, 38 children (24%) had an IGASI. Blood cultures were positive in seven cases (18.4%). Complicated infections of soft tissues were the most frequent infections while NF was the less frequent (Table 2). Median age was 7 years (min., 0; max., 15]. Despite the fact that the relative importance of infection types varied according to the study, skin and soft tissues were the most common or one of the most common foci of infection in most pediatric studies (Table 2) [8, 37, 49, 51, 56, 58].

Although the mortality rate in children is lower than that observed in adults (4.4% versus 19.5% in the study by Mulla) [14, 33, 49], the outcome of IGASI can be poor, and clinical condition may require hospitalization in the intensive care unit [62, 81]. Mortality of IGASI usually ranged from 3.6% to 8.3% depending on the study, a higher death rate being observed among children under 1 year of age (8%) than in older children (4% between 1 and 14 years) (Table 2) [14, 22, 34, 47, 70, 81]. Deaths are mainly or totally due to STSS [6], the most severe IGASI in children (27% death rate) [62, 76], and were related to a rapid clinical evolution that does not allow time for effective treatment [22] or to a misunderstanding in the choice of treatment [81]. In the case of partially favorable outcome, sequelae depend on the location of the infection, such as limitation of motion, scars, and loss of vision [22]. Early or late non-suppurative complications not further detailed herein may be observed. However, acute rheumatic fever (ARF), glomerulonephritis, and Sydenham's chorea as well as more complex inflammatory processes such as the still controversial pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections are more usually described in the immediate course of non-invasive GAS infections, particularly pharyngitis [15, 73]. In our institution, three cases of an as-yet little described complication, i.e., multifocal inflammatory syndrome, were observed after IGASI ([20], unpublished data).

Molecular epidemiology, virulence, and resistance of GAS causing invasive infections in children

Since the 1980s, when the increase in invasive infections due to GAS was noted in both patients with comorbid conditions and healthy individuals, including children, several attempts were made to search for specific bacterial clones with particular diffusion propensity and/or particular virulence that could be responsible for this new emergence of IGASI [8, 9, 71]. Although some geographic discrepancies have been noted, most studies based on M protein-encoding gene typing, so-called *emm* genotyping [2, 16], showed that strains belonging to the *emm*1 and *emm*3 types were related to invasive disease and associated with high mortality rates in the general population in developed countries [17, 26]. Studies focusing on the pediatric population remain scarce but showed that *emm*1 genotype predominated among strains involved in IGASI. Among 600 isolates collected from severe GAS disease in children across Europe, the most frequent *emm* types were *emm*1 (26%), *emm*12 (11%), *emm*4 and *emm*3 (10% each), and *emm*28 (7%) [40]. *emm*1, *emm*12, and *emm*3 types were further shown to be significantly more frequent in children than in adults with IGASI [39]. In 2009, 75 strains from pediatric IGASI were genotyped by the French reference laboratory for streptococci. Strains belonged to 20 genotypes, and 5 major *emm* types grouped 74% of the isolates, *emm*1 (33% of the strains) being the most frequent before *emm*3 (13%), *emm*12 (12%), *emm*4 (9%), and *emm*89 (7%) [58]. *emm*1 was the predominant genotype for several years (accounting for 40% to 45% of the strains in the two previous years) [57, 58] whilst *emm*3 genotype appeared as an emerging genotype in 2009. A monocentric study conducted in a French pediatric tertiary care center showed congruent results, with invasive strains of *emm*1 genotype being predominant (35.7%), followed by *emm*12, *emm*3, and *emm*4. Although the authors did not find a significant correlation between *emm* type and clinical data, *emm*1 genotype predominated among strains involved in osteoarticular infections [22].

Several studies suggested that “highly virulent clones” might be responsible for IGASI from the mid-1980s [9]. GAS has a diversified panel of virulence factors (Fig. 1) [4, 11], and some of them have been associated with specific clinical presentation such as the streptococcal pyrogenic exotoxin (Spe) C and NF in children [47]. Six virulence factor-encoding genes, i.e., *speA*, *speB*, *speC*, *smeZ*-1, *ssa*,

Table 2 Relative importance and mortality of invasive group A *Streptococcus* infections in children

Reference	Years of study	Number of cases (age of children)	Cutaneous/ soft tissue/ abdominal/ lymph node infection	Bacteremia without a source	Pulmonary infection	Septic arthritis/ osteomyelitis	NF	STSS	Endocarditis/ pericarditis	Meningitis/ CNS infection	Epiglottitis/ otitis media/upper respiratory tract infection	Other[a]	Death (%)
Laupland et al. [36]	1992–1996	211	44%	16%	6%	19%	4%	7%	0.8%	2%	18%	0.4%	4.1
Mulla et al. [49]	1996–2000	25 (0.05–17 years)	32%	16%	20%	16%	16%	4%	–	8%	16%	–	4.4
Lee et al. [38]	1996–2005	29	–	37.9%	24.1%	6.8%	–	–	–	3.4%	–	–	NS
Caetano et al. [6]	1996–2009	24	29.1%	25%	4.2%	20.8%	4.2%	8.3%	–	–	–	2.3%	8.3
Minodier et al. [47]	1999–2007	68	27.9%	5.9%	19.1%	17.6%	26.5%	–	–	5.9%	–	–	4.4
O'Loughlin et al. [55]	2000–2004	572 (<10 years)	34.8%	35.7%	16.3%	14.8%	0.9%	4.6%	0.2%	0.03%	3.9%	1.4%	4.9
Henriet et al. [22]	2000–2007	28	25%	–	11%	53%	–	11%	–	–	–	–	3.6
O'Grady et al. [54]	2001–2004	58 (<15 years)	60%	13%	60%	31%	–	–	–	–	10%	–	NS
Steer et al. [70]	2005–2007	12 (<14 years)	16.6%	41.6%	16.6%	25%	–	–	–	–	–	–	8.3
Our study	2007–2010	38	53%	–	10%	29%	7.8%	7.8%	–	–	–	–	0
Whitehead et al. [81]	2008	99	11%	66.6%	4%	16.1%	1%	6%	–	1%	1%	–	4

More than one diagnosis may be specified per patient

NF necrotizing fasciitis, *STSS* streptococcal toxic shock syndrome, *CNS* central nervous system, *NS* not specified

[a] Septic vein thrombosis, mastoiditis, hemolytic uremic syndrome, and unknown syndromes

and *sic* genes, are usually explored for subtyping strains within *emm* genotypes. This approach allowed the recognition of a globally disseminated *emm*1-type subclone harboring *speA*, *speB*, *smeZ*-1, and *sic* genes, also called the M1T1 subclone [22, 51]. Similarly, the rapid emergence in the mid-1980s of a new hypervirulent clone of *emm*3-type GAS harboring *speA*, *speB*, and *ssa* genes was noted [67, 78]. Genomic-based studies further showed that bacteriophages have contributed to the emergence of these new and unusually virulent GAS clones by generating strains with unique patterns of virulence [30]. However, whether these emerging subclones are involved in the increase of IGASI is still a matter of debate. Indeed, some studies revealed the association of GAS genotypes like *emm*1 with invasive disease [30] while others considered that this association might rather reflect the predominance of some *emm* types among non-invasive GAS strains than a true enhanced invasiveness [27, 45, 63]. In the pediatric population, 37% and 29% of the strains involved in invasive disease in France in 2008 and 2009, respectively, belonged to the widely disseminated M1T1 invasive clone. This epidemic strain was recognized in the pediatric population from various countries as observed in Canada [8]. Strains of *emm*3 genotype isolated from IGASI in children in France in 2009 all belonged to the hypervirulent subclone harboring *speA*, *speB*, and *ssa* genes [58]. These investigations suggested that new, possibly more virulent GAS strains also emerged in children.

Regarding susceptibility to antimicrobial agents, GAS strains displayed a full susceptibility to β-lactam agents while an increasing prevalence of resistance to other antibiotic groups such as macrolide–lincosamide–streptogramin B (MLSB) is observed for invasive isolates. For example, 17% of isolates recovered from IGASI in children were resistant to erythromycin, 8.9% of isolates had reduced susceptibility to ciprofloxacin, and 13% were tetracycline resistant [48]. Some of these emerging resistances were related to the diffusion of particular *emm* clones, strains of *emm*12 and *emm*4 genotypes being resistant to erythromycin by an efflux mechanism while strains of *emm*28 genotype usually displayed a multiresistant phenotype including resistance to MLSB [3].

Pathogenesis of IGASI

In addition to viral co-infections, medications, environmental factors, and virulence factor gene content of GAS, other bacterial and host factors play a key role in the pathogenesis of IGASI. Although scarcely investigated in children, recent advances in our knowledge on deregulation of virulence factor production, individual susceptibility, and immune response of the host that may explain the variety of GAS infections' clinical presentation are probably valuable for the pediatric population [80].

The invasive phase of the disease comprises the following sequence of events: adhesion, penetration, proliferation, and dissemination (Fig. 1). After a first step of weak adhesion, a switch to strong, high-affinity tissue-specific adhesion may be observed [56]. Differential adhesin expression between strains accounts at least in part for both the “tissue specificity” and the disease gravity. More generally, the multiple adhesin-based strategy enhances the overall virulence of the strains. During invasion, GAS develops several strategies to escape the host immune system. Mechanisms of complement evasion are: (1) binding and activation of factor H, an inhibitor factor of the alternative pathway of the complement cascade, (2) inhibition of immunoglobulin G fixation by SpeB, and (3) breakdown of C3 and C5a peptidase convertase cleavage [32]. SIC also binds the complement insertion site on the bacterial membrane thereby inhibiting GAS lysis [19]. Moreover, phage-encoded DNase activity could be upregulated leading to neutrophil extracellular traps and then phagocytosis inhibition [5]. Finally, both the hyaluronic capsule and protein M confer resistance to the host antimicrobial peptides and account for the prolonged life of GAS after phagocytosis [10]. Regarding GAS dissemination, alteration of the coagulation pathway by bacterially secreted enzymes plays a key role. Streptokinase activates plasminogen that dissolves fibrin leading to increased bacterial dissemination and severity of the disease in animal models [10].

Virulence factors that may be secreted depend on the strain considered [4, 11]. Some virulent strains like those belonging to the M1T1 subclone secrete a large panel of virulence factors including toxins with superantigen activity responsible for the superantigens' shape response (Fig. 1) [7, 11, 21, 29, 50, 59, 77]. These superantigens (Sag) are strong immune stimulator agents. In STSS, Sag-associated pathways are characterized by a massive cytokine release that could provoke multiple organ failure [35]. Some proteases such as C5 peptidase, lipoteichoic acid, and streptolysin O could directly increase cytokine secretion [72]. The protein M could bind the fibrinogen and activate polynuclear cells with a massive cytokine release [42]. Exuberant cytokine response was associated with the severity of GAS infections in children. Indeed, children with IGASI exhibited significant upregulation of plasma levels of interferon-gamma, interleukin (IL)-1-beta, IL-6, IL-8, IL-10, and IL-18, and suppression of tumor necrosis factor-alpha and IL-12 during the acute phase of illness [80]. Variation in the amount of virulence factors produced could also affect the severity of the disease. For example, expression of SpeA, SpeB, and SpeF was shown variable among isolates of the M1T1 subclone, strains involved in invasive disease producing significantly lower amounts of SpeB. It has been suggested

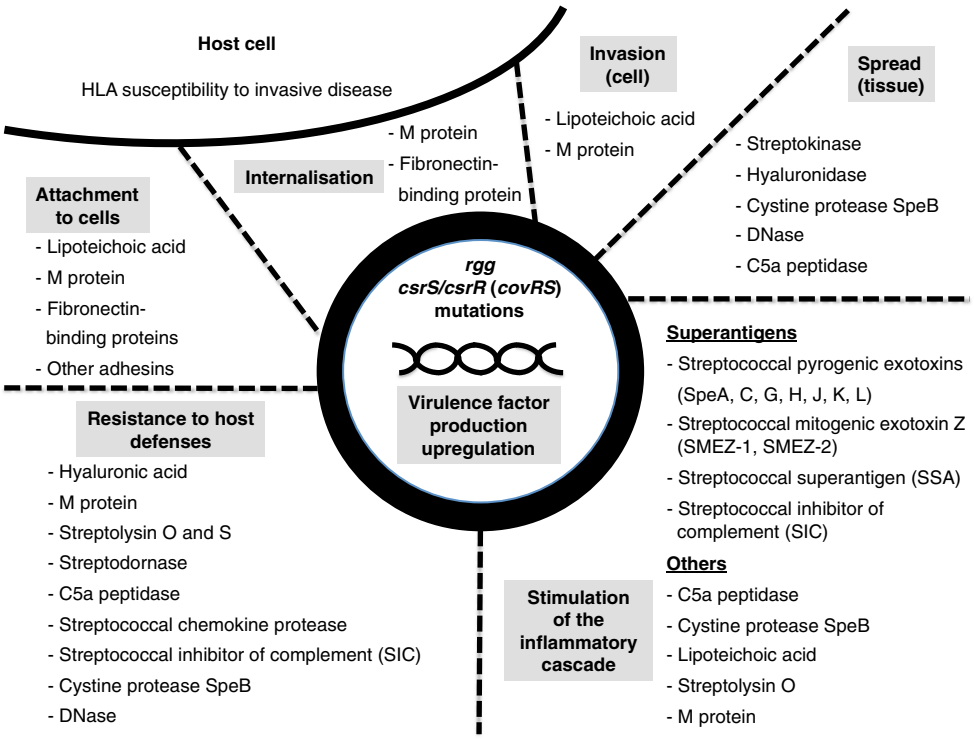

Fig. 1 Schematic representation of the group A *Streptococcus* major virulence factors and regulators according to the pathophysiological step of invasive infection

that decreased proteolytic activity of SpeB on several GAS virulence factors including the M protein may be involved in the higher virulence of these strains [28]. Although not explored, these observations may be extrapolated to members of the SpeB-producer *emm*3 clone. A recent study demonstrated that strains of *emm*1 and *emm*3 genotypes were M protein-high producers, and a high level of M protein production was attributed to amino acid substitution(s) occurring in one of the signal transduction systems implicated in virulence [43]. Finally, recent studies suggested that mutations in the negative regulators *csrS*/*csrR* (*covRS*) and *rgg* of GAS are crucial factors in the pathogenesis of STSS, as they lead to the overproduction of multiple virulence factors [23], thereby being able to amplify the cytokine release described above. These molecular events were thought to mediate the in vivo changes from non-invasive GAS serotype M1T1 to the invasive phenotype [11].

Host susceptibility data are largely lacking in pediatric studies despite human leukocyte antigens (HLA) being directly implicated in pathophysiology and influence the outcome of IGASI [31]. For example, the DRB1*15/DQB1*06 haplotype is associated with strong protection from STSS and reduced cytokine concentrations during GAS infection, whereas the DRB1*14/DQB1*05 haplotype is associated with predisposition to STSS [31, 52, 53]. Smeesters et al. reported two cases of children with GAS STSS followed by rheumatic fever sharing the HLA DQB1*0301 allele, an allele previously associated with susceptibility to NF [68].

Vaccine development

No vaccine against *S. pyogenes* is currently commercialized although several candidates are under evaluation. Despite recent advances in prospects for GAS vaccines, proposing an effective and secure vaccine remains a challenge due to the antigenic diversity of GAS and to the shared epitopes between GAS and human tissues. The use of the conserved region of the M protein, M type-specific protein, or well-described virulence factors such as C5a peptidase and GAS toxins as antigens has been successively considered [69]. Currently, a 26-valent M protein-based vaccine has entered clinical trials. It was constructed from type-specific amino-terminal epitopes that did not elicit tissue cross-reactive antibodies and covers 80% to 90% of pharyngeal and invasive isolates in North America [46]. However, it has been suggested that this vaccine would provide limited benefit in developing countries where higher incidence of IGASI as well as high incidence of ARF are observed, due to geographic discrepancies in *emm* genotype distribution [61]. More recently, the vaccine composition was redefined, and a 30-valent vaccine was proposed to more adequately represent the epidemiology of pharyngitis and invasive GAS infections in North America and Europe [12]. Due to the production of cross-reactive antibodies, the vaccine may also be effective against non-vaccine serotypes [12]. Great hopes are thus associated with the potential development of such a "worldwide-effective" GAS vaccine. In developed countries, ARF incidence decreased to less than 1 per

100,000 during the past five decades as the result of prevention programs consisting in the control of the preceding infections, mainly pharyngitis, by an appropriate course of antibiotic treatment. In these countries, an effective vaccine will be of public health concern to reduce the burden of IGASI in a context of increasing prevalence and severity of these infections observed since the 1980s.

Conclusions

GAS is a multi-facetted pathogen causing complex diseases associating invasive infection, toxic syndrome, and inflammatory cascade deregulation. IGASI remain of public health concern because of their global increasing incidence in children. Due to the severity of the disease, treatments have to be effective on both the etiologic agent and its toxins, notably intravenous immunoglobulin and antibiotic with antitoxin activity have to be considered as part of the therapeutic strategy against GAS. Although knowledge on IGASI in children increased in the past decades, many aspects of the host–pathogen interactions leading to diseases remain not fully elucidated and warrant further investigations. Due to the rarity of studies in children, additional studies should ideally focus on the pediatric population with the aim of clarifying (1) if GAS clones considered as hypervirulent on the basis of their virulence gene content are implicated in the increasing frequency and severity of IGASI in children, (2) the individual factors involved in the modulation of the immune response and disease severity in children, and (3) GAS characteristics that may be related to particular and/or severe forms of the disease. Indeed, determining GAS and host susceptibility factors that may be involved in the development of severe diseases is a challenge to predict complications and to determine the best way to treat and prevent them.

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Conflict of interest The authors declare that they have no conflict of interest.

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