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Management of invasive group A streptococcal infections

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Summary Invasive group A streptococcal (GAS) disease in children includes deep soft tissue infection, bacteraemia, bacteraemic pneumonia, meningitis and osteomyelitis. The expression of toxins and super antigens by GAS can complicate infection by triggering an overwhelming systemic inflammatory response, referred to as streptococcal toxic shock syndrome (STSS). The onset and progression of GAS disease can be rapid, and the associated mortality high. Prompt antibiotics therapy and early surgical debridement of infected tissue are essential. Adjunctive therapy with intravenous immunoglobulin and hyperbaric therapy may improve outcomes in severe disease. Nosocomial outbreaks and secondary cases in close personal contacts are not uncommon; infection control measures and consideration of prophylactic antibiotics to those at high risk are important aspects of disease control. To reduce a substantial part of the global burden of GAS disease, an affordable GAS vaccine with efficacy against a broad number of strains is needed.
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Introduction

The invasion of group A streptococci (GAS; *Streptococcus pyogenes*) into normally sterile parts of the body results in a range of severe disease, including bacteraemia, sepsis syndrome, bacteraemic pneumonia, meningitis, puerperal sepsis and deep soft tissue infection including necrotising fasciitis. Disease onset can be rapid, and can progress at

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an alarming rate.[1,2] Expression of bacterial toxins can lead to an overwhelming systemic inflammatory response causing streptococcal toxic shock syndrome (STSS).[3–5]

The mainstay of treatment for invasive GAS disease is prompt administration of antibiotics, surgical debridement of infected tissue, and supportive care.[6] Despite this, the associated mortality for invasive GAS disease is high.[7–9] To try to improve outcomes, a number of adjunctive therapies including intravenous immunoglobulin (IVIG) administration have been used, but definitive data supporting their use is lacking particularly in the paediatric context.[10–13]

Prevention of disease currently is limited to reduction in secondary transmission through prompt outbreak investigation and implementation of infection control measures.[14] The role of antimicrobial prophylaxis for the prevention of disease in close contacts of those with invasive GAS is uncertain.[10,14] Ultimately, it is hoped that the successful development of a vaccine against GAS will provide protection both for those at risk of invasive disease as well as for those in whom the sequelae of GAS disease, particularly acute rheumatic fever (ARF) and rheumatic heart disease (RHD), remain a significant burden.[15–17]

Epidemiology

The global burden of GAS disease is significant, and is one of the leading causes of death attributable to a specific pathogen.[7] GAS infection results in a remarkable range of disease of varying severity, from superficial skin infection and pharyngitis, through to life threatening invasive disease.[7,18] Superficial infections account for the greatest number of paediatric cases of GAS disease and are for the most part benign and self-limiting.[7] In contrast invasive infection is relatively rare but is often complicated by multi-organ failure and shock, and is associated with high mortality.[7] GAS infection can also lead to the development of immune-mediated sequelae, including ARF, RHD and post-streptococcal glomerulonephritis (PSGN), the chronic nature of which means that these conditions account for a significant proportion of the global burden of disease attributable to GAS.[7] Overcrowding and poor access to health care facilitate disease progression and spread leading to a disproportionately high overall disease burden in resource-limited settings.[7]

The incidence of invasive GAS disease in resource-rich settings ranges between 1.5 and 3.5 cases per 100,000 people.[8,18–20] Data from resource-poor settings are more limited; recent studies suggest that rates in developing countries as well as in indigenous populations living in high-resource settings are several-fold higher than that observed in affluent settings.[7,21–24] The highest incidence of invasive disease is seen in the elderly, followed by young children, particularly those under one years of age.[18–20] In the United States for example, the incidence of invasive GAS disease per 100,000 people was 5.3 in those aged under one year, 3.6 in those aged 1−≤2 years, and 2.6 in those aged 2−≤4 years.[18] Despite the availability of effective antibiotics against GAS, the mortality rate from invasive GAS disease is estimated to be between approximately 7% and 30%.[8,10,18,19,25,26] Furthermore, data from Europe, North America and Australia suggest that the incidence and severity of invasive GAS has increased over recent decades,[4,7,27–30] possibly due to changes in the predominant circulating GAS strains.[31]

Clinical features

Overall, skin and soft tissue infections are the most frequently encountered primary focus of invasive GAS disease, accounting for approximately one third of cases.[18,19,25] Respiratory tract infections, followed by septic arthritis, necrotising fasciitis, puerperal sepsis and meningitis account for most of the remaining cases.[19] In as many of a third of bacteraemic cases no identifiable focus of infection can be found.[18,19]

The frequency of different sites of infection varies by age; osteomyelitis, epiglottitis and meningitis are more frequent in children less than 10 years old, compared to older patients.[19] The most severe manifestations of invasive GAS disease are necrotising fasciitis and STSS, characterised by fever, rash, hypotension, shock and multi-organ failure. Necrotising fasciitis and STSS may occur together; fortunately, both are relatively rare in children.[32] In a cohort of 572 patients under the age of 10 years in the United States, 4.6% had STSS and 0.9% had necrotising fasciitis.[18]

Pre-existing skin lesions, serving as a portal for GAS invasion, are the most frequently identified risk factor for invasive GAS disease.[19] In children, primary varicella is an important predisposing condition.[19,20,33] Injecting drug use, alcoholism, immunosuppression, diabetes, malignancy, and recent childbirth are additional risk factors. The ability of GAS to cause severe disease in otherwise fit and healthy individuals is notable, with between a fifth and a third of cases occurring in individuals with no predisposing risk factors.[18,19] This is especially true in children; in the United States, only 22% of children aged less than 10 years with invasive GAS disease had an underlying risk factor compared to 72% of patients over 10 years of age.[18]

Pathology

Group A streptococci possess a large number of virulence mechanisms, with a high degree of variability in virulence determinants exhibited between different GAS serotypes.[34] The cell wall associated M protein, encoded for by the *emm* gene, is a major antigenic epitope and virulence factor of GAS,[35,36] and forms the basis of the serotyping of GAS isolates.[37] The M protein acts as an epithelial adhesion factor,[38] inhibits phagocytosis and allows the organism to overcome innate immune responses.[39–41] There are at least 180 different *emm* types of GAS, and new types are still being identified. Temporal, geographical and seasonal variations in the dominant strains are well described, and can result in variable disease epidemiology.[31,42–44] Strain diversity appears to be greater in resource poor settings compared to resource rich settings.[42,44] GAS strains also vary in terms of their tropism for different tissues such as skin and throat.[45,46] GAS serotypes isolated in invasive disease correspond with prevalent community carriage and pharyngitis-associated serotypes.[44] An exception to this is

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