Group A Streptococcus disease in Hong Kong children: an overview

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Introduction

Group A β-haemolytic Streptococcus (GABHS) is a gram-positive, non-motile, non-spore-forming coccus that tends to grow in chains. It produces a large variety of extracellular enzymes and toxins and has β-haemolytic properties. Streptococcus pyogenes is the most important species of GABHS, causing many human diseases. The terms GABHS and S pyogenes are often used synonymously in the literature. Infections with GABHS typically begin in the throat or skin. The spectrum of infections ranges from mild pharyngitis (strep throat) and localised skin infections (impetigo) to moderate-to-severe manifestations in the forms of scarlet fever, pneumonia, and rheumatic fever. Immune-mediated clinical conditions linked to GABHS infection include rheumatic fever, post-streptococcal glomerulonephritis, and paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). The manifestations of acute GABHS infection mostly affect schoolchildren. There has been a surge of GABHS in Hong Kong and worldwide in recent years, and its epidemiology and clinical manifestations in Hong Kong children are reviewed in this article. A PubMed search for references was performed using the MeSH terms “Streptococcus pyogenes” or “group A Streptococcus” and “Hong Kong”, limited to ‘human’, with no filters for article type and publication time. This discussion is based on, but not limited to, the search results.

Epidemiology of group A β-haemolytic Streptococcus

Infections related to GABHS have long been described throughout history, but Streptococcus was not discovered to be the causative organism of erysipelas and wound infection until 1847. It was further named Streptococcus pyogenes (pyo = pus, genes = forming) in 1884 after the bacteria were found in suppurative conditions. Scarlet fever was first identified in the medical literature in 1675 and named “scarlatina”. Before the era of antibiotics, epidemics of scarlet fever leading to high mortality had been described for centuries. Despite significant improvements to socioeconomic conditions over the past 50 years, S pyogenes still remains one of the top ten infective causes contributing to global childhood mortality.
A group B-β-haemolytic Streptococcus infection in Hong Kong children: an overview

A group B-β-haemolytic Streptococcus infection is a common cause of childhood infection, associated with significant mortality and morbidity. A review published by the World Health Organization (WHO) in 2005 estimated that approximately 18.1 million people had serious GABHS-related disease, including rheumatic heart disease, post-streptococcal glomerulonephritis, and over 650,000 cases of invasive diseases. The WHO review identified 1.78 million new cases of serious disease and over 500,000 deaths each year. In addition, the review indicated over 111 million new cases of streptococcal disease in children aged <5 years, from 3.3 per 100,000 population to 5.0 per 100,000 population in the previral period (2005–2010) to 18.1 per 100,000 population in 2012 to 2015.17

The prevalence of disease varies with age, time, season, and geographic location. Group A β-haemolytic Streptococcus infections predominantly affect children aged 5 to 15 years.24 With the wide range of diseases caused by GABHS and the lack of standard surveillance criteria, accurate data on its associated disease burden are limited. Over the years, reporting of scarlet fever and invasive GABHS diseases has become a statutory requirement in many countries. Scarlet fever has been a notifiable disease in Hong Kong since 1940, with its associated disease activity closely monitored by the Centre for Health Protection. However, reporting of invasive GABHS diseases not presenting as scarlet fever by individuals and institutions is voluntary.9

Scarlet fever outbreak

The incidence of scarlet fever has remained low in developed countries, in which health care and socioeconomic conditions have improved since the late 20th century. However, in 2011, a surge of scarlet fever was observed in East Asia, including in Hong Kong, China, South Korea, and Vietnam.2,10–12 Recently, a similar upsurge of reports has occurred in the United States, England, and European countries.13 In Hong Kong, there was an outbreak of 1535 total cases (2.17 cases per 100,000 population) of scarlet fever in 2011. This was almost 10 times the average annual incidence throughout the previous two decades, during which annual incidence ranged from 0.0351 to 3.37 cases per 100,000 population.4,15

During the outbreak, the age distribution was similar to that in past reports, with the majority of cases in children aged <10 years and a median age of 6 years.19 Two deaths were reported. The annual incidence has since remained high, with 1100 to 1500 cases reported in subsequent years, and there was a further increase to 2353 cases reported in 2017 (Fig).16 Epidemiological analysis of reported cases in Hong Kong from 2005 to 2015 indicated that the surge was more apparent among children aged <5 years, with the highest incidence at age 3 to 5 years. There was a 5-fold increase of annual incidence in children aged <5 years, from 3.3 per 10000 population in 2005 to 2010 to 18.1 per 10000 population in 2012 to 2015.17

The reason for the worldwide surge of scarlet fever is still mysterious. In the 2011 Hong Kong outbreak, the emergence of scarlet fever S. pyogenes emm12 clones was associated with toxin acquisition and multidrug resistance, which could have contributed to the outbreak.18,19 Environmental alterations and host immunity are other possible factors. Similar seasonal trends were observed in the pre-surge (2005–2010) and post-surge (2011–2015) periods, with troughs in early September and rises after school holidays, with peaks in January. There was a slight bimodal elevation in June during the post-surge period. Reductions by 30% to 40% of cases after school holiday weeks were observed during both periods.17 Meteorological factors including humidity, rainfall, and temperature were found to be associated with scarlet fever, but these factors sometimes had opposite valences at different periods and in different places.20

Clinical manifestations of group A β-haemolytic Streptococcus infection in children

Clinical presentations of streptococcal infections vary according to bacterial virulence factors and individual host response. In 1993, an informal group of microbiologists, clinicians, and epidemiologists formed a working group on severe streptococcal infections and classified GABHS infections into five groups: Streptococcal toxic shock syndrome, invasive infections, scarlet fever, non-invasive infections (throat and skin infections), and non-suppurative sequelae.
of streptococcal infection due to toxin-mediated acute illness. Patients present with fever, rash, hypotension, and organ failure, and it can be life-threatening. Endotoxins produced by \textit{S. pyogenes} are associated with disease invasiveness. Streptococcal pyrogenic exotoxin A and streptococcal superantigen, are two of the superantigens that stimulate T-cell response and induce cytokine-mediated inflammatory reactions, thereby leading to shock and organ dysfunction. Some exotoxins can also induce shock through non-cytokine-mediated mechanisms. Streptococcal pyrogenic exotoxin B has been shown to release bradykinsins, causing vasodilation, while streptolysin O can lead to dysfunction of cardiomyocytes. Mortality of streptococcal toxic shock syndrome in children has been reported to be 5% to 10%.

Streptococcal toxic shock syndrome was defined by the working group on severe streptococcal infections according to the following criteria: (1) identification of GABHS in sterile sites as definite cases or in non-sterile sites as probable cases and (2) the presence of features of shock and organ dysfunction. Streptococcal toxic shock syndrome is characterised by the co-existence of shock and organ dysfunction in the early course of the disease. In certain cases, organ dysfunction can precede hypotension. Septic shock leading to organ dysfunction differentiates it from other invasive GABHS infections. Streptococcal toxic shock syndrome is rarely associated with pharyngitis; rather, it more commonly follows skin infections. In 50% of cases, no obvious bacterial portal of entry can be identified. Diagnosis is often delayed, as patients present with non-specific symptoms of fever, vomiting, and abdominal pain without localising signs in early stage of illness. The clinical course can progress rapidly to shock and organ dysfunction, and the typical signs of deep-seated infection or necrotising fasciitis usually become obvious in later stages. Streptococcal toxic shock syndrome can occur with coinfections of viral infections such as varicella and influenza B infections. Use of nonsteroidal anti-inflammatory drugs has been reported to be associated with severe necrotising fasciitis, possibly because they mask the symptoms of inflammation. The clinical course of streptococcal toxic shock syndrome can be rapidly fatal, and early recognition is very important. Management is mainly supportive and consists of maintenance of haemodynamic stability, with administration of fluids and inotropic medications, prompt initiation of antibiotics for infection control, and surgical intervention as indicated in cases of necrotising fasciitis. Intravenous immunoglobulin may be considered as an adjunctive therapy to neutralise superantigens, although clinical evidence regarding mortality outcomes remains controversial.
Invasive infections
Invasive GABHS diseases are usually defined as clinical diseases associated with identification of *S. pyogenes* in sterile sites including blood, cerebrospinal or pleural fluids, deep wounds, and muscles. Before the introduction of antibiotics, bacteraemia was not uncommon, especially at extremes of age. In children, upper respiratory infections, varicella infections, and skin wounds are predisposing factors for invasive GABHS infections. Pneumonia usually starts as streptococcal pharyngitis, with 40% to 50% of cases complicated by empyema. Mortality is generally low with the appropriate use of antibiotics and management of empyema.

Scarlet fever
Scarlet fever is a clinical syndrome associated with *S. pyogenes* pharyngitis or, less commonly, skin and soft tissue infections (the latter is known as "surgical" scarlet fever). It typically presents as abrupt onset of fever, sore throat, beefy red pharynx, and enlarged and erythematous tonsils (with or without exudates) followed by the development of sandpaper-like erythematous skin rashes on the first to second day of the fever. Skin rashes often start from the trunk and spread to the limbs, being more prominent over flexures, axilla, and the groin (Pastia lines) while sparing the palms and soles. The cheeks become flushed, leaving the perioral region looking pale (circumoral pallor). The papillae of the tongue become swollen, leading to a strawberry-like appearance of the tongue. The rashes usually resolve in about 1 week, followed by desquamation of the hands and feet.

The clinical manifestations of scarlet fever are caused by streptococcal pyrogenic exotoxins produced by certain strains of *S. pyogenes*. No single toxin but rather a combination of 11 identified exotoxins are implicated. Strains of *S. pyogenes* producing streptococcal pyrogenic exotoxins A and C and streptococcal superantigen have been associated with a few outbreaks. In Hong Kong, the earliest epidemiological study of GABHS in a general practice setting was reported in 1968. It showed carrier rates of 6.1% in the general population, 7.6% to 8.3% in schoolchildren, and 27.5% in a residential children's home. Approximately 50% of skin infections and 29% of tonsillitis cases were due to GABHS infection. With a high carrier rate of GABHS in children, it is sometimes difficult to determine in a child presenting with fever, sore throat, and a positive GABHS culture whether the symptoms are caused by a concurrent viral infection in a carrier or genuine GABHS pharyngitis. Clues in favour of GABHS pharyngitis include epidemiologic factors or clinical findings suggestive of GABHS pharyngitis, a marked clinical response to antimicrobial therapy, negative throat swab cultures between episodes of pharyngitis, and a serological response to GABHS extracellular antigens (eg, anti-streptolysin O, anti-DNase, and antihyaluronidase).

In children with recurrent pharyngitis, it may be warranted to repeat throat cultures when they are asymptomatic after treatment with antibiotics to determine their carrier status and avoid indiscriminate use of antibiotics. Eradication of bacteria by use of antibiotics in asymptomatic carriers is generally not recommended, as the risks of development of complications and transmission to others are both low in these subjects. The American Academy of Pediatrics Committee on Infectious Diseases suggested the following indications for treatment of carriers: (1) family history of rheumatic fever or rheumatic heart disease; (2) parental anxiety or parents considering tonsillectomy solely because of the bacterial carriage; and (3) community outbreaks of *S. pyogenes* acute pharyngitis.

Non-invasive infections
Pharyngitis and tonsillitis
Group A β-haemolytic *Streptococcus* infection is the most common bacterial cause of pharyngitis and tonsillitis both in children and adults. The typical symptoms include fever, sore throat, exudative tonsils or pharynx, and cervical lymphadenopathy. However, none of these can differentiate bacterial from viral infections. According to population studies in high-resource settings, about 4% to 10% of adults and 15% of schoolchildren had episodes of symptomatic GABHS pharyngitis each year. The rates were 5 to 10 times higher in low-resource settings. A meta-analysis involving studies on patients aged <18 years presenting with sore throat in out-patient settings showed that the pooled prevalence of positive throat swabs for GABHS was 37%. The prevalence in children aged <5 years was lower (24%), and it was only 5% to 10% in adults. In a 2000 study, patients presenting to the accident and emergency department of a Hong Kong public hospital complaining of sore throat or suspected to have acute pharyngitis had throat swabs taken for culture. The prevalence of GABHS pharyngitis in patients aged ≤14 years was 38.2%, which was similar to that in other countries, but the prevalence in patients aged >14 years was only 2.7%. No patient was aged <3 years, and only one patient was aged >60 years. The findings concurred with those of previous studies, which indicated that GABHS infections are uncommon at extremes of age.

Carrier status of *S. pyogenes* in the throat is classically defined as isolation of the bacteria in subjects without clinical features of acute pharyngitis. Rates of *S. pyogenes* carrier status among asymptomatic schoolchildren have been reported as up to 15% to 20% in some studies. In Hong Kong, the earliest epidemiological study of GABHS in a general practice setting was reported in 1968. It showed carrier rates of 6.1% in the general population, 7.6% to 8.3% in schoolchildren, and 27.5% in a residential children's home. Approximately 50% of skin infections and 29% of tonsillitis cases were due to GABHS infection. With a high carrier rate of GABHS in children, it is sometimes difficult to determine in a child presenting with fever, sore throat, and a positive GABHS culture whether the symptoms are caused by a concurrent viral infection in a carrier or genuine GABHS pharyngitis. Clues in favour of GABHS pharyngitis include epidemiologic factors or clinical findings suggestive of GABHS pharyngitis, a marked clinical response to antimicrobial therapy, negative throat swab cultures between episodes of pharyngitis, and a serological response to GABHS extracellular antigens (eg, anti-streptolysin O, anti-DNase, and antihyaluronidase). In children with recurrent pharyngitis, it may be warranted to repeat throat cultures when they are asymptomatic after treatment with antibiotics to determine their carrier status and avoid indiscriminate use of antibiotics. Eradication of bacteria by use of antibiotics in asymptomatic carriers is generally not recommended, as the risks of development of complications and transmission to others are both low in these subjects. The American Academy of Pediatrics Committee on Infectious Diseases suggested the following indications for treatment of carriers: (1) family history of rheumatic fever or rheumatic heart disease; (2) parental anxiety or parents considering tonsillectomy solely because of the bacterial carriage; and (3) community outbreaks of *S. pyogenes* acute pharyngitis.
Skin and soft tissue infections

*Streptococcus pyogenes* can cause infections in all layers of the skin and underlying soft tissues. Superficial infections include impetigo with localised infections of the keratin layer of the epidermis. Erysipelas are characterised by multiplication and lateral spread of *S. pyogenes* in the superficial epidermis. They can spread through the lymphatic system, causing more widespread inflammation. In contrast, cellulitis results from deeper infections of subcutaneous tissues. *Streptococcus pyogenes* invasion and multiplication in the fascia can lead to necrotising fasciitis, which commonly involves all layers of the skin. *Streptococcus pyogenes* can also cause muscle infections, leading to myositis and myonecrosis.

Impetigo is prevalent in developing countries and commonly affects young children aged 2 to 5 years. Infections are usually localised, rarely causing systemic spread. Post-streptococcal glomerulonephritis may follow impetigo caused by nephrogenic strains of GABHS, but rheumatic fever has not been found to be associated with impetigo.

Cellulitis may result from infections of wounds or adjacent infections such as lymphadenitis or peritonsillar abscesses. Such infections may spread to involve large areas of subcutaneous tissue and be complicated by bacteraemia, toxic shock syndrome, and scarlet fever. Necrotising fasciitis is rare but has the potential to be rapidly fatal with high mortality. It may be preceded by only trivial injury or varicella infection in children. Early recognition with a low threshold for surgical debridement is of paramount importance in its management.

Immune-mediated late complications

*Streptococcus pyogenes* can also cause post-infectious non-suppurative diseases. These immune-mediated complications follow a small percentage of infections and include acute rheumatic fever, post-streptococcal reactive arthritis, acute post-streptococcal glomerulonephritis, guttate psoriasis, and Henoch-Schönlein purpura. Different strains of GABHS have been found to be related to acute rheumatic fever (rheumatogenic types) and acute post-streptococcal glomerulonephritis (nephrogenic types). The incidence rates of these conditions have declined dramatically in the previous half-century with the use of antibiotics. These conditions appear several weeks following initial untreated or partially treated streptococcal infections, but it is relatively common for the preceding symptoms of infection not to be recognised. The Jones diagnostic criteria for acute rheumatic fever were first established in 1944, with recent modifications by the American Heart Association (AHA). The 1992 version stated that two out of the five major criteria for GABHS infection (carditis, arthritis, Sydenham chorea, subcutaneous nodules, and erythema marginatum) or one major with two minor criteria indicate a high probability of acute rheumatic fever. In 2015, the AHA incorporated the use of serial echocardiography with Doppler studies to evaluate and monitor for clinical or subclinical carditis in any confirmed or suspected cases of acute rheumatic fever. Subclinical carditis refers to mitral or aortic valvulitis revealed by echocardiography/Doppler studies without the classic auscultatory findings of valvar dysfunction.

Acute post-streptococcal glomerulonephritis is caused by immune complexes deposited in the glomerulus. The typical clinical presentation includes acute nephritic syndrome, or less commonly, nephrotic syndrome approximately 7 to 10 days after streptococcal pharyngitis and 2 to 4 weeks after skin infections. Prognosis in children is usually excellent, and progressive renal failure rarely occurs. The clinical condition PANDAS was described by Swedo et al in 1998. The diagnostic criteria for PANDAS include: (1) the presence of obsessive–compulsive disorder and/or any other tic disorders, (2) pre-pubertal onset, (3) abrupt onset and relapsing remitting symptom course, (4) a distinct association with GABHS infection, and (5) association with neurological abnormalities, such as motoric hyperactivity and choreiform movements, during exacerbations. The pathogenesis of PANDAS is uncertain but likely linked to a post-infectious autoimmune phenomenon. Treatment is mainly symptomatic, and the efficacy of immunomodulatory therapies including plasmapheresis and intravenous immunoglobulin needs further evaluation.

Laboratory diagnosis of group A β-haemolytic *Streptococcus*

Laboratory diagnosis of GABHS infection is classically based on bacterial culture of clinical specimens. Bacterial colonies of *Streptococcus* produce rings of β-haemolysis on agar plates and appear as Gram-positive cocci in chains on microscopic examination. Group A β-haemolytic *Streptococcus* can be identified by detection of Lancefield group A antigens on the bacterial surface. Further differentiation of *S. pyogenes* from other GABHS requires pyrrolidonyl arylamidase colorimetric tests and tests of bacitracin susceptibility. Recently, more advanced automated laboratory systems based on molecular techniques have enhanced the identification of specific bacteria in blood cultures. The role of rapid antigen detection tests (RADTs) will be discussed in more detail below. Serology tests including anti-streptolysin O titre and anti-DNase B are useful for diagnosis of immune-mediated late complications of GABHS infections.
Serotyping of group A β-haemolytic Streptococcus

Group A β-haemolytic Streptococcus is serotyped according to the streptococcal M protein coded by the *emm* gene. Since the 1990s, *emm* sequence typing has replaced classical M protein serotyping to define GABHS strains. The epidemiology of *emm* strains varies geographically and temporally. A meta-analysis identified 205 *emm* types worldwide, with the most common *emm* types being *emm*1 and *emm*12. There was a greater diversity of *emm* types in Africa and the Pacific region than in high-income countries. 46 Local and overseas studies have shown a lack of association between GABHS *emm* type and invasiveness or disease severity. 45-48 Presumably, an increase in the prevalence of strains in the general population, host immunity, and environmental factors rather than the strains' virulence contributed to the surge of GABHS infections and severity of disease.

Diagnosis and management of group A β-haemolytic Streptococcus pharyngitis

Pharyngitis in children is commonly caused by viral infections, and GABHS is the most important bacterial cause. Throat swab culture is the gold standard for diagnosis, but the turnaround time is 2 to 3 days, limiting its utility for deciding whether antibiotics should be used for pharyngitis. The Centor score (0-4) is a 4-point clinical scale that was first reported in 1981 and is used for differentiation of GABHS pharyngitis from viral pharyngitis to decide about the use of antibiotics in adults presenting to emergency departments with sore throat. One point is scored for each of the following: fever >38°C, absence of coughing, presence of tonsillar exudates, and swollen and tender anterior cervical nodes. 37 The modified Centor score or McIsaac score includes an age score applicable to children by adding one point for age 3 years to <15 years and subtracting one point for age ≥45 years while keeping the minimum score as 0 (0 or -1) and the maximum score as 4 (4 or 5). 38 However, a large-scale validation study showed a positive predictive value of only about 35% to 55% for scores 3 and 4 and a negative predictive value of 80% for scores ≤2. 51

Since the 1980s, commercially available RADT for detection of GABHS in throat swabs has become more widely available. Various techniques including latex agglutination, enzyme immunoassays, optical immunoassays, and molecular tests have been developed. 35 In a Cochrane Review of RADT using enzyme immunoassay and optical immunoassay methods compared with throat swab cultures for diagnosis of streptococcal pharyngitis in children, the pooled sensitivity was 85.6% (95% confidence interval [CI]=83.3-87.6%), and the specificity was 95.5% (95% CI=94.5-96.2%). 52 In another meta-analysis identified by the review that included molecular tests, the molecular technique category had higher sensitivity and specificity than the other methods had. 53 Molecular tests are not truly point-of-care tests and require specialised equipment and personnel, limiting their application in primary care settings. International guidelines on management of acute pharyngitis for adults and children make varying recommendations about the use of the Centor or McIsaac scores and microbiological tests for diagnosis and management of acute pharyngitis. 54 The United States guidelines recommend performing RADT only in patients with suspicion of GABHS pharyngitis based on clinical signs and symptoms or according to the Centor score, while the United Kingdom and some guidelines from Europe do not suggest the use of RADT. 55 Practice recommendations published in the Hong Kong College of Paediatricians’ guidelines for management of acute pharyngitis do not recommend the use of any clinical scores for making management decisions. The guidelines suggest performing either a throat swab culture or RADT if clinical and epidemiological factors strongly suggest GABHS. Negative RADT is recommended to be confirmed by throat swab culture in these cases. 56

Antibiotic treatment and resistance

Group A β-haemolytic Streptococcus is generally sensitive to penicillin and other members of the β-lactam group of antibiotics. Failure of treatment with penicillin is generally attributed to other local commensal organisms producing β-lactamase or failure to reach adequate tissue levels in the pharynx. 57 In Hong Kong, macrolide-resistant strains of GABHS are common. 49 According to surveillance data from the University of Hong Kong and the Public Health Laboratory Centre of the Centre for Health Protection, GABHS isolates from 2011 were all sensitive to penicillin, while more than 50% were resistant to macrolides, clindamycin, and tetracyclines. 18-58 International and local management guidelines recommend either a 10-day course of penicillin or amoxicillin as first-line antibiotics for acute pharyngitis or scarlet fever due to GABHS. For patients allergic to penicillin, a narrow-spectrum cephalosporin (cephalexin, cefadroxil) is indicated, while macrolides such as azithromycin or clarithromycin are second-line options. 57-59 Oral penicillin V is highly sensitive, and its narrow spectrum makes it the drug of choice over amoxicillin for GABHS infection. Amoxicillin is often preferred in children because of the better taste of the suspension and its availability as chewable tablets. 55,56 The Centre for Health Protection of Hong
Kong recommends a shorter course of antibiotics of 5 to 7 days for streptococcal pharyngitis based on recent studies showing that shorter courses of antibiotics (mostly cephalosporins) are equally effective as a 10-day course of penicillins. However, for patients with positive GABHS cultures, scarlet fever, and in areas with high prevalence of rheumatic heart disease, a full 10-day course of treatment may still be needed. Effective treatment for GABHS infection is important for control of acute infection and prevention of late immunological manifestations including rheumatic heart disease, glomerulonephritis, and PANDAS.

Conclusion

Despite the availability of antibiotics, GABHS remains an important bacterial pathogen that causes a wide variety of diseases in children. Clinicians should be familiar with the clinical features of GABHS infections to decide on the appropriate use of microbiological tests and judicious use of empirical antibiotics. Early recognition of symptoms and signs of invasive infections and serious toxin-mediated conditions is the key to preventing mortality. The reasons for the recent surge of scarlet fever in Hong Kong and other parts of the world are still unclear. In addition to mandatory reporting of scarlet fever and laboratory surveillance of GABHS isolates according to current practice in Hong Kong, enhanced monitoring of severe acute GABHS infections and late immunological manifestations are important to provide a complete picture of the impact of the re-emergence of this pathogen. Further investigations on microbiological, environmental, and host factors are urgently needed to control the upsurge of GABHS infections.

Author contributions

All authors have made substantial contributions to the concept of this study, drafting of the article, and critical revision for important intellectual content.

Declarations

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