Scarlet Fever

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Abstract

Scarlet fever is an infection caused by Streptococcus pyogenes (group A streptococcus, or "GAS"), a bacterium specific to humans. This disease is characterized by a pale, erythematous, maculopapular rash, often described as "sandpaper-like," a sore throat, a "strawberry tongue," and exudative pharyngitis. Scarlet fever primarily affects children and often accompanies GAS pharyngitis, although it can also occur with other GAS infections. Scarlet fever is caused by streptococcal pyrogenic exotoxins, a type of superantigen produced by GAS. Penicillin remains the first-line treatment, but alternative treatments are available for individuals with a confirmed penicillin allergy. Scarlet fever can lead to complications such as rheumatic heart disease and glomerulonephritis, so early diagnosis and treatment are crucial.

Key words: scarlet fever; complications; rheumatic heart disease; glomerulonephritis

Introduction

Scarlet fever is an infection caused by Streptococcus pyogenes (group A streptococcus, or "GAS"), a bacterium specific to humans. This disease is characterized by a pale, erythematous, maculopapular rash, often described as "sandpaper-like," a sore throat, a "strawberry tongue," and exudative pharyngitis. Scarlet fever primarily affects children and often accompanies GAS pharyngitis, although it can also occur with other GAS infections. Scarlet fever is caused by streptococcal pyrogenic exotoxins, a type of superantigen produced by GAS. Penicillin remains the first-line treatment, but alternative treatments are available for individuals with a confirmed penicillin allergy. Scarlet fever can lead to complications such as rheumatic heart disease and glomerulonephritis, so early diagnosis and treatment are crucial. Scarlet fever caused by GAS infections can occur at any age. Although most commonly associated with GAS pharyngitis, it can also develop with other GAS infections, both invasive and noninvasive, such as erysipelas or necrotizing fasciitis. Historically, GAS serotypes have exhibited cyclical epidemiological patterns. Notably, GAS is one of the few bacteria that produces superantigen exotoxins, which are exceptionally potent T-cell activators. GAS superantigens, also called erythrogenic or scarlet toxins, are responsible for the characteristic erythematous, rough rash and "strawberry tongue" seen in scarlet fever. Superantigen genes such as speA, speC, and ssa enhance the viability and virulence of GAS, promoting the development of invasive disease. Scarlet fever epidemics and invasive GAS infections were common in the 19th century. Although the prevalence of scarlet fever declined in the 20th century, there was a resurgence of GAS infections in the 1980s. In the last decade, more virulent epidemic strains of GAS have emerged, leading to an increase in both GAS infections and scarlet fever. GAS infections can cause suppurative and non-suppurative complications, including rheumatic heart disease (RHD) and post-streptococcal glomerulonephritis (PSGN). Prompt treatment of acute infections is essentialto prevent these complications.

GAS produces streptococcal pyrogenic exotoxins (SPE), which act as superantigens released during infection. These exotoxins are the primary cause of the erythematous rash associated with scarlet fever. Bacterial pharyngitis caused by group A streptococcus (GAS) and scarlet fever most often affect school-aged children and adolescents due to their higher transmissibility in school settings. However, these infections can also occur in other age groups, especially in congregate settings such as homes and nursing homes.

Etiology

Group A streptococcus (GAS) is a Gram-positive, nonspore-forming, catalase- and oxidasenegative bacterium that grows in pairs and chains.[1] GAS grows well on blood agar when incubated at 35°C to 37°C; optimal growth is observed in an environment containing 10% carbon dioxide. The bacterium forms smooth, moist, grayish-white colonies with distinct margins, larger than 0.5 mm in size.[2] Colonies are surrounded by a zone of complete hemolysis (β-hemolysis).[2] GAS is ubiquitous in nature and is adapted to humans. The only known human reservoirs are mucous membranes and skin. GAS commonly causes a wide range of upper respiratory tract and skin infections, such as pharyngitis, scarlet fever, impetigo, cellulitis, and erysipelas. These infections

can vary in severity, from mild and superficial to severe and invasive streptococcal infections (iGAS).[2][3] Invasive infections typically occur in normally sterile sites, such as the bloodstream, cerebrospinal fluid, or pleura. Both streptococcal and invasive streptococcal infections are distributed worldwide, characterized by high rates of morbidity and mortality.[2][3] In addition to acute infections, streptococcal infections can cause immune-mediated sequelae such as acute rheumatic fever (ARF), post-streptococcal glomerulonephritis (PSGN), and complications such as rheumatic heart disease (RHD). Recent data suggest that in the United States, 1% to 3% of patients with untreated streptococcal infections, usually streptococcal pharyngitis, develop ARF, and 60% of these cases develop chronic RHD.[4] The Lancefield classification divides streptococci into serologic groups, designated by letters A through O, based on reactions between antisera and carbohydrate antigens on the streptococcal cell wall.[5] At least 20 serologic groups have been identified, including groups A, B, and C. Group A streptococcus (GAS) is classified as group A in the Lancefield classification.[6][7] Other streptococci from different Lancefield groups can cause syndromes similar to those caused by GAS. In particular, group B streptococcus (GBS; S. agalactiae) colonizes the human gastrointestinal and genital mucosa and can cause puerperal sepsis and neonatal infections such as pneumonia, bacteremia, and meningitis.[8] GAS has been identified as having multiple virulence factors that enable it to carry out key processes such as adherence, colonization, immune evasion, invasion, and dissemination within the host.[9] Important virulence factors include the M protein, hyaluronic acid, streptokinase, and DNase B. Known toxins, such as pyrogenic toxins (also known as scarlet toxins or erythrogenic toxins), are responsible for the rash associated with scarlet fever. These toxins also stimulate mononuclear cells to produce tumor necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-6, which may contribute to fever and shock in patients with streptococcal toxic shock syndrome (STSS).[2 [10]

Group A streptococci are further classified based on the serotypes of the M and T antigens expressed on their surface.[5] Traditional serotyping methods for detecting these antigens have largely been replaced by sequencing of the N-terminal region of the M protein (emm) gene, which is now widely used for genotyping group A streptococci, particularly in epidemiological studies.[5] [11] Whole genome sequencing (WGS) is increasingly used to identify epidemic strains. To date, more than 250 emm types have been identified based on the M protein gene sequence.[12][5] The streptococcal M protein, encoded by the emm gene and used for epidemiological typing, serves as a virulence factor and has potential as a vaccine antigen.[11] Emm1 strains are particularly virulent and are often associated with invasive infections.[13] Certain emm types, such as M1, M2, M3, M4, M6, M12, and M22, have been associated with scarlet fever outbreaks. Global resurgences of scarlet fever have been reported in regions such as the United Kingdom, Hong Kong, mainland China, and Korea, often associated with the emergence of new emm clones.[14][15] Group A streptococcus (GAS) is one of the few bacteria capable of producing superantigenic exotoxins, which are among the most potent T-cell activators. These superantigens, also known as erythrogenic or scarlet toxins, are responsible for the sandpaper-like erythematous rash and "strawberry tongue" characteristic of scarlet fever.In conditions such as toxic shock syndrome (TSS), certain superantigen exotoxins cause atypical polyclonal lymphocyte activation, leading to the rapid development of shock and multiple organ failure with high mortality. Key identified superantigen exotoxins include toxic shock syndrome toxin-1 (TSST-1) and enterotoxins.[10]

Epidemiology

Epidemic scarlet fever, also known as scarlet fever, is a skin rash caused by SPEs that form during GAS infections in humans and is most often associated with GAS pharyngitis. However, it can also occur with other GAS infections. Scarlet fever is a toxin-mediated disease that typically occurs in epidemics approximately every 5–6 years, likely due to herd immunity specific to a particular type of pathogen. Historically, it caused significant morbidity and mortality in the 19th and early 20th centuries.[16] The prevalence of scarlet fever declined significantly in the second half of the 20th century, likely due to the introduction of antibiotics, which reduced its publichealth impact.[17][18] Characteristic symptoms of scarlet fever include a rough, papular, erythematous rash, "strawberry tongue," and exudative pharyngitis.[18] GAS exclusively infects humans and can involve many sites on the body.[19] Group A streptococcal (GAS) infections are increasing worldwide, resulting in significantly increased morbidity and mortality.[20][21] GAS is transmitted through respiratory secretions, fomites, and contact with infected skin, such as impetigo. Although GAS infections can affect people of any age, children, the elderly, and immunocompromised individuals are at higher risk.[22][23] The incubation period for GAS is 1 to 5 days, during which patients remain infectious and can transmit the bacteria to others.[3] Environmental factors and congregate settings, such as schools, homes, and nursing homes, increase the transmission of GAS.[23][24] GAS commonly causes a variety of upper respiratory tract and skin infections, ranging from mild to severe and from superficial to invasive (iGAS).[20][21] Heavy shedding of GAS in classrooms or other crowded settings, even by asymptomatic carriers, can lead to outbreaks.[23]

Group A streptococcus has been reported to cause illness in young, healthy individuals, with a study showing its presence in 25% of people without risk factors.[24] Group A streptococcus can exist asymptomatically in the pharynx or act as a pathogen, causing group A streptococcal pharyngitis. It is estimated that 5% to 15% of people in the population are asymptomatic carriers. Pharyngitis results from person-to-person transmission via oropharyngeal secretions and droplets from infected individuals.[25] Group A streptococcal infections can be classified by site and depth of involvement, including pharyngitis, scarlet fever, impetigo (superficial keratin layer), cellulitis (subcutaneous tissue), erysipelas (superficial epidermis), STTS, myositis and myonecrosis (muscle), and necrotizing fasciitis (fascia).[27] In addition to these infections, group A streptococcus can cause immune-mediated sequelae such as acute kidney failure and poststreptococcal glomerulonephritis, as well as direct sequelae of immune-mediated processes such as rheumatic heart disease.[28]

The epidemiology of group A streptococcal (GAS) infections varies depending on the type of infection. Pharyngitis caused by GAS is most common in children aged 5 to 15 years and is the most common bacterial cause of acute bacterial pharyngitis in this age group. It is often associated with contact with sick or asymptomatic children at school.[23] GAS is the most common bacterial cause of acute pharyngitis and accounts for 5–15% of sore throat visits in adults and 20–30% in children complaining of pharyngitis.GAS pharyngitis typically occurs in winter and early spring. Severe illness and invasive infections have a bimodal distribution, with a higher incidence in individuals aged 2 years and younger and 50 years and older.[26][29] Risk factors for increased mortality include older age, male gender, nursing home residence, chronic comorbidities, immunosuppression, recent surgery, septic shock, necrotizing fasciitis, concomitant viral infection, isolated bacteremia, and the presence of emm strains type 1 or 3.[24] [29] The global prevalence of severe group A streptococcal (GAS) infections is estimated at 18.1 million cases, with 1.78 million new cases of GAS and 616 million cases of GAS pharyngitis reported annually.[30] Severe GAS infections cause approximately 500,000 deaths worldwide each year, with the majority of these deaths related to rheumatic heart disease (RHD) and invasive infections.[30] The burden of invasive GAS infections (iGAS) is significant, with approximately 663,000 new cases and 163,000 deaths reported annually.[30] Skin and soft tissue are the most common sites of infection, with 32% of patients developing cellulitis and 8% developing ecrotizing fasciitis. emm1 GAS strains are highly virulent, and the M protein encoded by the emm gene serves as a key virulence factor for GAS. The resurgence of GAS infections in the 1980s was attributed to the

emergence of emm1 as a major cause of invasive GAS infections following genetic changes. GAS emm1 strains are highly virulent and associated with invasive infections.[31] Specific strains, including M1, M2, M3, M4, M6, M12, and M22, have been associated with scarlet fever outbreaks. Global resurgence of scarlet fever has been reported in countries such as the United Kingdom, Hong Kong, mainland China, and Korea, and is often associated with new emm clones.Epidemiological surveillance is critical for monitoring epidemics, particularly as the incidence and burden of group A streptococcal (GAS) infections, particularly invasive group A streptococcal (iGAS), increases worldwide. Whole genome sequencing (WGS) plays a key role in this monitoring. [32][29][30] Since 2000, the dominant emm types in Europe and North America have been emm1 and emm3, with emm1 being the dominant type associated with invasive infections in highincome countries.[32] The seven emm types responsible for 50–70% of iGAS infections are emm1, emm28, emm89, emm3, emm12, emm4, and emm6.[5][34] These emm types are collectively referred to as M1global. In 2011, an outbreak of scarlet fever in Hong Kong documented a tenfold increase in casescompared to the baseline and was associated with GAS types emm12 and emm1. Among isolates cultured that year, emm12 was the dominant clone.[35] GAS strains containing these emm types have acquired mutations that have enhanced their virulence and transmissibility.[35]

Surveillance of emm types in Hong Kong revealed that these new strains exhibit increased resistance to macrolides and clindamycin due to the internalization of resistance genes from bacteria found in the human genitourinary and gastrointestinal tracts.[36] Following the Hong Kong outbreak, whole-genome sequencing revealed an increase in scarlet fever cases in mainland China, with the spread of emm12 clones contributing to the increased number of infections.[24] Furthermore, analysis revealed that the mobile genetic elements involved in the spread were the φHKU.vir and φHKU.ssa prophages encoding streptococcal toxin, as well as the macrolide- and tetracycline-resistant ICE-emm12 and ICE-HKU397. This suggests that multiclonal emm12 isolates played a significant role in the spread of scarlet feverlineages both in China and globally.[24]

A new emm1 sublineage, termed "M1UK," was identified in 2008 in the United Kingdom and was associated with increased expression of scarlet fever toxin and SPE-A (speA). Surveillance during the 2014 scarlet fever outbreak in the United Kingdom revealed that regional outbreaks were caused by multiple emm types, including emm3, emm12, emm1, and emm4, as well as different phylogenetic lineages. A significant increase in the prevalence of the ssa gene was associated with scarlet fever cases. The M1UK lineage was responsible for an increase in cases, outbreaks, and invasive infections in the United Kingdom from 2014 to 2018, eventually becoming the dominant strain in the country. By 2020, the M1UK lineage accounted for 91% of invasive emm1 isolates in England. Scarlet fever incidence has declined during the COVID-19 pandemic. Following the COVID-19 pandemic, three emerging M1UK clades rapidly spread across the United Kingdom, leading to severe consequences for children. In the UK, a new dominant clone within the emm1 lineage, dubbed "M1UK," was first reported in 2019. This clone was associated with seasonal scarlet fever outbreaks and an increase in invasive infections, likely caused by a tenfold overproduction of the speA superantigen, also known as erythrogenic toxin A or scarlet fever toxin.[38] The genomic structure of the M1UK lineage differed from the classic M1T1 strain, accumulating an additional 27 single-nucleotide polymorphisms, resulting in enhanced production of the speA superantigen compared to M1T1 isolates.[39]

The M1UK lineage appears to have displaced the globally dominant emm1 M1global strain, which has been widespread since the 1980s. M1UK strains have been found to produce higher levels of the scarlet fever superantigen toxin speA compared to modern M1global strains.[41] Although immunodeficiency may contribute to outbreaks of streptococcal infections, the genetic characteristics of M1UK suggest an advantage in pathogenicity and an exceptional ability to tolerate population bottlenecks. M1UK is currently the dominant strain in England. Two other lineages, M113SNPs and M123SNPs, have also been identified.[41][40] emm1 GAS strains are responsible for more than 50% of invasive infections in children in the United Kingdom in the 2022–2023 season.[31][40] All globally sequenced M1UK(speA) isolates can be traced back to the United Kingdom, where they caused an epidemic and have since spread to Europe and overseas. [40]

Pathophysiology

Many GAS virulence factors contribute to key processes, including adhesion, colonization, evasion of the innate immune system, invasion, and dissemination within the host.[42] Key virulence factors include the M protein, hyaluronic acid, streptokinase, and DNase B. Notable toxins include pyrogenic toxins (also known as scarlet fever or erythrogenic toxins), which cause the rash of scarlet fever. These toxins also induce mononuclear cells to produce TNF-α, IL-1, and IL-6, potentially contributing to fever and shock in patients with STTS. [43,44] Streptococcal M protein, encoded by the emm gene and used for epidemiological typing, serves as a critical virulence factor and a potential vaccine antigen.[45] Strains classified as emm1 are particularly virulent and frequently cause invasive infections. Certain emm types, including M1, M2, M3, M4, M6, M12, and M22, have been associated with scarlet fever outbreaks. A global resurgence of scarlet fever has been reported in countries such as the United Kingdom, Hong Kong, mainland China, and Korea, and is often associated with the emergence of new emm clones.[46][47] Group A streptococcus (GAS) is one of the few bacteria that produces superantigenic exotoxins, which are among the most potent T-cell activators. GAS superantigens, also known as erythrogenic or scarlet fever toxins, are responsible for the erythematous "sandpaper" rash and "strawberry tongue" characteristic of scarlet fever.[48] In syndromes such as STTS, certain bacterial superantigen exotoxins cause atypical polyclonal lymphocyte activation, leading to the rapid development of shock, multiple organ failure, and high mortality. The major superantigenexotoxins include TSST-1 and enterotoxins.[49] The rash of scarlet fever was previously thought to result from primary toxicity caused by group A streptococcus (GAS). However, it is nowunderstood that it results from a delayed hypersensitivity reaction acquired by the host to streptococcal superantigens. Furthermore, the rash typically appears in individuals who have previously been exposed to GAS and are therefore presensitized, whereas it is absent in those who have not had a previous GAS infection. Cutaneous reactivity is likely due to the rapid release of cytokines and the presence of leukocytes induced by an enhanced response to GAS superantigens during secondary antigen exposure.[50][51]

Histopathology

Scarlet fever is not characterized by specific histological changes. Histological findings may include neutrophilic infiltration, spongiosis, and parakeratosis in the epidermis. A physical examination of the patient reveals During the physical examination, it is important to be vigilant for any spread of the rash to the trunk and medial aspects of the elbows and palms. An enlarged anterior cervical node is also observed, along with a high fever. When a child has fever and tachycardia, it is important to examine the skin just below the underwear line. Other signs include enlarged papillae on the tongue (strawberry papillae, sometimes called raspberry tongue) and petechiae on the soft palate.

Treatment

Streptococcal pharyngitis almost always resolves on its own, and many wonder whether antibiotic treatment is justified. However, such treatment may be justified for three reasons: Treatment reduces the duration and severity of the illness. Several studies show that specific therapy shortens the duration of fever and sore throat by approximately 1 day on average. Treatment prevents rheumatic fever. Acute rheumatic fever is a potential complication of pharyngitis caused by S. pyogenes, and studies conducted primarily among US military personnel in the mid-20th century showed that treatment with penicillin reduced the risk of subsequent rheumatic fever. While this rationale for treatment remains compelling in many resource-poor countries where the incidence of acute rheumatic fever is high, in industrialized countries, the relative risks and benefits no longer clearly justify such treatment in routine cases. Treatment prevents purulent complications of pharyngitis. Antibiotic treatment has been shown to reduce the incidence of secondary infectious complications, such as otitis media and sinusitis (Spinks, Glasziou, & Del Mar, 2013). An additional benefit of treatment is that it reduces the spread of infection to others—an important factor for outbreak control. Clinical guidelines in the United States recommend treatment for children and adults with confirmed pharyngitis caused by S. pyogenes (Gerber et al., 2009; Shulman et al., 2012). Guidelines in some European countries are similar, while others do not recommend specific diagnostic testing or treatment because treatment has little effect on the natural history of pharyngitis and the incidence of purulent and non-purulent complications in these populations is low (Van Brusselen et al., 2014). Penicillin has been the mainstay of treatment for pharyngitis caused by S. pyogenes for many years. Clinical isolates remain universally susceptible to penicillin and many other beta-lactam antibiotics. Amoxicillin is equally effective and is often preferred due to its longer half-life, especially in children. Once-daily dosing of amoxicillin appears to have similar efficacy to twicedaily dosing (Clegg et al., 2006; Lennon, Farrell, Martin, & Stewart, 2008). A cephalosporin may be used in patients with a history of penicillin or amoxicillin allergy that is not of the immediate hypersensitivity type. Macrolide antibiotics are an additional alternative, but resistance to them is relatively common (Liu et al., 2009; Tamayo, Pérez-Trallero, Gómez-Garcés, Alós, & Spanish Group for the Study of Infection, 2005; Tanz et al., 2004). Table 1 lists the antibiotic regimens recommended in the Infectious Diseases Society of America guidelines.Some argue that clinical and/or bacteriological cure rates are lower with penicillin (or amoxicillin) than with alternative agents, including cephalosporins (Casey & Pichichero, 2004; Pichichero et al., 2000). The counterargument is that studies demonstrating the superiority of alternative drugs inadvertently included S. pyogenes carriers, and that penicillin is inferior to other drugs in combating carriage but comparable in efficacy in treating true infection (Bisno, 2004; Shulman & Gerber, 2004). Penicillin continues to be recommended as a first-line drug in clinical guidelines due to its well-established safety and efficacy, narrow spectrum of activity, and low cost.

Differential Diagnosis

The differential diagnosis of fever and rash is extensive. When a sandpaper-like rash is observed, additional clinical findings, signs, and symptoms should be assessed to confirm the diagnosis of scarlet fever and differentiate it from other potential causes. Key confirmatory features of scarlet fever include the presence of a "strawberry tongue" and Pastia lines, which strongly suggest the diagnosis. If scarlet fever is suspected, it is important to determine the source of the GAS infection, such as pharyngitis, impetigo, or erysipelas caused by GAS.Other diseases to consider in the differential diagnosis of the rash include rubella, measles, mononucleosis (caused by Epstein-Barr virus or cytomegalovirus), parvovirus B19, chickenpox, enteroviruses (eg, coxsackievirus, which causes hand, foot, and mouth disease), Arcanobacterium haemolyticum, Kawasaki disease, toxic shock syndrome, staphylococcal scalded skin syndrome (SSSS), other viral exanthems, and drug reactions.

Complications

Historically, scarlet fever was characterized by a high complication rate and significant mortality in children. However, with the advent of antibiotics, scarlet fever is now considered a relatively mild illness. It should be noted that delayed or untreated infections caused by group A streptococcus (GAS) can still lead to serious complications, which are divided into suppurative and nonsuppurative. Suppurative complications typically arise from worsening or spread of the initial infection. For example, bacterial pharyngitis can spread to the ear, leading to otitis media, to the sinuses, causing sinusitis, or to the meninges, leading to bacterial meningitis. In contrast, non-suppurative complications are usually immune-mediated and occur after the initial infection has resolved. Rheumatic fever, which affects the heart valves, is a notable nonsuppurative complication of group A streptococcal infections and can lead to significant long-term morbidity. Although scarlet fever itself does not cause complications, group A streptococcal infections can lead to the

problems listed below.
Suppurative complications:
-Peritonsillar or pharyngeal abscess
-Otitis media
-Sinusitis
-Necrotizing fasciitis
-Streptococcal bacteremia
-Meningitis or brain abscess
Septic thrombophlebitis of the jugular vein
Non-suppurative complications:
-Acute rheumatic fever
-Post-streptococcal reactive arthritis
-Streptococcal toxic shock syndrome
-Acute glomerulonephritis
-Childhood autoimmune neuropsychiatric disorder associated with group A streptococcal infections

Patient Prevention

Scarlet fever and other diseases transmitted through contact with objects and respiratory droplets can be prevented by practicing good hand hygiene, covering your mouth and nose when coughing and sneezing, regularly disinfecting surfaces, and avoiding close contact with others if you are infected. Public awareness campaigns, such as posters and media reports, can promote these hygiene practices. Furthermore, it is important to educate the public about the risks of antibiotic overuse, which can contribute to the emergence of antibiotic-resistant strains of group A streptococcus.

Improving Healthcare Team Performance

Scarlet fever is most effectively treated through collaboration within a multidisciplinary healthcare team, with patient education being a central component of treatment. Pharmacists should emphasize the importance of completing the full course of antibiotics for a full recovery. Physicians should collaborate to educate patients on proper hand and personal hygiene to prevent the spread of bacteria. Furthermore, patients should be informed of potential complications, such as peeling of the rash, and when to seek medical attention if complications arise.

Comparison with existing literature and guidelines

the clinical features of scarlet fever described by respondents confirm classical descriptions of the disease from the early 20th century, as well as information contained in current public health and clinical practice guidelines worldwide. The ability of clinicians and parents to distinguish scarlet fever from more common and less severe infections is key to its effective treatment. Current UK clinical guidance on sore throat advises primary care physicians to prescribe antibiotics only if a more serious condition (eg, a purulent infection or sepsis) is suspected. The FeverPAIN and Centor scores are validated in the rapid assessment of GAS pharyngitis, but scarlet fever is outside their scope. When it appears and is recognized, scarlet fever should prompt practitioners to initiate antibiotics, particularly during the spring season when incidence typically increases (March to May). The importance of rapid diagnosis and treatment for public health is highlighted by the 12-fold greater risk of invasive GAS among household contacts

of scarlet fever cases. The advice to avoid unnecessary antibiotics for most sore throats is valuable for antimicrobial stewardship: the caveat is that scarlet fever and other GAS infections require antibiotics to prevent complications and reduce spread. In some contexts, the risk of a patient developing autoimmune sequelae of a GAS infection (acute rheumatic fever or Poststreptococcal glomerulonephritis (PST) may influence a physician's decision to prescribe antibiotics. For example, clinical guidelines in Australia and New Zealand recommend that patients at higher risk of such sequelae (e.g., some Indigenous people and children living in overcrowded settings) may justify a lower threshold for prescribing antibiotics. In this study (conducted in the UK), 80% of children missed school/nursery for 3 days. The time to recovery and return to school was longer when diagnosis was delayed. Since the average primary school student misses 7.4 days per year, this increase is significant. Scarlet fever affected nearly 32,000 children in the UK in 2018; direct medical costs, including hospitalization (1 in 40 cases in 2014), plus the risk of secondary GAS infections, as well as non-medical costs of childcare, loss of education, and time off from work for parents and caregivers, account for significant medical and economic time.

Strengths and Limitations

By examining reported cases of scarlet fever, this study draws on the experiences of patients accessing primary care. However, the low response rate to survey invitations highlights the risk of selection bias. Parents of cases with more severe illness may have been more motivated torespond to the survey; in this case, the failure to include mild or atypical cases could have led to an overestimation of the disease burden. Alternatively, if parents facing greater barriers to care were less likely to participate, underserved communities may have been underrepresented in the survey. Compared to the at-risk population, more cases were white than would be expected by chance. This discrepancy may represent a recognition or notification bias, given that invasive GAS infection occurs at higher rates in non-White ethnic groups. It is important that educational materials for the public and clinicians represent the at-risk population equally: failure to depict a diverse population may hinder understanding of how the rash presents on all skin types. Respondents noted difficulty finding illustrations of the rash on non-White skin, confirming the underrepresentation in educational materials noted elsewhere. Systematically collecting ethnicity data when notifying conditions such as scarlet fever can help identify inequalities in access to care so they can be addressed. The timing of interviews in relation to the clinical episode presents challenges and risks ascertainment bias. Interviewing a parent/caregiver too soon after a clinical episode risks not establishing the full duration of the illness in the patient if long-term complications are not identified; Surveying too late may introduce recall bias if parents incorrectly recall details of the illness and its treatment. A longitudinal study of cases and households affected by scarlet fever would overcome these limitations and provide further insight into the clinical and economic impact of the infection and variables associated with adverse outcomes. Because this survey sought the perspectives of parents and caregivers, it did not fully reflect the views and practices of clinicians. We report aspects of clinical management, such as differential diagnosis, GAS isolation, and antibiotic selection, to the extent that they were known and recalled by respondents. Clinicians may also have identified subtle clinical symptoms and signs not recognized by respondents: this may explain the small number of cases diagnosed with scarlet fever in which rash or fever were not reported. A parallel survey of primary care physicians' wit access to medical records would confirm these observations, reduce the likelihood of recall bias, and help identify clinical decision-making challenges for patients with possible scarlet fever.

Implications for Practice and Research

Distinguishing scarlet fever from viral infections poses a clinical challenge: sore throat is commonin both conditions, and the scarlet fever rash, while characteristic, can be subtle or delayed. The challenge of maintaining diagnostic algorithms and guidelines up-to-date is further highlighted by the emergence of a new cause of acute febrile illness, namely COVID-19. In the presence of diagnostic uncertainty, clinical priorities include excluding measles (for which links to known cases and vaccination history are key) and appropriately directing antibiotic therapy. Point-of-care molecular testing may play a role in GAS outbreak management to guide decisions on clinically equivocal cases when the likelihood of pretest failure is high, although their use in this setting requires further evaluation. Until the sensitivity, timeliness, and cost-effectiveness of diagnostic tests improve, diagnosis of scarlet fever generally relies on clinical assessment of symptoms and signs in the context of current epidemiological trends, followed by microbiological confirmation where possible. Vigilance for seasonal peaks of scarlet fever and the emergence of local outbreaks can help establish an appropriate index of suspicion. Increased local incidence should encourage greater communication between physicians and the public about symptoms of concern (e.g., sandpaper rash) so that new symptoms can be assessed as they develop. The need for sound antimicrobial stewardship should not impede access to timely clinical diagnosis of scarlet fever, microbiological testing, and empirical prescription where indicated.

Reference

1. Gera K, McIver KS. Laboratory growth and maintenance of Streptococcus pyogenes (the Group A Streptococcus, GAS). Curr Protoc Microbiol. 2013
2. Brouwer S, Rivera-Hernandez T, Curren BF, Harbison-Price N, De Oliveira DMP, Jespersen MG, Davies MR, Walker MJ. Pathogenesis, epidemiology and control of Group A Streptococcus infection. Nat Rev Microbiol. 2023 Jul;21(7):431-447.
1. Dunne EM, Hutton S, Peterson E, Blackstock AJ, Hahn CG, Turner K, Carter KK. Increasing Incidence of Invasive Group A Streptococcus Disease, Idaho, USA, 2008-2019. Emerg Infect Dis. 2022 Sep;28(9):1785-1795.

2. de Loizaga SR, Beaton AZ. Rheumatic Fever and Rheumatic Heart Disease in the United States. Pediatr Ann. 2021 Mar;50(3): e98-e104.
3. Gherardi G, Vitali LA, Creti R. Prevalent emm Types among Invasive GAS in Europe and North America since Year 2000. Front Public Health. 2018; 6:59.
4. van Sorge NM, Cole JN, Kuipers K, Henningham A, Aziz RK, Kasirer-Friede A, Lin L, Berends ETM, Davies MR, Dougan G, Zhang F, Dahesh S, Shaw L, Gin J, Cunningham M, Merriman JA, Hütter J, Lepenies B, Rooijakkers SHM, Malley R, Walker MJ, Shattil SJ, Schlievert PM, Choudhury B, Nizet V. The classical lancefield antigen of group a Streptococcus is a virulence determinant with implications for vaccine design. Cell Host Microbe. 2014 Jun 11;15(6):729-740.
5. Lancefield RC. THE ANTIGENIC COMPLEX OF STREPTOCOCCUS HAEMOLYTICUS: I. DEMONSTRATION OF A TYPE-SPECIFIC SUBSTANCE IN EXTRACTS OF STREPTOCOCCUS HAEMOLYTICUS. J Exp Med. 1928 Jan 01;47(1):91-103.
6. Raabe VN, Shane AL. Group B Streptococcus (Streptococcus agalactiae). Microbiol Spectr. 2019
7. Walker MJ, Barnett TC, McArthur JD, Cole JN, Gillen CM, Henningham A, Sriprakash KS, Sanderson-Smith ML, Nize V. Disease manifestations and pathogenic mechanisms of Group A Streptococcus. Clin Microbiol Rev. 2014 Apr;27(2):264-301.
8. 10.Atchade E, De Tymowski C, Grall N, Tanaka S, Montravers P. Toxic Shock Syndrome: A Literature Review. Antibiotics (Basel). 2024 Jan 18;13(1) [PMC free article] [PubMed]
9. Sanderson-Smith M, De Oliveira DM, Guglielmini J, McMillan DJ, Vu T, Holien JK, Henningham A, Steer AC, Bessen DE, Dale JB, Curtis N, Beall BW, Walker MJ, Parker MW, Carapetis JR, Va Melderen L, Sriprakash KS, Smeesters PR., M Protein Study Group. A systematic and functional classification of Streptococcus pyogenes that serves as a new tool for molecular typing and vaccine development. J Infect Dis. 2014 Oct 15;210(8):1325-3
10. Tagini F, Aubert B, Troillet N, Pillonel T, Praz G, Crisinel PA, Prod'hom G, Asner S, Greub G. Importance of whole genome sequencing for the assessment of outbreaks in diagnostic laboratories: analysis of a case series of invasive Streptococcus pyogenes infections. Eur J Clin Microbiol Infect Dis. 2017 Jul;36(7):1173-1180.
11. Rodriguez-Ruiz JP, Lin Q, Lammens C, Smeesters PR, van Kleef-van Koeveringe S, Matheeussen V, Malhotra-Kumar S. Increase in bloodstream infections caused by emm1 group A Streptococcus correlates with emergence of toxigenic M1UK, Belgium, May 2022 to August 2023. Euro Surveill. 2023 Sep;28(36)
12. Wong SSY, Yuen KY. The Comeback of Scarlet Fever. EBioMedicine. 2018 Feb; 28:7-8.
13. You Y, Davies MR, Protani M, McIntyre L, Walker MJ, Zhang J. Scarlet Fever Epidemic in China Caused by Streptococcus pyogenes Serotype M12: Epidemiologic and Molecular Analysis. EBioMedicine. 2018
14. Wong SS, Yuen KY. Streptococcus pyogenes and re-emergence of scarlet fever as a public health problem. Emerg Microbes Infect. 2012 Jul;1(7): e2.
15. Wong SSY, Yuen KY. The Comeback of Scarlet Fever. EBioMedicine. 2018 Feb; 28:7-8. [PMC free article] [PubMed]
16. Walker MJ, Brouwer S. Scarlet fever makes a comeback. Lancet Infect Dis. 2018 Feb;18(2):128-129.
17. Gera K, McIver KS. Laboratory growth and maintenance of Streptococcus pyogenes (th Group A Streptococcus, GAS). Curr Protoc Microbiol. 2013 Oct 02; 30:
18. Brouwer S, Rivera-Hernandez T, Curren BF, Harbison-Price N, De Oliveira DMP, Jespersen MG, Davies MR, Walker MJ. Pathogenesis, epidemiology and control of Group A Streptococcus infection. Nat Rev Microbiol. 2023 Jul;21(7):431-447. [PMC free article]
19. Dunne EM, Hutton S, Peterson E, Blackstock AJ, Hahn CG, Turner K, Carter KK. Increasing Incidence of Invasive Group A Streptococcus Disease, Idaho, USA, 2008-2019. Emerg Infect Dis. 2022 Sep;28(9):1785-1795. [PMC free article]
20. Avire NJ, Whiley H, Ross K. A Review of Streptococcus pyogenes: Public Health Risk Factors, Prevention and Control. Pathogens. 2021 Feb 22;10(2)
21. Cordery R, Purba AK, Begum L, Mills E, Mosavie M, Vieira A, Jauneikaite E, Leung RCY, Siggins MK, Ready D, Hoffman P, Lamagni T, Sriskandan S. Frequency of transmission, asymptomatic shedding, and airborne spread of Streptococcus pyogenes in schoolchildren exposed to scarlet fever: a prospective, longitudinal, multicohort, molecular epidemiological, contact-tracing study in England, UK. Lancet Microbe. 2022 May;3(5): e366-e375
22. Lamagni TL, Darenberg J, Luca-Harari B, Siljander T, Efstratiou A, Henriques-Normark B, Vuopio-Varkila J, Bouvet A, Creti R, Ekelund K, Koliou M, Reinert RR, Stathi A, Strakova L, Ungureanu V, Schalén C, Strep-EURO Study Group. Jasir A. Epidemiology of severe Streptococcus pyogenes disease in Europe. J Clin Microbiol. 2008 Jul;46(7):2359-67.
23. Walker MJ, Barnett TC, McArthur JD, Cole JN, Gillen CM, Henningham A, Sriprakash KS, Sanderson-Smith ML, Niz V. Disease manifestations and pathogenic mechanisms of Group A Streptococcus. Clin Microbiol Rev. 2014 Apr;27(2):264-301.
24. Thompson KM, Sterkel AK, McBride JA, Corliss RF. The Shock of Strep: Rapid Deaths Due to Group a Streptococcus. Acad Forensic Pathol. 2018 Mar;8(1):136-149.
25. Stevens DL, Bryant AE. Streptococcus pyogenes Impetigo, Erysipelas, and Cellulitis. In: Ferretti JJ, Stevens DL, Fischetti VA, editors. Streptococcus pyogenes: Basic Biology to Clinical Manifestations [Internet]. 2nd ed. University of Oklahoma Health Sciences Center; Oklahoma City (OK): Sep 7, 2022.
26. Martin JM, Green M. Group A streptococcus. Semin Pediatr Infect Dis. 2006 Jul;17(3):140-8.

27. Nelson GE, Pondo T, Toews KA, Farley MM, Lindegren ML, Lynfield R, Aragon D, Zansky SM, Watt JP, Cieslak PR, Angeles K, Harrison LH, Petit S, Beall B, Van Beneden CA. Epidemiology of Invasive Group A Streptococcal Infections in the United States, 2005-2012. Clin Infect Dis. 2016
28. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis. 2005 Nov;5(11):685-94.
29. Zhi X, Li HK, Li H, Loboda Z, Charles S, Vieira A, Huse K, Jauneikaite E, Reeves L, Mok KY Coelho J, Lamagni T, Sriskandan S. Emerging Invasive Group A Streptococcus M1UK Lineage Detected by Allele-Specific PCR, England, 20201. Emerg Infect Dis. 2023 May;29(5):1007-1010.
30. Gherardi G, Vitali LA, Creti R. Prevalent emm Types among Invasive GAS in Europe and North America since Year 2000. Front Public Health. 2018; 6:59.
31. Tagini F, Aubert B, Troillet N, Pillonel T, Praz G, Crisinel PA, Prod'hom G, Asner S, Greub G Importance of whole genome sequencing for the assessment of outbreaks in diagnostic laboratories: analysis of a case series of invasive Streptococcus pyogenes infections. Eur J Clin Microbiol Infect Dis. 2017 Jul;36(7):1173-1180
32. Luca-Harari B, Darenberg J, Neal S, Siljander T, Strakova L, Tanna A, Creti R, Ekelund K, Koliou M, Tassios PT, van der Linden M, Straut M, Vuopio-Varkila J, Bouvet A, Efstratiou A,
33. Schalén C, Henriques-Normark B, Strep-EURO Study Group. Jasir A. Clinical and microbiological characteristics of severe Streptococcus pyogenes disease in Europe. *J Clin Microbiol*. 2009
34. 35.Lau EH, Nishiura H, Cowling BJ, Ip DK, Wu JT. Scarlet fever outbreak, Hong Kong, 2011. Emerg Infect Dis. 2012 Oct;18(10):1700-2. [PMC free article]
35. Hsieh YC, Huang YC. Scarlet fever outbreak in Hong Kong, 2011. J Microbiol Immunol Infect. 2011 Dec;44(6):409-11.
36. You Y, Davies MR, Protani M, McIntyre L, Walker MJ, Zhang J. Scarlet Fever Epidemic in China Caused by Streptococcus pyogenes Serotype M12: Epidemiologic and Molecular Analysis EBio
37. Schlievert PM, Bettin KM, Watson DW. Reinterpretation of the Dick test: role of group Astreptococcal pyrogenic exotoxin. Infect Immun. 1979 Nov;26(2):467-72.