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REVIEW

Streptococcus pyogenes and re-emergence of scarlet fever as a public health problem

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Explosive outbreaks of infectious diseases occasionally occur without immediately obvious epidemiological or microbiological explanations. Plague, cholera and *Streptococcus pyogenes* infection are some of the epidemic-prone bacterial infections. Besides epidemiological and conventional microbiological methods, the next-generation gene sequencing technology permits prompt detection of genomic and transcriptomic profiles associated with invasive phenotypes. Horizontal gene transfer due to mobile genetic elements carrying virulence factors and antimicrobial resistance, or mutations associated with the two component CovRS operon are important bacterial factors conferring survival advantage or invasiveness. The high incidence of scarlet fever in children less than 10 years old suggests that the lack of protective immunity is an important host factor. A high population density, overcrowded living environment and a low yearly rainfall are environmental factors contributing to outbreak development. Inappropriate antibiotic use is not only ineffective for treatment, but may actually drive an epidemic caused by drug-resistant strains and worsen patient outcomes by increasing the bacterial density at the site of infection and inducing toxin production. Surveillance of severe *S. pyogenes* infection is important because it can complicate concurrent chickenpox and influenza. Concomitant outbreaks of these two latter infections with a highly virulent and drug-resistant *S. pyogenes* strain can be disastrous.

INTRODUCTION

There are currently 74 species under the genus *Streptococcus*.[1] The type species of the genus, *Streptococcus pyogenes*, is one of the most virulent species causing human infections. *S. pyogenes* is a prototype bacterium that causes exotoxin-mediated infections. It produces a plethora of exotoxins, superantigens and cell wall-associated proteins resulting in diverse clinical manifestations, ranging from classical pyogenic infections, to toxic shock syndrome and post-infectious immune-mediated sequelae. Despite the fact that systemic infections, such as meningitis and endocarditis, are rare nowadays, streptococcal pyoderma and pharyngotonsillitis remain common infections with a heavy global burden of disease.[2] The past two decades have also witnessed a resurgence of several infective syndromes of *S. pyogenes*, most notably necrotizing skin and soft tissue infections and scarlet fever. Here we review the bacteriology, epidemiology and clinical manifestations of *S. pyogenes* infection and scarlet fever with respect to the genesis of outbreaks and their management.

BACTERIOLOGY AND MICROBIAL FACTORS

S. pyogenes is a catalase-negative aerobic Gram-positive coccus arranged in chains. The species is almost synonymous with Lancefield's group A *Streptococcus*, with the exception of the occasional strains of *Streptococcus dysgalactiae* and *Streptococcus anginosus* that may possess the group A antigen.[3] Differentiation from other

group A streptococci is generally simple using the pyrrolidonylarylamidase and Voges–Proskauer reaction.[4]

In addition to the Lancefield's antigen, the M and T surface antigens are also important in the classification of *S. pyogenes*. The M protein is a fibrillar protein located at the cell wall surface and is encoded by the *emm* gene. Functionally, in the absence of opsonizing antibodies, the M protein is anti-phagocytic, inhibits deposition of complements, interacts with a large number of host proteins, possesses pro-inflammatory activities and contribute to mucosal adhesion.[5] Molecular mimicry of M proteins is also implicated in the pathogenesis of post-streptococcal glomerulonephritis and acute rheumatic fever. Antibodies towards M proteins confer type-specific immunity in humans, but there is little heterologous immunity to other M types and the protective opsonizing activity of antibodies appears to be restricted to closely related strains even within the same M types.[6,7] The persistence of type-specific antibodies after natural infection is variable; some decline in antibody titer with time occurs, but in some individuals, the antibodies can persist for as long as 32 years.[8] M protein typing has been used for over 60 years and has proved to be very useful in distinguishing strains with certain tissue tropism. With the increasing number of M protein types being described over the year, a new system based on *emm* gene sequence analysis is adopted. Currently, there are 139 named *emm* types (with 941 subtypes) and 326 unnamed sequence types.[9] The M typing correlates strongly with the tissue tropism of individual *S. pyogenes* strains. The presence of

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multiple M types and possible strain-restricted protective immunity means that re-infections due to *S. pyogenes* is inevitable and this also impacts the development of M protein-based vaccines.

Streptococcal genomes are noted for a high degree of plasticity. At least 16 complete genomes of *S. pyogenes* have been published, covering M types 1, 2, 3, 4, 5, 6, 12, 18, 28 and 49.[10–19] The size of sequenced *S. pyogenes* genomes is about 1.88 Mbp (range: 1.82–1.94 Mbp), with a G+C content of about 38.6%. One important feature of the *S. pyogenes* genome is that its genetic variation is largely determined by the presence of prophages or prophage-like elements. Each genome contains on the average 5 such elements (range: 3–8) which together make up about 10% of the total genome. These prophage-like elements frequently carry virulence mechanisms such as exotoxin, adhesin, and superantigen genes.[20] Besides genetic changes due to mobile genetic elements, spontaneous mutations of the genes encoding the operon of the CovRS two-component system can alter the transcriptomic pattern of 10% of all the genes in the genome of *S. pyogenes* M1T1 to an invasive transcriptomic profile. Such mutations can lead to strong upregulaton of many virulence associated genes encoding the hyaluronic acid capsule synthesis, streptolysin O, streptococcal inhibitor of complement, nicotinamide adenine dinucleotide glycohydrolase (NAD glycohydrolase), interleukin-8 protease and DNase Sda1 which allows *S. pyogenes* to escape killing by neutrophils through the degradation of the DNA-based neutrophil extracellular traps.[21,22] Some other mutations of CovRS operon can decrease the expression of the streptococcal pyrogenic exotoxin B (SpeB) which is a broad-spectrum secreted cysteine protease. SpeB can cleave many virulence factors produced by *S. pyogenes*. The downregulaton of SpeB will stop the degradation of the plasminogen activator streptokinase, M1 surface protein and host plasminogen and therefore the accumulation of plasmin activity on the bacterial cell surface. This will enable the dissemination of the bacterium from the skin or mucosal surfaces to normally sterile anatomical sites.[23]

Horizontal gene transfer has been found to be a major mechanism in generating *emm* gene diversity through intragenic and intergenic recombination.[24] Such gene transfer events occur not only within the *S. pyogenes* species, but also among other streptococcal species such as *S. dysgalactiae* and group G *Streptococcus*.[25] *S. dysgalactiae* subsp. *equisimilis*, which is closely related to *S. pyogenes* phylogenetically, also possesses the *emm* gene and causes infections classically associated with *S. pyogenes*, such as streptococcal toxic shock syndrome, post-streptococcal glomerulonephritis and acute rheumatic fever.[26] In addition to the *emm* gene diversity, horizontal gene transfer also confers new antibiotic resistance mechanisms (such as quinolone and sulphonamide resistance) and virulence mechanisms.[27–29] A recent study also demonstrated the presence of *S. pyogenes* virulence genes in *S. dysgalactiae* subsp. *dysgalactiae*.[30] Although further proofs are necessary, it has been suggested that generation of new subclones of the bacterium through these phages and horizontal gene transfer could account for the sudden occurrence of epidemics and changes in the virulence of *S. pyogenes*.[11,29]

EPIDEMIOLOGY AND ENVIRONMENTAL FACTORS

Asymptomatic pharyngeal carriage of *S. pyogenes* occurs in 3%–26% of healthy children, and 3%–17% of children younger than 5 years of age.[31] Among children with sore throat, 23%–58% of them have *S. pyogenes* being detected (17%–24% in children younger than 5 years).[31] Screening performed during outbreak investigations in long-term care facilities and military training camps showed that the prevalence of *S. pyogenes* colonization was around 16%–17%,[32,33] and up to 12%–88% among children in schools and day care centres during community outbreaks.[34,35] The risk of transmission of *S. pyogenes* from index cases to contacts depends on the duration of exposure and the distance from the index case.[36] In one study, the risk of colonization was significantly higher if the contact time was more than 24 h per week (27% versus 1.8% for contacts having ⩾24 h versus 12–24 h per week, respectively).[36] About 12% of asymptomatic household contacts may carry the same strain of bacterium.[37]

The sites of colonization include the mucosal surfaces and, to a lesser extent, the skin. The oropharyngeal mucosa is the main site of colonization, but other locations such as the gastrointestinal tract and lower female genital tract can also be colonized. Person-to-person transmission involves respiratory droplets and direct contact. The bacterium can readily be found in the air and inanimate environment (such as dust and linen) where there are patients with *S. pyogenes* infections,[38–41] though environmental objects such as blankets and dusts appeared to be unimportant sources of human infection, presumably due to a reduction in infectivity after desiccation.[40,41] However, since *S. pyogenes* may survive on the inanimate objects for up to 4 weeks,[42] environmental hygiene and disinfection should be strictly observed especially within institutions and families.

S. pyogenes is considered to be a human-adapted pathogen. The bacterium has occasionally been found in companion animals, but acquisition from household humans might have occurred and pets are not considered to be an important source of human infection.[43]

One peculiarity in the epidemiology of *S. pyogenes* is the occurrence of foodborne transmission, often resulting in common source outbreaks. Foodborne streptococcal pharyngitis and occasionally scarlet fever have long been recognized. Unpasteurized milk used to be a common food vehicle, which was often derived from cows with clinical mastitis.[44–46] As *S. pyogenes* is considered to be a sole human pathogen, transmission of the bacterium from humans to the cattle was believed to be the source of mastitis.[45] Milk-borne epidemics have become less common with the widespread adoption of pasteurization, but other food items can still be contaminated by asymptomatically colonized food handlers (through hands or respiratory secretions) resulting in outbreaks with high attack rates.[47–49] Eggs and salads are often involved in these outbreaks, as a result of contamination by food handlers and inappropriate holding temperatures after food preparation. In contrast to pharyngitis resulting from droplet transmission, foodborne cases tend to have a high attack rate (50%–90%) and shorter incubation periods.[49]

S. pyogenes is the streptococcal species most commonly associated with epidemics, and outbreaks are characterized by the diversity of clinical syndromes, and their occurrence in both the community (such as within families, schools, day-care centres and prisons) and health-care institutions. Injecting drug users are at high risks of developing *S. pyogenes* infections, which can range from pyoderma to pneumonia and other invasive diseases.[50] *S. pyogenes* outbreaks in military facilities have been reported frequently, which may manifest as pyoderma, ecthyma, streptococcal pharyngitis, acute rheumatic fever and pneumonia.[32,51,52] In long-term care facilities, such outbreaks can be particularly devastating with high mortality rates because of the large number of residents who may have other concurrent medical illnesses, and can linger on for several months.[33]

The epidemiology of major syndromes caused by *S. pyogenes* has seen some dramatic changes in the past decades. The incidence of acute rheumatic fever has decreased in most developing countries in the first three quarters of the twentieth century. Although a variety of explanations have been postulated, a change in the prevalence of

rheumatogenic M types of *S. pyogenes* is possibly an important factor contributing to the decline.[53] However, a resurgence of acute rheumatic fever occurred in the mid-1980s in the United States which was not restricted to the underprivileged of the community.[54] In many communities, the resurgence is associated with the reappearance of mucoid strains of *S. pyogenes* type *emm*18.1.[55] From the late 1980s to 1990s, the epidemiology of *S. pyogenes* was dominated by a surge of invasive infections with high case-fatality rates, including necrotizing skin and soft tissue infections (such as necrotizing fasciitis and myositis) and streptococcal toxic shock syndrome in Europe and North America.[56]

One of the most recent resurgence of *S. pyogenes* infections is scarlet fever. The disease was rampant before the twentieth century, causing frequent widespread epidemics or localized outbreaks and carrying high mortality.[57,58] In the nineteenth-century England and Wales, for example, epidemics occurred with regularity every 5–6 years, and appeared to be correlated with years of low rainfall.[59,60] In temperate countries, the disease is more prevalent in autumn and winter, and is more commonly seen in children (especially under 10 years of age), although adults are also susceptible to the development of scarlet fever.[61,62] Scarlet fever outbreaks are particularly problematic in schools with attack rates over 20%–30%, because of the close proximity of a large number of susceptibility of children in a relatively confined environment. School outbreaks can last for weeks and in the pre-antibiotic era, had persisted for about 10 months.[63]

Scarlet fever outbreaks became less frequently reported in the twentieth century, but are increasingly recognized in the past decade. Scarlet fever outbreaks have been reported in Vietnam (2009, over 23 000 cases); Guernsey, the United Kingdom (2011, 6 cases); Valencia, Spain (2011, 40 cases); Shanghai, China (2011, over 40 cases); Guangdong, China (2011, over 841 cases); Northwest Territories, Canada (2012, over 100 cases); Kansas, USA (2012); and Hong Kong (2011, 1534 cases, ongoing in 2012 at the time of writing).[64,65]

The appearance of outbreaks and changes in the epidemiology could be contributed by changes in herd immunity, genetic mutations or replacement by new circulating *S. pyogenes* strains. Data on

seroprevalence and level protective immunity in the community are sparse and difficult to obtain because of the multitude of M types and possible strain-specific immunity. In a genome-wide study of *S. pyogenes* M3 strains which causes an epidemic of invasive disease in Canada, a four-amino acid duplication at the extreme N terminus of the M protein was found to be a consistent feature of the isolates, as well as the predominance of subclones carrying an SpeA-encoding prophage, the latter presumably increased the fitness and virulence of the strains.[66] A recent analysis showed that even relatively small accumulations of genetic polymorphism can lead to substantial alterations in the transcriptome and extracellular secretome of the bacterium, which may lead to altered virulence and changing epidemiology of the infections.[67] On the other hand, although virulence markers such as the *Streptococcus* invasive locus (*sil*) could be associated with invasive diseases, the prevalence of the markers could be the same among both invasive and non-invasive isolates.[68] Therefore, while alterations in the virulence genes may contribute to the changing epidemiology of *S. pyogenes*, they may interact with other epidemiological and host factors in shaping the epidemiology of diseases.

Changes in the predominant *emm* clones in the community can also account for fluctuations in the incidence of *S. pyogenes* infections.[69] It has also been shown that the main driver for the increase in the prevalence of group A streptococcal infections may not be related to emergence of new hypervirulent strains; rather, widespread transmission and a high prevalence in the community is the more important factor.[70] Changes in the disease rate in the community is also related to strain displacements on a wide geographical scale.[71]

Genetic changes have been detected in *S. pyogenes* strains causing the 2011 epidemic of scarlet fever in Hong Kong. Scarlet fever has been a notifiable disease in Hong Kong since the 1940s. The annual notification of scarlet fever had remained low with only a peak incidence of 124 cases in 1976 (2.8 cases per 100 000 population). However, since the late 1990s, there appeared to be a gradual increase in the number of cases reported (Figure 1). In March 2011, there was an abrupt epidemic of scarlet fever in the community, with 1534 cases being reported in 2011 (annual incidence of 21.58 cases per 100 000
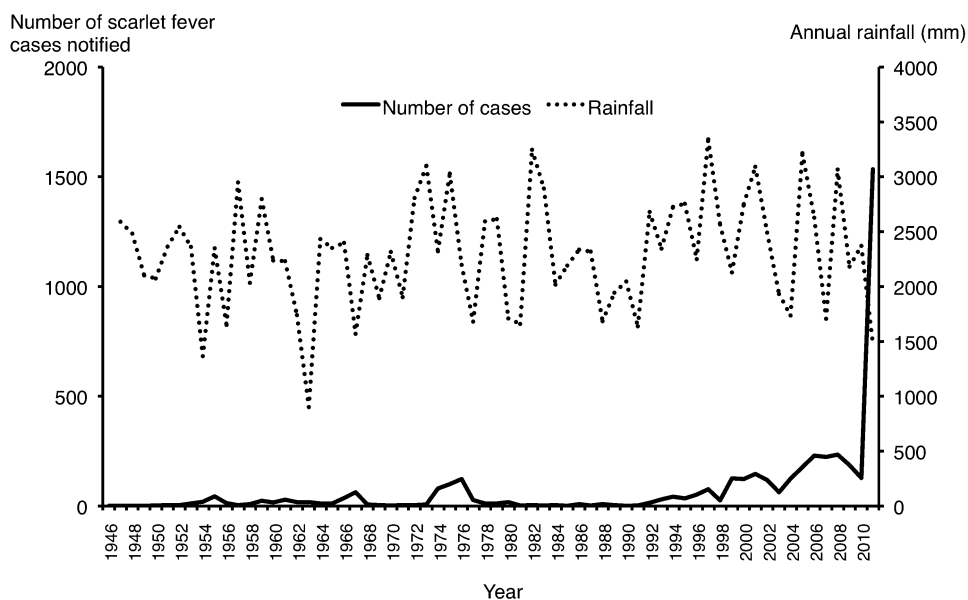

Figure 1 Annual reported cases of scarlet fever yearly rainfall in Hong Kong (1946–2011). Data from Department of Health, Hong Kong and Hong Kong Observatory. Rainfall information was not available for the year 1946 due to the Second World War.

population) with at least three fatalities and several severe cases requiring intensive care. The majority of the strains belongs to the *emm*12 type, which is also commonly encountered globally and in nearby regions such as China and Taiwan.[72,73] Pulsed-field gel electrophoresis of 22 *emm*12 strains isolated from scarlet fever patients in 2011 showed that they are polyclonal in nature.[74]

Whole-genome analysis of an *emm*12 strain isolated from a fatal patient (the HKU16 strain) revealed a circular genome of 1 908 100 bp with G+C content of 38.5% (similar to previously reported genome size of *S. pyogenes*).[74] As in MGAS9249 and MGAS2096 (two previously sequenced *emm*12 genomes), HKU16 also possesses the *speC* and *spd1* genes, but the superantigen gene *ssa* is present in HKU16 and not in the other two genomes. However, the Φ9429.1 prophage which carries the *speC* and *spdI* genes is absent in HKU16. Instead, HKU16 contains a novel prophage termed ΦHKU.vir which also harbours *ssa*. In addition, the genome of HKU16 differs from MGAS9429 and MGAS2096 by a large genomic inversion encompassing 81% of the genome. The HKU16 genome also contains two novel genomic insertions of the sizes 64.9 kb and 46.4 kb. The 64.9 kb insert contains a Tn*916*-type transposon embedded within another putative conjugative transposon. This integrative and conjugative element, ICE-*emm*12, carries the *ermB* (macrolide–lincomycin–streptogramin resistance) and *tetM* (tetracycline resistance) genes, as well as a MATE-type efflux pump and multi-drug ABC-type transporter. The 46.4 kb insertion is a prophage containing the *ssa* (streptococcal superantigen), *speC* (pyrogenic exotoxin C) and *spd1* (DNase) genes. Phenotypically, HKU16 demonstrates a significantly higher level of adherence to HEp-2 human epithelial cells as compared to the hyper-virulent clone M1T1 strain 5448, but a similar level of resistance to killing by human neutrophils and lethality to mice. How relevant are such laboratory findings to the clinical and epidemiological situations require further investigations.

The presence of these unique genetic markers in HKU16 was examined in other contemporary and historical *S. pyogenes* strains in Hong Kong.[74] Among 36 *emm*12 scarlet fever strains in 2011, 86.4% of them possessed ICE-*emm*12 and 81.8% had ΦHKU.vir. Among non-scarlet fever-associated 2011 *S. pyogenes emm*12 strains (*n*=7), ICE-*emm*12 and ΦHKU.vir were present in 5.7% and 4.3% of the strains, respectively. In *emm*12 strains isolated from 2005 to 2010 (*n*=18), 66.7% and 72.2% of them were positive for ICE-*emm*12 and ΦHKU.vir respectively.

The reasons for the 2011 outbreak of scarlet fever in Hong Kong are still unknown. Although it is tempting to attribute the epidemic to such novel genetic findings, the biological significance of these changes has to be confirmed by further studies. In addition to the virulence mechanisms of such new strains, one should closely scrutinize for any potential enhancement in interpersonal transmission or environmental survival. The earliest time of appearance of this strain in Hong Kong, whether such genetic alterations *per se* are sufficient to generate an epidemic, and whether bacteriological factors interact with other environmental factors are unknown. The presence of *emm*12 *S. pyogenes* isolates carrying ICE-*emm*12 and ΦHKU.vir from 2005 onwards appears to be consistent with a moderate increase in scarlet fever cases since that time (Figure 1). It would be informative to see if historical strains from 1999 to 2002 also carried these genetic markers, during which period there was a modest rise in the incidence of scarlet fever. Interestingly, 2011 was also the driest year in Hong Kong since 1963,[75] which echoes earlier findings of the relationship between scarlet fever and rainfall.

It is almost a dogma that different strains of *S. pyogenes* are associated with different propensity to cause acute rheumatic fever and post-streptococcal glomerulonephritis. The *emm*/M type of the infecting strains bears correlation with the potential to cause either one of these sequelae. M proteins of rheumatogenic strains bear epitopes that cross-react with heart, synovium and brain tissues, which results in autoimmune damages in susceptible hosts.[76] Acute rheumatic fever typically follows pharyngotonsillitis, while glomerulonephritis more often follows cutaneous infections (such as impetigo), though it can also complicate respiratory infections. Various streptococcal antigens have been proposed to have a causal role in glomerulonephritis, with SpeB likely to be an important antigen.[77,78] M types 1, 3, 5, 6, 14, 18, 19, 24, 27 and 29 are commonly rheumatogenic, while M types 1, 2, 4, 12, 15, 18, 25, 42, 49, 55, 56, 57, 59, 60 and 61 are the nephritogenic types.[53,78,79] There are, however, geographic variations in that some less commonly encountered M types could be important causes of non-suppurative sequelae in some parts of the world. Examples include the association of M types 71, 92, 93, 98, 103 and 112 with acute rheumatic fever in Hawaii, M types 48 and 73 with glomerulonephritis in Trinidad, and M type 63 with glomerulonephritis in China.[80–82]

It is perhaps remarkable that the 2011–2012 outbreak of scarlet fever in Hong Kong has not been followed by a major epidemic of acute rheumatic fever. The reason is unknown, but possibly due to the fact that the M12 is not classically a rheumatogenic strain,[76] though there had been previous associations between M12 and acute rheumatic fever.[55,83] Heightened awareness among clinicians with earlier use of appropriate antibiotics may have contributed to preventing the development of acute rheumatic fever.[84]

CLINICAL DISEASES AND HOST FACTORS

The clinical manifestations of *S. pyogenes* infection range from asymptomatic carriage to fulminant and fatal diseases. Infections have been classified into: (i) streptococcal toxic shock syndrome; (ii) other invasive infections, defined as the isolation of *S. pyogenes* in normally sterile sites but not meeting the criteria for streptococcal toxic shock syndrome; (iii) scarlet fever; (iv) non-invasive infections, including cutaneous and mucosal infections; and (v) non-suppurative sequelae.[85]

The commonest sites of group A streptococcal infection are the upper respiratory tract and the skin and soft tissues. Streptococcal pharyngitis and tonsillitis can be followed by local and distant suppurative complications (such as peritonsillar and retropharyngeal abscesses) or non-suppurative sequelae (acute rheumatic fever being commoner than post-streptococcal glomerulonephritis after respiratory tract infections). Soft tissue infections range from superficial pyoderma such as impetigo, to erysipelas, cellulitis and more devastating necrotizing infections including necrotizing fasciitis and myositis. Other infections such as meningitis and puerperal sepsis are less commonly seen nowadays. Bacteraemia can complicate infections in any organ system. The presence of skin pathologies should alert one to the potential complication by invasive diseases.[86] An antecedent episode of varicella is one of the most important risk factors for invasive *S. pyogenes* infections in children, which often presents as necrotizing fasciitis.[86,87] In adults, risk factors include various comorbidities, such as diabetes mellitus, malignancies, alcoholism, use of immunosuppressive agents and steroids, chronic heart, lung, liver or renal diseases, HIV infection and injection drug use.[37,86–89] The presence of gastrointestinal symptoms should alert the clinicians to the potential development of severe group A streptococcal diseases.[90]

Pneumonia is not a frequent manifestation of *S. pyogenes* infection in recent years. However, during the latest 2009 pandemic influenza, *S. pyogenes* has re-emerged as a cause of bacterial superinfection. Clusters

of invasive group A streptococcal infection was noted in England, France and the United States, often with high case-fatality rates.[91,92] A concurrent viral respiratory illness has also been suggested as a possible contributing factor in a nursing home outbreak of invasive *S. pyogenes* infection.[93] Thus, as in the cases of *S. pneumoniae* and *S. aureus*, *S. pyogenes* acts synergistically with influenza viruses and possibly other respiratory viruses in causing secondary bacterial infections. Enhanced adherence and internalization of *S. pyogenes* to host cells in the presence of influenza virus infection may explain the synergism.[94–96]

Any form of *S. pyogenes* infection may potentially lead to systemic manifestations due to release of toxins or superantigens. Scarlet fever typically follows an episode of upper respiratory tract infection, but may also complicate skin and soft tissue or wound infections, as well as varicella in children.[97] The incubation period is typically short, commonly 2–3 days (range: 1–6 days), with a sudden onset of fever, headache, malaise, and evidence of tonsillitis and pharyngitis.[98] The tongue is furry with enlarged papillae (white strawberry tongue), later becoming red and inflamed (red strawberry tongue). The rash—called punctate erythema—appears on day 2 of illness, consisting of fine, raised, red spots (which may become confluent) on a background of erythema.[98,99] It spreads from the face (where there is usually no puncta but often characterized by a circumoral pallor) downwards to the neck and upper trunk, and then to the limbs, sometimes with a sandpaper texture of the skin. Pastia's sign, which are deep red, linear exanthem, is commonly observed on the antecubital fossa, but sometimes also seen on other areas of skin folds. The eyes are usually not catarrhal. Resolution of the rash completes in about a week's time, and is often followed by peeling of the skin. Toxic and septic forms of scarlet fever have also been described in which there is extremely prominent tonsillitis with or without ulcerations, profuse purulent rhinorrhoea, and the rash is often dusky, petechial or haemorrhagic.[98] Streptococcal toxic shock syndrome is another systemic inflammatory disease with rash, hypotension and evidence of end organ impairment (kidney, liver, lung and coagulopathy). It often occurs in otherwise immunocompetent individuals with concurrent skin and soft tissue infections and bacteraemia.

TREATMENT AND PREVENTION

Penicillin remains the drug of choice for *S. pyogenes* infections despite over 60 years of use. Nonetheless, bacteriological treatment failure and sometimes clinical failure is well reported. Many postulations have been put forward to explain the phenomenon, including intracellular survival of the bacterium, coexistence of beta lactamase-producing bacteria, and penicillin tolerance.[100] Penicillin tolerance in *S. pyogenes* has been described since the 1980s, but the clinical significance of this phenomenon remains disputable.[101] *S. pyogenes* is also susceptible to most other beta lactams such as the cephalosporins. When penicillin V is used for the treatment of streptococcal pharyngitis, the standard regimen is a 10-day course. When oral cephalosporins such as cefuroxime axetil is used, a 5-day course give similar or slightly superior bacteriological response as compared to penicillin V.[102]

Uncomplicated *S. pyogenes* infections generally respond well to treatment with beta lactams. For the treatment of severe infections, three other modalities of treatment should also be considered. Firstly, urgent surgical interventions remain the cornerstone in treating surgical emergencies such as necrotizing soft tissue infections. Secondly, in addition to penicillins, an antibiotic that inhibits protein synthesis is often added, which is believed to reduce *in vivo* toxin synthesis by the bacterium. Clindamycin is the most commonly used antibiotic in this

setting. In fully susceptible strains, clindamycin is superior to penicillins in suppressing the production of streptococcal pyrogenic exotoxins (SpeA and SpeB) and superantigens *in vitro*.[103,104] The extent of release of SpeA from *S. pyogenes* is higher at lower penicillin concentrations.[105] The usefulness of this strategy has been threatened in recent years with the growing prevalence of clindamycin-resistant *S. pyogenes* isolates. In addition to being ineffective as an antibacterial agent, exposure of these clindamycin-resistant strains to clindamycin actually increases the amount of toxins produced.[106] The optimal antimicrobial strategy for infections caused by clindamycin-resistant strains is uncertain, though linezolid may be considered in severe infections since it also reduces release of SpeA *in vitro*.[107] Fluoroquinolones and rifampicin does not significantly reduce exotoxin production *in vitro*.[108]

Thirdly, intravenous immunoglobulin has been widely used in severe *S. pyogenes* infections, such as toxic shock syndrome and necrotizing soft tissue infections. The mechanism of action of intravenous immunoglobulin probably involves neutralization of toxins and its immunosuppressive activities. Although not all studies have demonstrated unequivocal clinical benefits, the use of intravenous immunoglobulin should still be considered especially in toxic shock syndromes because of its high mortality.[109,110]

The absence of any commercially available vaccine and the bacterium's genetic plasticity due to mobile genetic elements are two key factors which contribute to the occurrence of repeated explosive outbreaks of scarlet fever or other *S. pyogenes* invasive infections. Control and preventive measures against such outbreaks should target towards reduction of transmission and prevention of severe complications. The following measures should therefore be considered.

Surveillance for infections due to *S. pyogenes*

Although invasive group A streptococcal infections are part of the infectious disease surveillance system in some countries, such data are not available in most countries. Passive laboratory surveillance of positive cultures in normally sterile body fluid and throat swab can help to monitor the prevalence of the infection in the community. If resources permit, monitoring of the prevalence of *emm* types would be helpful for early identification of emergence of new strains.

Exclusion of sick patients from school or work

During outbreaks of scarlet fever, infected children should be excluded from schools until he or she has received at least 24 h of an effective antibiotic and the patient is improving.[111,112] While the 24-h recommendation is generally sufficient, it should be noted that in some cases positive cultures of *S. pyogenes* may last longer than 24 h, and more prolonged isolation may be necessary in the health-care setting.[113] For health-care workers, the 24-h recommendation also applies for asymptomatic carriers, while a longer period of exclusion is needed for symptomatic cases or those with skin lesions.[113]

Hand hygiene, droplet and contact precautions

These should be reinforced, especially in school or institutional settings. For young children who may not be able comply with the recommended infection control measures, supervision by teachers or care-givers is essential. Infection control measures are equally important for health-care workers in view of the known nosocomial transmission of invasive group A streptococcal infections to patients and health-care workers.[114] Adherence to droplet and contact precautions with appropriate isolation (single room or cohort) and use of personal protective equipment is important, not only to protect the

health-care workers themselves but to prevent nosocomial spread of the infection.[113] Lapses in proper infection control precautions have resulted in health care-associated *S. pyogenes* outbreaks.[33,93]

Environmental hygiene

Although previous volunteer studies have not consistently demonstrated direct transmission of *S. pyogenes* from fomites, proper maintenance of environmental hygiene remains a prudent measure to take because of the prolonged survival of *S. pyogenes* in the environment and that peak seasons of scarlet fever often coincide with other viral infections such as influenza, for which fomites do play a role in transmission. Previous outbreak investigations of streptococcal pyoderma in a military training establishment showed that environmental contamination with *S. pyogenes* was common, and that contact with contaminated objects contributed to the dissemination of the bacterium.[51] Disinfection can be achieved with cleaning followed by the use of 1000 ppm sodium hypochlorite.[113]

Early and accurate diagnosis

Differentiation from other viral upper respiratory tract is important because *S. pyogenes* is treatable with antibiotics and early antibiotic treatment will reduce the risk of non-suppurative sequelae such as rheumatic fever and possibly suppurative complications. However, in the absence of the classical clinical signs of scarlet fever, differentiation from viral pharyngitis is not always possible. Scoring systems such as the Breese score and Centor score have been used to aid clinical diagnosis,[115,116] and the combination fever ⩾38 ℃, absence of cough, tonsillar exudates and anterior cervical lymphadenopathy are considered to be suggestive of streptococcal pharyngitis. However, no scoring systems are 100% sensitive or specific. A bacterial culture of the throat swab remains the gold standard for laboratory confirmation, but the test may not be readily available in primary health-care settings. Rapid antigen detection tests are useful adjuncts if culture is not available. The specificity of these tests are generally over 95%, but the sensitivity ranges from 70%–90% compared to culture.[117] As a balance between prompt treatment versus unnecessary antibiotic prescription, these point-of-care tests can be useful to supplement clinical diagnosis where microbiology laboratory support is unavailable.[118]

Antibiotic misuse and abuse

The relationship between outpatient antibiotic prescription rates and the prevalence of antibiotic resistance in the community is well established.[119,120] In many countries, there is a disturbing trend to prescribe broader spectrum antibiotics in the primary care setting.[119] In most parts of the world, upper respiratory tract infections constitute the commonest reason for antibiotic prescription in the primary care setting.[121] While it is generally recommended that children and adults with common cold, acute rhinosinusitis, acute cough or bronchitis, acute pharyngitis (except those suggestive of streptococcal infection clinically) and many cases of acute otitis media do not require immediate antibiotic treatment,[122] antibiotics are still very commonly prescribe for a variety of reasons, including various patient- and doctor-related factors.[123] Common reasons for prescription include uncertainties in diagnosis and management, the need to meet patient expectations and pressures, and fear of medicolegal consequences.[123,124] To avoid unnecessary antibiotic prescriptions, education, training and monitoring by various professional bodies are essential for both clinicians and patients. On the practical side, apart from the no-prescribing strategy for obvious diagnoses that do not require antibiotics, a delayed-prescribing strategy can also be used for some patients.[122]

In contrast to beta lactam susceptibility, resistance to macrolides, lincosamides and fluoroquinolones is rising among *S. pyogenes* isolates in many parts of the world.[125–127] Under such circumstances, the macrolides and clindamycin should not be used as first line antibiotics for the treatment of *S. pyogenes* infections. Unfortunately, the use of macrolides in primary health-care settings is very common and frequently being overused even in the absence of any history of beta lactam allergy.[128] In many countries, the newer macrolides (azithromycin and clarithromycin) are among the commonest antibiotics prescribed for respiratory tract infections because of the broad spectrum of coverage (including atypical bacterial pathogens), ease of administration (once daily dosing) and relatively free from adverse reactions.[129] The level of macrolide consumption is correlated with the prevalence of macrolide-resistant bacteria, including *S. pneumoniae* and *S. pyogenes*.[130,131] The association is especially strong with the use of long-acting macrolides such as azithromycin in some studies, presumably due to extended exposure of the bacteria to a low level of antibiotic.[132]

The widespread use of macrolides has four important repercussions. Firstly, inappropriate use of antibiotics will adversely affect the colonization resistance at the musosal surfaces, which reduces the antagonism to colonization by potential pathogens including *S. pyogenes*.[133] Secondly, a large proportion of patients will not received adequate antibiotic coverage for *S. pyogenes* infection. In Hong Kong, 25.6% of the isolates collected between 2005 and 2008 were resistant to macrolides.[134] Recent studies from China showed that over 95% of the *S. pyogenes* isolates were resistant to macrolides and clindamycin.[135,136] This means not only are the macrolides unable to control the active infection, but also fail to prevent complications such as acute rheumatic fever.[137] One has to note that the problem of macrolide resistance is not just a problem with *S. pyogenes* and *S. pneumoniae*, but is also increasingly prevalent among other respiratory pathogens such as *Haemophilus influenzae*, *Staphylococcus aueus* and *Mycoplasma pneumoniae*, with up to 92% of *M. pneumoniae* strains in China being resistant to macrolides.[138,139] Thirdly, the use of a resistant antibiotic may actually increase the level of toxin secretion from *S. pyogenes*. Therefore, giving the wrong antibiotics may actually do more harm than not giving antibiotics initially and adopting a delayed-prescription strategy. Fourthly, macrolide resistance in *S. pyogenes* is not evenly distributed among all *emm* types. Certain clones or *emm* types are more likely to harbor macrolide resistance.[140,141] If such clones concomitantly possess a higher transmissibility and/or virulence for invasive disease, widespread use of macrolides may then drive an epidemic of severe group A streptococcal disease.

Early use of appropriate antibiotics for empirical treatment

Unless there are other contraindications (such as severe allergies to beta lactam antibiotics), penicillins (including penicillin V and amoxicillin) or cephalosporins (if a broader spectrum of coverage is clinically indicated) should remain the first-line antibiotics if *S. pyogenes* infection is suspected clinically.[142] Macrolides and clindamycin should never be the sole agents for empirical treatment of group A streptococcal infections, unless the susceptibility of the infecting strain to these antibiotics is confirmed by laboratory testing. In patients with a history of allergy to penicillin, depending on the nature and severity of the hypersensitivity reactions, the severity of disease and spectrum of coverage needed, suitable alternative antibiotics for empirical coverage include cephalosporins, carbapenems, vancomycin and

linezolid. On the other hand, one should be cautious not to shift the misuse or abuse of macrolides to other classes of antibiotics, especially in the primary care setting.

Varicella and influenza vaccination

Although they do not directly protect against *S. pyogenes* infections, these vaccines should be considered where indicated. Antecedent chickenpox and influenza are known to be predisposing factors for severe group A streptococcal infection, including necrotizing soft tissue infections and pneumonia.[92,95,96,143,144] Protective effects of influenza vaccination against group A streptococcal illness have also been demonstrated in animals and humans.[145–147] Protection against these co-pathogens is most valuable when community outbreaks of *S. pyogenes* infections coincide with the influenza season or when the incidence of chickenpox is also high.

Prudent use of non-steroidal anti-inflammatory drugs (NSAID)

There is currently no evidence that the use of non-steroidal anti-inflammatory drugs predisposes to the development of scarlet fever. However, case series, *in vitro* and animal studies suggested a possible link between non-steroidal anti-inflammatory drug's use and predisposition to severe *S. pyogenes* disease, especially skin and soft tissue infections and toxic shock syndrome.[148] Although results from epidemiological studies did not show a consistent relationship between the two entities, these drugs should be avoided patients with suspected or confirmed *S. pyogenes* infections whenever possible in view of the theoretical risk.[148–152]

Antibiotic prophylaxis

The occurrence of intra-familial and health care-associated outbreaks of invasive group A streptococcal infections has prompted the consideration of antibiotic prophylaxis to close contacts.[86,153–155] While there is evidence that close contacts have a higher risk of developing severe disease than the general population, and that antibiotic prophylaxis does reduce the risk of intra-familial transmission, especially when cephalosporins are used,[37,156,157] routine chemoprophylaxis has not been recommended as the standard practice.[113] The only exception would be a direct percutaneous injury by or mucosal exposure to infective materials.[113] No controlled trials have been performed to quantify the effectiveness of chemoprophylaxis. Benzathine penicillin has been used successfully to control outbreaks of *S. pyogenes* infection in military situations, though this practice will unlikely be applicable to the general community except perhaps in extraordinary circumstances.[32,158] Education and monitoring of close contact for early symptoms of infection are important, especially within 30 days after the diagnosis in the index patient.[159] Chemoprophylaxis may be offered to the household if there are two or more cases of invasive disease within the 30-day period.[113]

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