Mini review

Clinical manifestations, diagnosis, and antimicrobial resistance of group A streptococci infections
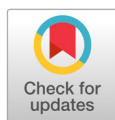
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Abstract

Group A streptococci (GAS) cause diverse diseases ranging from mild to severe illnesses, and the global burden of GAS infections is enormous. Serological typing has been replaced by *emm* genotyping for the epidemiological study of GAS. Acute bacterial pharyngitis is a common illness, which requires either throat culture or rapid Ag test for diagnosis. Moreover, molecular point-of-care tests have been introduced owing to their higher sensitivity. Optimal diagnosis of bacterial pharyngitis is necessary for the adequate use of antibiotics. Although antimicrobial resistance (AMR) to erythromycin or clindamycin does not seem serious in Korea, it is very high in China, being reported at over 90%. Antibiotic surveillance and relevant education are necessary for primary clinical physicians and pediatricians. It is necessary to monitor AMR and develop a system for reporting the appearance of highly virulent diseases, such as necrotizing fasciitis or streptococcal toxic-shock syndrome, to the government authority.

Keywords: Anti-bacterial agents, Bacterial drug resistance, Pharyngitis, Point-of-care testing, *Streptococcus pyogenes*

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Introduction

Group A streptococci (GAS, *Streptococcus pyogenes*) is an important pathogen for human beings as it leads to a range of diverse diseases, from mild diseases such as pharyngitis, scarlet fever, impetigo, and erysipelas, to severe illnesses such as necrotizing fasciitis, streptococcal toxic-shock syndrome (STSS), and puerperal sepsis. The most important sequelae of GAS infections are rheumatic fever (RF) and post-streptococcal glomerulonephritis (PSGN). Although these sequelae are rare in developed countries, they are still a burden in developing countries [1]. It has been estimated that more than 500,000 people have died of severe GAS infections [2]. As upper respiratory tract infections are the most common illness for human beings, optimal diagnosis and treatment of a sore throat is required. Over-usage of antibiotics for acute pharyngitis has been reported in many countries [3,4]. Considering the seriousness of antimicrobial resistance (AMR) worldwide, vigilant usage of antibiotics is necessary. In this study, the author reviewed the diseases, diagnosis, epidemiological methods, and AMR associated with GAS, especially from the perspective of the current situation in Korea.

Diseases

1. Acute pharyngitis

Acute bacterial pharyngitis, mostly caused by GAS, is rather common in kindergarten- or young elementary school-age children [5,6]. However, it should be noted that most etiological agents for sore throats are viruses. Therefore, optimal diagnosis and treatment is crucial to avoid the misuse or overuse of antibiotics. It has been reported that more than 50% of sore throat patients visiting clinics were prescribed with antibiotics [3,4]. Considering that the proportion of GAS pharyngitis is less than 10% among sore throat patients, the overuse of antibiotics seems to be a serious problem. More education and consensus are needed for primary clinical physicians or pediatricians, in order to promote adequate diagnosis and treatment of this very common upper respiratory tract infection. With the introduction of a rapid Ag test (RAT) for streptococcal sore throat [7-9], the highly sensitive RAT can be used for the diagnosis of bacterial pharyngitis, in order to avoid ambiguous antibiotic treatment before receiving the bacterial culture result 1–2 days later.

2. Scarlet fever

Although scarlet fever is not a fatal illness, caregivers often worry about their children due to rashes spreading to the face or trunk. Pediatricians sometimes diagnose scarlet fever based on clinical manifestations if the throat culture is negative. There was a nationwide outbreak of scarlet fever in Korea in the mid-2010s [10,11], and *emm*4 or *emm*3 were the most common causes of scarlet fever [10,11]. As this is classified as a mandatory disease to report to the government agency, the statistics of scarlet fever are easily accessible.

3. RF and PSGN

Although RF and PSGN are classical GAS sequelae, at present they have almost disappeared in Korea; however, they may reappear at any time. For example, a resurgence of RF was reported in the USA during the 1980s, after lapsing for several decades [12]. Although these sequelae are a very serious public health concern in developing countries [1,2], we still do not understand their exact immunological mechanisms, as developing animal models for these sequelae is challenging [13].

4. Necrotizing fasciitis

GAS may cause necrotizing fasciitis (NF), which is rapidly progressing and fatal [14]. In NF, GAS spreads through the fascia rapidly. Early diagnosis and prompt surgical debridement are essential to cure necrotizing fasciitis.

5. STSS

STSS is the most fatal illness of GAS, with a mortality of over 40% [15], much higher than that of staphylococcal toxic-shock syndrome. STSS progresses rapidly throughout non-specific T-cell immune response [16]. Many different organs, such as the liver and kidney, may be damaged and become

dysfunctional [16]. In particular, *emm*1 presented higher mortality compared to other *emm* types in Japan [15]. As this is the most fatal illness based on GAS, STSS as well as NF should be reported and monitored by the government authority, as is the case in Japan.

6. Asymptomatic infections

It is assumed that asymptomatic infections are widely present in elementary schools [17]. From an anti-opacity factor (OF) analysis, more than 75% of school children harbored anti-OF in their sera [8]. The same percentage showed a higher than upper limit of normal (ULN; 200 IU/mL) anti-streptolysin O (ASO) level [18]. As these antibodies are proof of previous GAS infections, it can be assumed that a majority of school children have become immune to various M-types of GAS without evident symptoms [19]. Therefore, it is plausible that many carriers of GAS may undergo asymptomatic infections [17], or serve as a GAS reservoir [20] and build up herd immunity to the circulating M-types of GAS. There might be a tendency to more likely catch influenza in the case of these asymptomatic infections [21].

Diagnosis

1. Culture

Bacterial culture is the gold standard for diagnosis of GAS infections or pharyngitis. However, it is largely affected by the sampling procedure, streaking technique on blood agar plate, and expertise of the technician [22]. Some GAS strains are not inhibited by a bacitracin disk [23], whereas non-GAS are sometimes inhibited by a bacitracin disk. Therefore, further confirmation tests using biochemical reaction, slide agglutination, or MALDI-TOF should be carried out in addition to bacitracin screening for optimal identification. In addition, for epidemiological survey in a given region, bacterial culture is needed to procure the GAS strains.

2. RAT

RAT has been used for testing sore throat patients in Western countries since the 1980s. RAT for streptococcal sore throat is the first developed point-of-care (POC) test for infectious diseases. Taking samples from the throat seems easy, simple, and RAT may prevent the decision to prescribe antibiotics without waiting 1–2 days for the throat culture results. Therefore, RAT for streptococcal sore throat has been widely adopted in primary clinics [3,5]. Due to the advancement of quality for in vitro diagnostic devices, the sensitivity of RAT is practically equivalent to that of bacterial culture at present [24,25]; however, the utilization of RAT for streptococcal sore throat is not well-documented in Korea, due to its low insurance cost and lack of education for physicians or pediatricians.

3. Molecular POC test

As molecular tests using PCR techniques give high sensitivity and short turn-around time [26], they are

expected to become standard diagnostic tests for GAS pharyngitis [27]. Most importantly, any diagnostic test—such as culture, RAT, or molecular POC test—cannot differentiate between the carriers and true infections. Differentiation is not always necessary for symptomatic patients and the optimal diagnosis is largely affected by clinical expertise [5,28,29].

4. ASO

ASO is not commonly used at present, as very few cases of RF or PSGN are observed. For the diagnosis of acute pharyngitis, an ASO test is not recommended, as ASO will appear 2–3 weeks later. Furthermore, the physicians should be very careful when interpreting the ASO result, as the ULN of ASO differs by age group [30]. The ULN of ASO is defined as 80% of the cumulative ASO in the population, and has been found to be over 400 IU/mL for elementary school children [18,19].

Epidemiological methods

1. Serotyping

Although T- and M-typing have previously been used for the serological epidemiological study of GAS in the past, these tests became disused after the introduction of *emm* genotyping. T-typing is based on slide agglutination by using commercially available anti-T sera (Fig. 1). The T-protein is not associated with disease and presents a cross-reaction [7]. M-typing is based on double immuno-diffusion on agarose gel using anti-M sera produced from rabbits (Fig. 1). The M-protein is related to disease and is the most important virulence factor of GAS [7]. However, some strains do not produce anti-M sera in rabbits; instead, they make horse sera opaque. This protein is called OF [7]. Anti-OF sera can be procured from human beings who have been infected with a specific OF type [8].

2. *Emm* genotyping

The serotyping procedure is time-consuming and is difficult to carry out in the clinical laboratory. Serotyping was replaced by *emm* genotyping in early 2000s. *Emm* is the M protein-encoding gene, which has hypervariable sequences at the $5'$-N-terminal with a size of 500–1500 bp [9]. More than 220 *emm* genotypes have been reported [31]. *Emm* genotyping is rather simple and easy to perform for the molecular epidemiological study of GAS. Although GAS infections are type-specific [7], indicating that an individual may not be protected against another M-type, but only immune to the same M-type, several *emm* genotypes have presented cross-immunity characteristics. These *emm* genotypes are classified as the *emm* clades [32], and are important for the development of vaccines. At present, a 30-valent vaccine is under development [10,11,32]. Dynamic changes in distribution of *emm* genotypes have been observed in regions or countries, suggesting the waxing and waning of circulating GAS M-types in the community [33,34].

3. Whole-genome sequencing (WGS)

With the technical advancement and lower cost, WGS is becoming more available. Through WGS, more

(a) Slide agglutination for T-typing. Extracted T Ag (red broth) is reacted on the slide with the commecially available anti-T sera.
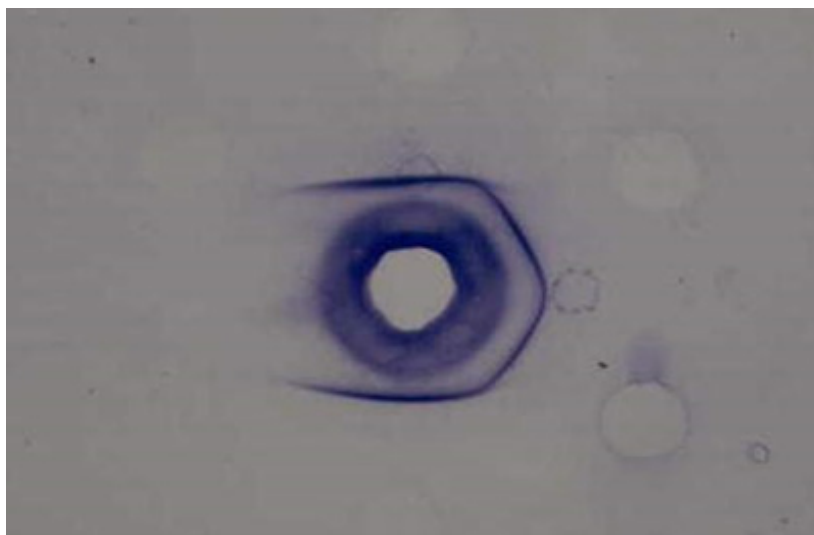
(b) Double immunodiffusion for M typing. Extracted M proteins diffuse in the agarose gel and make precipitation with anti-M sera in the center. Four out of 6 show positive.

Fig. 1. Serotyping of group A streptococci by (a) T typing and (b) M typing.

information regarding not only *emm* genotypes, but also sequence types, AMR genes, and virulence genes can be obtained. In addition, through WGS, we can understand the size of the whole genome, as well as similarities and differences between genomes [9,20]. With the widespread application of WGS technology in routine clinical laboratories, this technique can provide multi-faceted information on GAS.

Antimicrobial resistance

Fortunately, AMR to erythromycin and clindamycin is not yet a serious concern in Korea. AMR to these antibiotics is reported in less than 5%, which has remained stable since 2004 [6,35] (Fig. 2). As antibiotic-

resistant strains such as *emm*12 have decreased and antibiotic-susceptible strains, such as *emm*4, are prevalent these days, the change in distribution of *emm* genotypes may have affected the reported decrease in AMR [32,36,37]. As many new macrolides, such as azithromycin and clarithromycin, have widely been used for respiratory tract infections in the clinics, more efforts for keen use of these drugs are needed. Furthermore, AMR to erythromycin and clindamycin has been reported to be around 25% in the United States [36] and as high as 95% in China [36,38,39]. This is a serious concern, considering that these drugs should be secured for patients who are allergic to penicillin. Still, no penicillin-resistant GAS has been reported to date [36,38,39]. Although penicillin or amoxicillin are regarded as drugs of choice for bacterial pharyngitis [5,40], there are cases of treatment failure when GAS is located inside the cells, as these drugs are less effective in such a scenario [41].
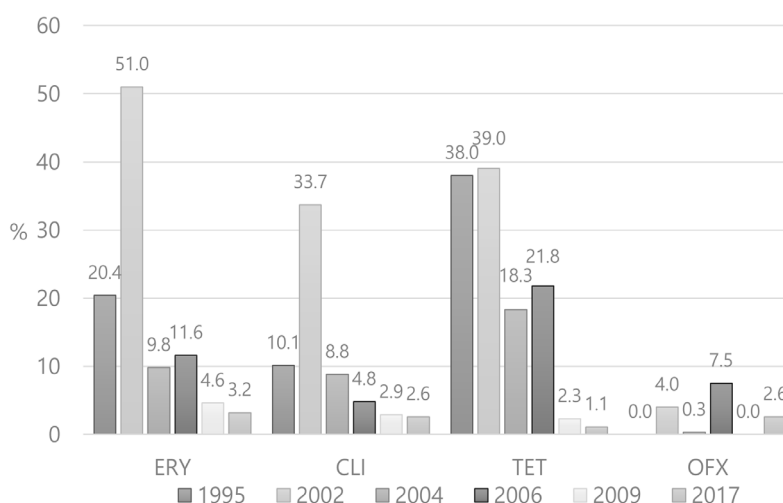

Fig. 2. Antimicrobial resistance of group A streptococci against erythromycin (ERY), clindamycin (CLI), tetracycline (TET), and ofloxacin (OFX) isolated from Gyeongnam Province between 1995-2017.

Conclusion

GAS is an important pathogen causing diverse diseases. Although GAS is the most common cause of bacterial pharyngitis, the prescription of antibiotics for sore throats seems to be much higher than necessary. Antibiotic stewardship and education regarding optimal diagnostic tests are required for primary physicians or pediatricians. RAT seems more practical than throat culture, the results of which can be returned in about 2 days. Molecular POC testing is expected to become more popular in clinics and hospitals due to its feasibility and high sensitivity. STSS or NF should be reported to the appropriate government authority in order to monitor the spread of highly virulent strains in the community. At present, AMR does not seem to be a serious concern in Korea. However, AMR may increase if we do not pay attention to the right usage of antibiotics and/or if resistant *emm* genotypes re-appear.

Ethics statement

It is not a human population study; therefore, approval by the institutional review board or the obtainment of informed consent is not required.

Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

Funding

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