EBioMedicine 28 (2018) 7–8

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

The Comeback of Scarlet Fever

Samson S.Y. Wong, Kwok-Yung Yuen *

Department of Microbiology, Carol Yu Centre for Infection, Faculty of Medicine, The University of Hong Kong, China

Streptococcus pyogenes (group A *Streptococcus*, GAS) is arguably the most virulent of all clinically important streptococci with a propensity to cause severe invasive diseases, toxic shock syndrome, and immunopathological damages such as acute rheumatic fever. Since the 1980s, severe GAS infections such as necrotizing fasciitis and toxic shock syndrome have been increasingly recognized (Stevens and Bryant, 2016). Scarlet fever, a toxin-mediated disease, occurred in epidemics in the nineteenth century but was relatively uncommon in the second half of the twentieth century in most developed countries. However, there has been a re-emergence of scarlet fever in the past decade in some countries such as the United Kingdom (since 2014), Hong Kong (since 2011), and mainland China (Lamagni et al., 2017; Tse et al., 2012; You et al., 2018). Historically, epidemics of scarlet fever often occurred every five to six years, possibly due to the accumulation of type-specific herd immunity among the susceptible population in the community, but also affected by various environmental and meteorological factors (Wong and Yuen, 2012). The appearance of GAS epidemics has sometimes been attributed to the introduction of hitherto uncommon *emm* types or acquisition of new mobile genetic elements which may carry virulence determinants, although these have not been consistently demonstrated in all outbreaks.

Different *emm* types predominate in different parts of the world. For example, the increase in scarlet fever incidence in England since 2014 was caused by multiple lineages of GAS, especially *emm*3, *emm*4, and *emm*12 types, while the acapsular *emm*89 has emerged as an important cause of invasive GAS diseases (Chalker et al., 2017). In the UK outbreak of scarlet fever in 2014, no single lineage of GAS or virulence gene predominated in all the strains (Chalker et al., 2017). In contrast, the 2011 epidemics of scarlet fever in Hong Kong and mainland China were predominantly caused by *emm*12 strains (Tse et al., 2012; You et al., 2018). Similarly, the commonest strains found in scarlet fever cases also belonged to *emm*12 type in northern Taiwan in 2010–2011 (Wu et al., 2014). However, even in scarlet fever epidemics where a particular *emm* type predominated, genomic studies showed that the strains often belonged to multiple phylogenetic lineages rather than a single clone (Tse et al., 2012; You et al., 2018). The *emm*12 type is not new to the Far East region. In China, *emm*12 was already the commonest *emm* type found in *S. pyogenes* isolates between 2005 and 2008. (Liang et al., 2012) The 2011 scarlet fever outbreak in Hong Kong was notable in that most of the outbreak *emm*12 strains were associated with new genomic insertions containing tetracycline and macrolide resistance genes, and the presence of novel prophages ΦHKU.ssa and ΦHKU.vir, which carried genes for superantigens and DNase (*ssa*, *speC*, *spd1*) (Tse et al., 2012). The ΦHKU.vir and ΦHKU.ssa prophages were also present in half of the contemporary Chinese scarlet fever-associated *emm*12 strains (You et al., 2018). In addition to the possible roles of these virulence factors in pathogenesis, the presence of macrolide resistance may impart survival advantages to these strains in areas where antibiotic consumption is high, especially where macrolides are commonly prescribed for respiratory tract infections in the primary care setting. Although the 2014 UK scarlet fever outbreak was caused by multiple *emm* types and lineages (but especially *emm*3, 4, and 12), a ΦHKU.ssa-like prophage was found in 68.3% of the *emm*12 isolates but not in other *emm* types (except for one [3.5%] *emm*28 isolate) (Chalker et al., 2017).

The problem of clindamycin resistance has been a clinically pertinent issue for many years. Historically, clindamycin plus penicillin is the recommended treatment of severe GAS infections by reducing toxin and superantigen production (Wong and Yuen, 2012). However, the use of clindamycin is potentially detrimental in the presence of clindamycin resistance because it can paradoxically increase the production of exotoxins. In the recent scarlet fever outbreaks in Hong Kong and mainland China, clindamycin resistance was present in 85.6% and 97% of the isolates respectively (Luk et al., 2012; You et al., 2013). This high prevalence of macrolide and clindamycin resistance may necessitate the use of alternative adjunctive therapy such as linezolid in the treatment of severe GAS infections (Wong and Yuen, 2012).

The use of whole genome sequencing has enhanced our understanding of the molecular epidemiology of *S. pyogenes* infections. It allows for detailed analysis of the *emm* types of strains, phylogenetic analysis, antibiotic resistance genes characterization, and discovery of novel genetic elements. The approach has been used in the study of invasive GAS infections and scarlet fever outbreaks in different countries (Chalker et al., 2017; Tse et al., 2012; You et al., 2018). The wider availability of whole genome sequencing will allow a better understanding of the epidemiology and pathogenesis of infections due to *S. pyogenes*.

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.01.010.

* Corresponding author at: Department of Microbiology, The University of Hong Kong, 16/F Block T, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong, China.
E-mail address: kyyuen@hku.hk (K.-Y. Yuen).

https://doi.org/10.1016/j.ebiom.2018.01.030

Disclosure

The authors declared no conflicts of interest.

References

Chalker, V., Jironkin, A., Coelho, J., Al-Shahib, A., Platt, S., Kapatai, G., Daniel, R., Dhami, C., Laranjeira, M., Chambers, T., Guy, R., Lamagni, T., Harrison, T., Chand, M., Johnson, A.P., Underwood, A., Scarlet Fever Incident Management Team, 2017. Genome analysis following a national increase in scarlet fever in England 2014. BMC Genomics https://doi.org/10.1186/s12864-017-3603-z.

Lamagni, T., Guy, R., Chand, M., Henderson, K.L., Chalker, V., Lewis, J., Saliba, V., Elliot, A.J., Smith, G.E., Rushton, S., Sheridan, E.A., Ramsay, M., Johnson, A.P., 2017. Resurgence of scarlet fever in England, 2014–16: a population-based surveillance study. Lancet Infect. Dis. https://doi.org/10.1016/S1473-3099(17)30693-X.

Liang, Y., Liu, X., Chang, H., L, J., Huang, G., Fu, Z., Zheng, Y., Wang, L., Li, C., Shen, Y., Yu, S., Yao, K., Ma, L., Shen, X., Yang, Y., 2012. Epidemiological and molecular characteristics of clinical isolates of *Streptococcus pyogenes* collected between 2005 and 2008 from Chinese children. J. Med. Microbiol. 61, 975–983.

Luk, E.Y., Lo, J.Y., Li, A.Z., Lau, M.C., Cheung, T.K., Wong, A.Y., Wong, M.M., Wong, C.W., Chuang, S.K., Tsang, T., 2012. Scarlet fever epidemic, Hong Kong, 2011. Emerg. Infect. Dis. 18, 1658–1661.

Stevens, D.L., Bryant, A.E., 2016. Severe group A streptococcal infections. In: Ferretti, J.J., Stevens, D.L., Fischetti, V.A. (Eds.), *Streptococcus pyogenes*: Basic Biology to Clinical Manifestations. University of Oklahoma Health Sciences Center, Oklahoma City : pp. 741–769. https://www.ncbi.nlm.nih.gov/books/n/spyogenes/pdf/, Accessed date: 15 January 2018.

Tse, H., Bao, J.Y., Davies, M.R., Maamary, P., Tsoi, H.W., Tong, A.H., Ho, T.C., Lin, C.H., Gillen, C.M., Barnett, T.C., Chen, J.H., Lee, M., Yam, W.C., Wong, C.K., Ong, C.L., Chan, Y.W., Wu, C.W., Ng, T., Lim, W.W., Tsang, T.H., Tse, C.W., Dougan, G., Walker, M.J., Lok, S., Yuen, K.Y., 2012. Molecular characterization of the 2011 Hong Kong scarlet fever outbreak. J. Infect. Dis. 206, 341–351.

Wong, S.S., Yuen, K.Y., 2012. *Streptococcus pyogenes* and re-emergence of scarlet fever as a public health problem. Emerg. Microbes. Infect. 1, e2. https://doi.org/10.1038/emi.2012.9.

Wu, P.C., Lo, W.T., Chen, S.J., Wang, C.C., 2014. Molecular characterization of Group A streptococcal isolates causing scarlet fever and pharyngitis among young children: a retrospective study from a northern Taiwan medical center. J. Microbiol. Immunol. Infect. 47, 304–310.

You, Y.H., Song, Y.Y., Yan, X.M., Wang, H.B., Zhang, M.H., Tao, X.X., Li, L.L., Zhang, Y.X., Jiang, X.H., Zhang, B.H., Zhou, H., Xiao, D., Jin, L.M., Feng, Z.J., Luo, F.J., Zhang, J.Z., 2013. Molecular epidemiological characteristics of *Streptococcus pyogenes* strains involved in an outbreak of scarlet fever in China, 2011. Biomed. Environ. Sci. 26, 877–885.

You, Y., Davies, M.R., Protani, M., McIntyre, L., Walker, M.J., Zhang, J., 2018. Scarlet fever epidemic in China caused by *Streptococcus pyogenes* serotype M12: epidemiologic and molecular analysis. EBioMedicine https://doi.org/10.1016/j.ebiom.2018.01.010.