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Streptococcus pyogenes: Virulence Factors and Prevention Measures

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Abstract. Group A streptococcus (GAS) is a common name for *Streptococcus pyogenes*, a significant bacterial pathogen that is particular to humans and can cause a wide range of symptoms, from minor localized infections to potentially fatal invasive infections. The bacterium that causes GAS infections is typically spread by respiratory droplets, skin sores that are touched by GAS, or coming into contact with contaminated objects or materials. Foodborne transmission is another possibility, but further investigation is required to determine the extent of this infection route. It was discovered that GAS illnesses are quite common in indigenous groups, low-socioeconomic areas in developed countries, and emerging countries. Many of the extracellular secretion produced or released by *S. pyogenes* strains are virulence factors because they aid in the promotion of illness and/or the pathogen's survival in the host. The virulence factors that are released or secreted from the bacterial surface are, Streptococcal Cysteine Protease (SpeB), Streptococcus C5a Peptidase (ScpA), Streptolysin O (SLO) and *S. pyogenes* Cell-Envelope Proteinase (SpyCEP), reviewed in this article. SpeB is the predominant secreted cysteine protease of GAS. SpeB cleaves or degrades host serum proteins such as human extracellular matrix, immunoglobulins, complement components, and even GAS surface and secreted proteins. C5a peptidase (ScpA) is a highly specific proteolytic enzyme that cleaves the complement-derived chemotaxin C5a. The C5a peptidase gene (*scpA*) is encoded towards the 3′ end of the *mga* regulon and is highly conserved amongst GAS genotypes. Streptolysin-O binds cholesterol in cell membranes, resulting in rapid lysis of polymorphonuclear neutrophils **(**PMNs), including their lysosomes, releasing their toxic contents, which may have additional deleterious effects on neighboring cells. SpyCEP is a surface-exposed serine protease that inactivates chemokines. Overcrowding and the increased degree of social interaction in these environments have attributed to GAS infections. Improving living conditions and hand and personal cleanliness should be the main goals of prevention and control strategies. In high-risk environments, adherence to infection prevention and control measures should be prioritized.

Keywords: GAS, *Streptococcus pyogenes*, virulence factors, Group A streptococcus.

1. Introduction

Streptococcus pyogenes (Group A *Streptococcus*; GAS) is a Gram-positive host-adapted bacterial pathogen causing benign human infections such as pharyngitis and impetigo, through to rare yet severe invasive diseases such as septicaemia, streptococcal toxic shock-like syndrome (STSS) and necrotizing fasciitis. Repeated GAS infections may trigger autoimmune sequelae including rheumatic fever that can lead to rheumatic heart disease (RHD) [1]. Epidemiologically, GAS can be classified into more than 220 *emm* types (based on the gene sequence of the amino terminal of the surface-exposed M protein) which show differing patterns of regional and global distribution [2,3]. As a host-adapted human pathogen, GAS survival requires an unbroken cycle of transmission, adherence to the primary infection site

(skin or throat), colonization and proliferation, defence against both innate and adaptive immune systems, and subsequent dissemination to a new host. New virulence strategies employed by GAS to manipulate host defence mechanisms are being discovered. For example, the cleavage of Gasdermin A (GSDMA) by the GAS protease streptococcal pyrogenic exotoxin B (SpeB) has been shown to trigger host cell pyroptosis [4,5], whereas mucosal-associated invariant T cells (MAIT cells) have been recently identified as highly activated in patients with STSS, and as primary contributors to the cytokine storm associated with this disease [6].

In the absence of a commercial GAS vaccine, medical intervention against GAS revolves around the use of antibiotics to treat or prevent infection. However, GAS antibiotic resistance is on the rise and the first mutations that confer reduced penicillin sensitivity have been reported [7-11]; nonetheless, GAS remains susceptible to β-lactam antibiotics. To expedite GAS vaccine development, the World Health Organization (WHO) has developed a GAS research and technology road map and has outlined preferred product characteristics [12]. Large-scale genomics has been applied to define global GAS population structure and predict vaccine antigen coverage [13]. New GAS vaccine formulations directed against M protein and non-M protein antigens are in development [14]. The non-human primate model of GAS pharyngitis has recently been used to assess GAS vaccine efficacy [15], and the development of a controlled human infection model (CHIM) of GAS pharyngitis [16], provides a future opportunity for assessment of vaccine efficacy in the human host.

GAS secretes several virulence agents that harm host cells, tissues, and the immune system. For instance, the capacity of the GAS M protein to attach to fibronectin (Fn) on the surface of the host cell to penetrate epithelial or endothelial cells is thought to be essential to the organism's ability to adapt and thrive over time [17]. To infiltrate deeper tissue areas and cause serious infections, GAS must escape the host's innate immune system after colonization. One such innate immunological defence mechanism against intracellular GAS is autophagy; however, autophagy adaptor proteins p62, NDP52, and NBR1 can be degraded by streptococcal cysteine protease (SpeB) to circumvent the autophagy pathway's clearance mechanism [18]. The World Health Organization (WHO) noted at the end of 2022 that invasive infections and scarlet fever had significantly increased in some affluent nations, with a disproportionate number of cases affecting children [19, 20]. According to studies conducted in the US, GAS infections were thought to have caused between 1136 and 1607 deaths annually between 2005 and 2012, and over 2250 deaths in 2019 [21]. Moreover, the rate of GAS infection in Canada in 2017 was over ten times higher than it was in 2003 [22]. It follows that the number of disorders linked to GAS infections is clearly rising quickly. Penicillin and other beta-lactam antibiotics are still useful in the treatment of GAS today. On the other hand, there is rising concern around the globe about the growing resistance to other antibiotics used in illness treatment. This review describes the virulent factors of GAS and prevention measures.

2. GAS Virulence Factors

Bacterial and host variables influence the pathogenesis of infection in the complicated and multidimensional process of GAS infection in humans. Numerous virulence factors linked with and secreted from GAS (Fig.1) have been described elsewhere [23]. Here, we highlight the most recent developments in this field and concentrate on critical virulence factors that are crucial for the colonization of epithelial tissues and the development of invasive illness.

2.1 GAS Adhesins

It is thought that there are two steps involved in the adherence of GAS to certain epithelial cells. Initially, a weak, reversible, and non-specific contact between lipoteichoic acid and epithelial surfaces is mediated [25]. Surface-anchored and surface-associated proteins are involved in the second phase of adhesion. These adhesins function as bridging molecules by using matrix and/or plasma proteins, or they can attach directly to the receptors on human host cells [26]. The most prevalent surface-anchored protein of GAS and arguably one of the most well-studied virulence factors is streptococcal M protein. Numerous proteinaceous and non-proteinaceous interaction partners have been identified. For example, M protein interacts with glycosaminoglycans on human skin fibroblasts, binds directly to CD46 on human keratinocytes, and employs fibronectin as a major target on epithelial cells [27-29]. The ability of GAS to attach itself to host cells is demonstrated by the interactions of the M protein with these three ligands, to name just a few. Numerous other GAS adhesins, both classical and non-classical, exist. These consist of many collagen binding proteins Cpa [30], vitronectin binding proteins [31], plasminogen binding proteins [32], and fibronectin binding proteins [33]. It should be highlighted that not all GAS serotypes express them, that their expression varies depending on the stage of infection and growth, and that some of them exhibit cell type specificity [34].

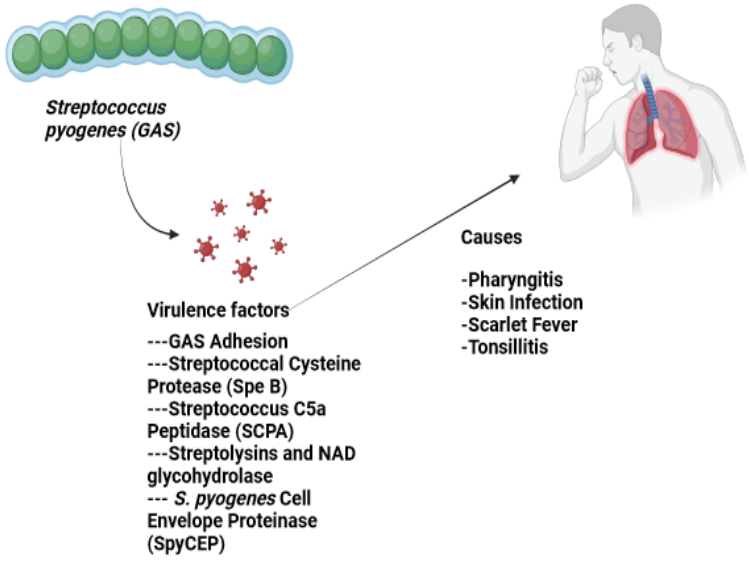

Fig. 1. GAS virulence factors [24].

Unlike the earlier belief that GAS are external pathogens, it is now recognized that GAS can enter and remain in human cells. GAS can effectively integrate into and persist in non-phagocytic cells at a frequency comparable to those of Listeria and Salmonella, as demonstrated for the first time by LaPenta and associates [35]. The M protein-fibronectin-α5β1-integrin axis is one example of how GAS causes the host cell's cytoskeleton to reorganize. Actin builds up around the pathogen as a result, and GAS is then trafficked inside the cell [36]. GAS can live intracellularly in the phagolysosome or a secure caveosomal compartment [37].

2.2 The Streptococcal Cysteine Protease (SpeB)

Many host and bacterial proteins, such as complement factors, autophagy components, chemokines, the cathelicidin-derived antimicrobial peptide LL-37, host extracellular matrix proteins, and intercellular barrier proteins at epithelial junctions, are cleaved by SpeB due to its broad substrate specificity [38–43]. By directly cleaving and activating the precursors of IL-1β and epithelial IL-36γ, two strong pro-inflammatory cytokines essential for host defense responses to infection and injury, SpeB also exhibits pro-inflammatory qualities [44, 45]. Another recently identified pro-inflammatory mechanism is the cleavage and activation of pore-forming GSDMA in skin epithelial cells, which results in pyroptosis, a lytic form of inflammatory cell death. Highly selective caspase-independent cleavage of GSDMA by SpeB necessitates SpeB entry into the cytoplasm of infected cells. Interestingly, SpeB-negative variants often result from immune selection during severe invasive infections in M1T1 GAS and, to a lesser extent, in non-M1 GAS, even though SpeB is necessary during the early phases of the infection process [46–49]. When the covR/S regulatory system mutates, SpeB expression is lost. This leads to a buildup of surface-bound plasmin activity, which in turn causes the systemic spread of GAS in vivo [50].

2.3 Streptococcus C5a Peptidase (SCPA)

The primary function of the serine proteinase SCPA is to cleave the proteins C3a and C5a, which in turn disables the complement pathway [51]. This significantly hinders neutrophil infiltration and activation, a crucial innate immune defense mechanism. In the meanwhile, tonsillitis and pharyngitis can be brought on by SCPA, a surface-binding protein of GAS [52]. Numerous anti-SCPA antibodies were generated in serum during the later stages of infection in children with acute pharyngitis, suggesting that SCPA is a highly immunogenic substance [53]. Furthermore, SCPA and GAC can merge, which can significantly activate T cells.

2.4 Streptolysins and NAD Glycohydrolase

Two strong cytolytic toxins called streptolysin S (SLS) and streptolysin O (SLO), which induce hole development in eukaryotic cell membranes, are secreted by nearly all clinical isolates of GAS. Both cytolysins are lethal to a variety of host cells, such as immunological and epithelial cells. SLS and SLO have been linked to several processes, including pro-inflammatory responses, soft-tissue injury, tissue invasion, and innate immune evasion [54, 55]. Another target of SLS is the peripheral neurological system, where it stimulates sensory neurons to cause pain and inhibits the recruitment of immune cells, hence enhancing the survival of bacteria during infection [56]. In GAS, the co-expressed toxin NAD glycohydrolase (NADase; also called SPN or NGA), which depletes host cells of their cellular energy stores, and the action of the cholesterol-dependent cytolysin SLO are functionally interdependent [57, 58]. Following secretion, SLO and NADase physically interact and co-stabilize [59]. In contrast, SLO's pore development is encouraged by NADase-dependent membrane binding, which in turn makes it easier for NADase to translocate into host cells [60, 61]. By causing Golgi fragmentation to compromise host defenses in macrophages and epithelial cells, SLO and its co-toxin NADase together enhance GAS intracellular survival and cytotoxicity, and aid in in vivo pathogenesis [62, 63]. Increased expression of the SLO and NADase toxins is the outcome of a high-activity promoter recombination event at the NADase–SLO locus, which has been linked to streptococcal strain emergence and epidemicity [64]. Although the molecular underpinnings of this association are yet unknown, the frequent observation of recombination-related genome

remodeling in acapsular isolates suggests that capsule manufacturing may not be necessary in bacteria that express large levels of toxins [65].

2.5 S. Pyogenes Cell-Envelope Proteinase (SpyCEP)

The activity of SpyCEP, a conserved and surface-exposed GAS serine protease, is correlated with the severity of invasive human illnesses [66]. SpyCEP is not required, but it helps GAS survive in the nasopharynx in the upper respiratory system [67]. On the other hand, SpyCEP is necessary for the transfer of GAS from the nasopharynx to the lungs. All CXC chemokines with glutamic acid leucine arginine (ELR) motifs, including CXCL1, CXCL2, CXCL6, and so on, can be cleaved and rendered inactive by SpyCEP. More significantly, SpyCEP cleaves IL-8 (CXCL8), giving GAS a way to avoid being killed by neutrophils [68]. Moreover, SpyCEP cleaves antimicrobial peptide LL-37 with specificity, promoting the persistence of GAS infections [69]. In addition to its enzymatic function, SpyCEP can selectively induce GAS uptake into endothelial cells. Consequently, SpyCEP has a variety of roles in the pathogenesis of GAS infection.

3 Prevention Measures

Particularly in low-resource environments, strategies for treating or preventing GAS infections should be workable, inexpensive, and accessible [70]. Public, environmental health and clinical perspectives have all been used to address the prevention of GAS infections; however, the majority of intervention programs available place a greater emphasis on clinical intervention, and there is a dearth of information regarding potential community-based infection prevention strategies [71]. The current public health approaches concentrate on reducing the spread of GAS infections and safeguarding those who are most susceptible to them in all locations where the risk of infection is elevated. Primary preventive measures are particularly essential because they avert the development of permanent health issues that could result from GAS infection complications [72]. Enhanced monitoring systems and epidemiological studies, better housing, effective hand hygiene-which involves frequent, adequate hand washing with soap and water or the use of alcohol hand rub [73–76]-and avoiding crowding are some of these strategies. Additionally important to preventing transmission is improved personal cleanliness, particularly for boys who are typically more susceptible than girls [77]. To minimize the transmission of GAS infections, sharing of personal things, like towels and blankets, should be discouraged or limited. It's also advisable to refrain from sharing things like drinking glasses, utensils, water bottles, and other items that could be tainted with saliva [78].

All regions deemed hazardous transmission zones should maintain environmental sanitation, which includes routinely cleaning and sanitizing common spaces and surfaces [79]. According to reports, GAS illnesses can be affected by dry heat of 170 °C for at least one hour and moist heat of 121 °C for at least fifteen minutes. Furthermore, 1% sodium hypochlorite, 4% formaldehyde, 2% glutaraldehyde, 70% ethanol, 70% propanol, 2% peracetic acid, 3-6% hydrogen peroxide, and 16% iodine can all affect the bacteria [80]. It is advisable to promote the regular cleaning and disinfection of shared equipment, particularly in hospitals [81]. Additionally, this review emphasizes the importance of decontamination and complete cleaning of curtains and public restrooms, such as bathrooms and toilets, as preventative measures against GAS infections [82]. Hospital settings and other high-risk regions should routinely

replace their curtains. In high-risk locations, this should be done once a month; in low-risk areas, it should be done twice a year. In addition, hospitals ought to think about switching from washable curtains to plastic screens or disposable curtains [83].

In hospitals and other healthcare settings, appropriate infection control practices have also been found to be essential for preventing GAS infections. This includes handling wounds aseptically, using personal protective equipment appropriately, and properly disposing of medical waste [84]. To avoid the spread of GAS, patients or residents in hospitals or care facilities who are infected with the disease should also be isolated [85]. To prevent GAS transmission among giving birth to women and newborns, it has also been determined that antisepsis measures during delivery and neonatal cord care are crucial [86]. To effectively control GAS infections, medical professionals must also follow the recommendations for diagnosis and treatment [87].

4 Conclusion

S. pyogenes is an extremely potent pathogen that can result in substantial morbidity and mortality. An essential part of the disease process is the wide range of virulence factors they create to colonize an area and subdue the host's defenses. Globally, GAS infections and their aftermath pose a substantial threat to public health. However, indigenous groups, low socioeconomic areas in developed countries, and underdeveloped countries are where GAS infections are most common. The goal of public health policy should be to stop the spread of GAS. The main ways that this happens are by respiratory droplets and direct contact with GAS-caused skin lesions or contaminated objects or equipment. To fully understand the impact of foodborne transmission and other environmental sources, more research is required. Encouraging nationwide reporting of GAS diseases would support research and public health efforts aimed at lessening the effects of these illnesses. More equity in resource distribution is another important issue for governments to address if they want to improve living conditions and lower the prevalence of infectious diseases like GAS infections. Furthermore, as early detection and treatment can shorten the window of time during which GAS can spread and avert complications from the disease, steps should be taken to guarantee that everyone has access to high-quality healthcare.

References

[1] Wrighton, S., Ahnlide, V. K., André, O., Bahnan, W., & Nordenfelt, P. (2023). Group A streptococci induce stronger M protein-fibronectin interaction when specific human antibodies are bound. *Frontiers in microbiology*, *14*, 1069789.

[2] Barnett, T. C., Liebl, D., Seymour, L. M., Gillen, C. M., Lim, J. Y., LaRock, C. N., ... & Walker, M. J. (2013). The globally disseminated M1T1 clone of group A Streptococcus evades autophagy for intracellular replication. *Cell host & microbe*, *14*(6), 675-682.

[3] Guy, R., Henderson, K. L., Coelho, J., Hughes, H., Mason, E. L., Gerver, S. M., ... & Lamagni, T. (2023). Increase in invasive group A streptococcal infection notifications, England, 2022. *Eurosurveillance*, *28*(1), 2200942.

[4] Courtney, H. S., Hasty, D. L., & Dale, J. B. (2002). Molecular mechanisms of adhesion, colonization, and invasion of group A streptococci. *Annals of medicine*, *34*(2), 77-87.

[5] Kreikemeyer, B., Klenk, M., & Podbielski, A. (2004). The intracellular status of Streptococcus pyogenes: role of extracellular matrix-binding proteins and their regulation. *International journal of medical microbiology*, *294*(2-3), 177-188.

[6] Courtney, H. S., Ofek, I., Simpson, W. A., Hasty, D. L., & Beachey, E. H. (1986). Binding of Streptococcus pyogenes to soluble and insoluble fibronectin. *Infection and immunity*, *53*(3), 454-459.

[7] Okada, N., Liszewski, M. K., Atkinson, J. P., & Caparon, M. (1995). Membrane cofactor protein (CD46) is a keratinocyte receptor for the M protein of the group A streptococcus. *Proceedings of the National Academy of Sciences*, *92*(7), 2489-2493.

[8] Frick, I. M., Schmidtchen, A., & Sjöbring, U. (2003). Interactions between M proteins of Streptococcus pyogenes and glycosaminoglycans promote bacterial adhesion to host cells. *European journal of biochemistry*, *270*(10), 2303-2311.

[9] Rohde, M., & Cleary, P. P. (2022). Adhesion and invasion of Streptococcus pyogenes into host cells and clinical relevance of intracellular streptococci. *Streptococcus pyogenes: Basic Biology to Clinical Manifestations [Internet]. 2nd edition*.

[10] Kreikemeyer, B., Nakata, M., Oehmcke, S., Gschwendtner, C., Normann, J., & Podbielski, A. (2005). Streptococcus pyogenes collagen type I-binding Cpa surface protein: expression profile, binding characteristics, biological functions, and potential clinical impact. *Journal of Biological Chemistry*, *280*(39), 33228-33239.

[11] Valentin-Weigand, P., Grulich-Henn, J., Chhatwal, G. S., Müller-Berghaus, G., Blobel, H., & Preissner, K. T. (1988). Mediation of adherence of streptococci to human endothelial cells by complement S protein (vitronectin). *Infection and immunity*, *56*(11), 2851-2855.

[12] Boël, G., Jin, H., & Pancholi, V. (2005). Inhibition of cell surface export of group A streptococcal anchorless surface dehydrogenase affects bacterial adherence and antiphagocytic properties. *Infection and immunity*, *73*(10), 6237-6248.

[13] Courtney, H. S., Hasty, D. L., & Dale, J. B. (2002). Molecular mechanisms of adhesion, colonization, and invasion of group A streptococci. *Annals of medicine*, *34*(2), 77-87.

[14] LaPenta, D., Rubens, C., Chi, E., & Cleary, P. P. (1994). Group A streptococci efficiently invade human respiratory epithelial cells. *Proceedings of the national academy of sciences*, *91*(25), 12115-12119.

[15] Rohde, M., & Cleary, P. P. (2022). Adhesion and invasion of Streptococcus pyogenes into host cells and clinical relevance of intracellular streptococci. *Streptococcus pyogenes: Basic Biology to Clinical Manifestations [Internet]. 2nd edition*.

[16] Dombek, P. E., Cue, D., Sedgewick, J., Lam, H., Ruschkowski, S., Finlay, B. B., & Cleary, P. P. (1999). High-frequency intracellular invasion of epithelial cells by serotype M1 group A streptococci: M1 protein-mediated invasion and cytoskeletal rearrangements. *Molecular microbiology*, *31*(3), 859-870.

[17] Blöchl, C., Holzner, C., Luciano, M., Bauer, R., Horejs-Hoeck, J., Eckhard, U., ... & Huber, C. G. (2021). Proteolytic Profiling of Streptococcal Pyrogenic Exotoxin B (SpeB) by Complementary HPLC-MS Approaches. *International Journal of Molecular Sciences*, *23*(1), 412.

[18] Terao, Y., Mori, Y., Yamaguchi, M., Shimizu, Y., Ooe, K., Hamada, S., & Kawabata, S. (2008). Group A streptococcal cysteine protease degrades C3 (C3b) and contributes to evasion of innate immunity. *Journal of biological chemistry*, *283*(10), 6253-6260.

[19] Kapur, V., Majesky, M. W., Li, L. L., Black, R. A., & Musser, J. M. (1993). Cleavage of interleukin 1 beta (IL-1 beta) precursor to produce active IL-1 beta by a conserved extracellular cysteine protease from Streptococcus pyogenes. *Proceedings of the National Academy of Sciences*, *90*(16), 7676-7680.

[20] Deng, W., Bai, Y., Deng, F., Pan, Y., Mei, S., Zheng, Z., ... & Liu, X. (2022). Streptococcal pyrogenic exotoxin B cleaves GSDMA and triggers pyroptosis. *Nature*, *602*(7897), 496-502.

[21] Jain, M., Teçza, M., Kagawa, T. F., & Cooney, J. C. (2022). Exosite binding modulates the specificity of the immunomodulatory enzyme ScpA, a C5a inactivating bacterial protease. *Computational and Structural Biotechnology Journal*, *20*, 4860-4869.

[22] Park, H. S., & Cleary, P. P. (2005). Active and passive intranasal immunizations with streptococcal surface protein C5a peptidase prevent infection of murine nasal mucosa-associated lymphoid tissue, a functional homologue of human tonsils. *Infection and immunity*, *73*(12), 7878-7886.

[23] Walker, M. J., Barnett, T. C., McArthur, J. D., Cole, J. N., Gillen, C. M., Henningham, A., ... & Nizet, V. (2014). Disease manifestations and pathogenic mechanisms of group A Streptococcus. *Clinical microbiology reviews*, *27*(2), 264-301.

[24] Brouwer, S., Rivera-Hernandez, T., Curren, B. F., Harbison-Price, N., De Oliveira, D. M., Jespersen, M. G., ... & Walker, M. J. (2023). Pathogenesis, epidemiology and control of Group A Streptococcus infection. *Nature Reviews Microbiology*, *21*(7), 431-447.

[25] Nozawa, T., Iibushi, J., Toh, H., Minowa-Nozawa, A., Murase, K., Aikawa, C., & Nakagawa, I. (2021). Intracellular Group A streptococcus induces golgi fragmentation to impair host defenses through streptolysin O and NAD-glycohydrolase. *MBio*, *12*(1), 10-1128.

[26] Bryant, A. E., Bayer, C. R., Chen, R. Y., Guth, P. H., Wallace, R. J., & Stevens, D. L. (2005). Vascular dysfunction and ischemic destruction of tissue in Streptococcus pyogenes infection: the role of streptolysin O–induced platelet/neutrophil complexes. *The Journal of infectious diseases*, *192*(6), 1014-1022.

[27] Turner, C. E., Kurupati, P., Jones, M. D., Edwards, R. J., & Sriskandan, S. (2009). Emerging role of the interleukin-8 cleaving enzyme SpyCEP in clinical Streptococcus pyogenes infection. *The Journal of infectious diseases*, *200*(4), 555-563.

[28] Kurupati, P., Turner, C. E., Tziona, I., Lawrenson, R. A., Alam, F. M., Nohadani, M., ... & Sriskandan, S. (2010). Chemokine-cleaving Streptococcus pyogenes protease SpyCEP is necessary and sufficient for bacterial dissemination within soft tissues and the respiratory tract. *Molecular microbiology*, *76*(6), 1387-1397.

[29] McKenna, S., Malito, E., Rouse, S. L., Abate, F., Bensi, G., Chiarot, E., ... & Matthews, S. (2020). Structure, dynamics and immunogenicity of a catalytically inactive CXC chemokine-degrading protease SpyCEP from Streptococcus pyogenes. *Computational and Structural Biotechnology Journal*, *18*, 650-660.

[30] Biswas, D., Ambalavanan, P., Ravins, M., Anand, A., Sharma, A., Lim, K. X. Z., ... & Hanski, E. (2021). LL-37-mediated activation of host receptors is critical for defense against group A streptococcal infection. *Cell Reports*, *34*(9).

[31] Chhatwal, G. S. (Ed.). (2013). *Host-pathogen interactions in streptococcal diseases*. Berlin: Springer.

[32] Turner, C. E., Bedford, L., Brown, N. M., Judge, K., Török, M. E., Parkhill, J., & Peacock, S. J. (2017). Community outbreaks of group A Streptococcus revealed by genome sequencing. *Scientific reports*, *7*(1), 8554.

[33] Kumar, R., Sharma, Y. P., Thakur, J. S., Patro, B. K., Bhatia, A., Singh, I. P., ... & Ganguly, N. K. (2014). Streptococcal pharyngitis, rheumatic fever and rheumatic heart disease: eight-year prospective surveillance in Rupnagar district of Punjab, India. *Natl Med J India*, *27*(2).

[34] Thielemans, E., Oliver, J., McMinn, A., Baker, C., Britton, P. N., Clark, J., ... & Steer, A. C. (2020). Clinical description and outcomes of Australian children with invasive group A streptococcal disease. *The Pediatric infectious disease journal*, *39*(5), 379-384.

[35] Tartof, S. Y., Reis, J. N., Andrade, A. N., Ramos, R. T., Reis, M. G., & Riley, L. W. (2010). Factors associated with Group A Streptococcus emm type diversification in a large urban setting in Brazil: a cross-sectional study. *BMC infectious diseases*, *10*, 1-8.

[36] Cummins, A., Millership, S., Lamagni, T., & Foster, K. (2012). Control measures for invasive group A streptococci (iGAS) outbreaks in care homes. *Journal of Infection*, *64*(2), 156-161.

[37] Francis, J. R., Gargan, C., Remenyi, B., Ralph, A. P., Draper, A., Holt, D., ... & Hardie, K. (2019). A cluster of acute rheumatic fever cases among Aboriginal Australians in a remote community with high baseline incidence. *Australian and New Zealand journal of public health*, *43*(3), 288-293.

[38] Sumitomo, T., Nakata, M., Higashino, M., Terao, Y., & Kawabata, S. (2013). Group A streptococcal cysteine protease cleaves epithelial junctions and contributes to bacterial translocation. *Journal of Biological Chemistry*, *288*(19), 13317-13324.

[39] Schmidtchen, A., Frick, I. M., Andersson, E., Tapper, H., & Björck, L. (2002). Proteinases of common pathogenic bacteria degrade and inactivate the antibacterial peptide LL-37. *Molecular microbiology*, *46*(1), 157-168.

[40] Terao, Y., Mori, Y., Yamaguchi, M., Shimizu, Y., Ooe, K., Hamada, S., & Kawabata, S. (2008). Group A streptococcal cysteine protease degrades C3 (C3b) and contributes to evasion of innate immunity. *Journal of Biological Chemistry*, *283*(10), 6253-6260.

[41] Schmidtchen, A., Frick, I. M., Andersson, E., Tapper, H., & Björck, L. (2002). Proteinases of common pathogenic bacteria degrade and inactivate the antibacterial peptide LL-37. *Molecular microbiology*, *46*(1), 157-168.

[42] Barnett, T. C., Liebl, D., Seymour, L. M., Gillen, C. M., Lim, J. Y., LaRock, C. N., ... & Walker, M. J. (2013). The globally disseminated M1T1 clone of group A Streptococcus evades autophagy for intracellular replication. *Cell host & microbe*, *14*(6), 675-682.

[43] Egesten, A., Olin, A. I., Linge, H. M., Yadav, M., Mörgelin, M., Karlsson, A., & Collin, M. (2009). SpeB of Streptococcus pyogenes differentially modulates antibacterial and receptor activating properties of human chemokines. *PLoS One*, *4*(3), e4769.

[44] Kapur, V., Majesky, M. W., Li, L. L., Black, R. A., & Musser, J. M. (1993). Cleavage of interleukin 1 beta (IL-1 beta) precursor to produce active IL-1 beta by a conserved extracellular cysteine protease from Streptococcus pyogenes. *Proceedings of the National Academy of Sciences*, *90*(16), 7676-7680.

[45] Macleod, T., Ainscough, J. S., Hesse, C., Konzok, S., Braun, A., Buhl, A. L., ... & Stacey, M. (2020). The proinflammatory cytokine IL-36γ is a global discriminator of harmless microbes and invasive pathogens within epithelial tissues. *Cell Reports*, *33*(11).

[46] Kansal, R. G., McGeer, A., Low, D. E., Norrby-Teglund, A., & Kotb, M. (2000). Inverse relation between disease severity and expression of the streptococcal cysteine protease, SpeB, among clonal M1T1 isolates recovered from invasive group A streptococcal infection cases. *Infection and immunity*, *68*(11), 6362-6369.

[47] Sumby, P., Whitney, A. R., Graviss, E. A., DeLeo, F. R., & Musser, J. M. (2006). Genome-wide analysis of group A streptococci reveals a mutation that modulates global phenotype and disease specificity. *PLoS pathogens*, *2*(1), e5.

[48] Walker, M. J., Hollands, A., Sanderson-Smith, M. L., Cole, J. N., Kirk, J. K., Henningham, A., ... & Nizet, V. (2007). DNase Sda1 provides selection pressure for a switch to invasive group A streptococcal infection. *Nature medicine*, *13*(8), 981-985.

[49] Maamary, P. G., Sanderson-Smith, M. L., Aziz, R. K., Hollands, A., Cole, J. N., McKay, F. C., ... & Walker, M. J. (2010). Parameters governing invasive disease propensity of non-M1 serotype group A streptococci. *Journal of innate immunity*, *2*(6), 596-606.

[50] Cole, J. N., McArthur, J. D., McKay, F. C., Sanderson-Smith, M. L., Cork, A. J., Ranson, M., ... & Walker, M. J. (2006). Trigger for group A streptococcal M1T1 invasive disease. *The FASEB journal*, *20*(10), 1745-1747.

[51] Lee, C. F., Cowling, B. J., & Lau, E. H. (2017). Epidemiology of reemerging scarlet fever, Hong Kong, 2005–2015. *Emerging infectious diseases*, *23*(10), 1707.

[52] Adebanjo, T., Mosites, E., Van Beneden, C. A., Onukwube, J., Blum, M., Harper, M., ... & Gounder, P. (2018). Risk factors for group A Streptococcus colonization during an outbreak among people experiencing homelessness in Anchorage, Alaska, 2017. *Clinical Infectious Diseases*, *67*(11), 1784-1787.

[53] Sarangi, J., & Rowsell, R. (1995). A nursing home outbreak of group A streptococcal infection: case control study of environmental contamination. *The Journal of hospital infection*, *30*(2), 162-164.

[54] Uchiyama, S., Döhrmann, S., Timmer, A. M., Dixit, N., Ghochani, M., Bhandari, T., ... & Nizet, V. (2015). Streptolysin O rapidly impairs neutrophil oxidative burst and antibacterial responses to group A Streptococcus. *Frontiers in immunology*, *6*, 581.

[55] Goldmann, O., Sastalla, I., Wos-Oxley, M., Rohde, M., & Medina, E. (2009). Streptococcus pyogenes induces oncosis in macrophages through the activation of an inflammatory programmed cell death pathway. *Cellular microbiology*, *11*(1), 138-155.

[56] Pinho-Ribeiro, F. A., Baddal, B., Haarsma, R., O'Seaghdha, M., Yang, N. J., Blake, K. J., ... & Chiu, I. M. (2018). Blocking neuronal signaling to immune cells treats streptococcal invasive infection. *Cell*, *173*(5), 1083-1097.

[57] Kimoto, H., Fujii, Y., Yokota, Y., & Taketo, A. (2005). Molecular characterization of NADase-streptolysin O operon of hemolytic streptococci. *Biochimica et Biophysica Acta (BBA)-Gene Structure and Expression*, *1681*(2-3), 134-149.

[58] Michos, A., Gryllos, I., Håkansson, A., Srivastava, A., Kokkotou, E., & Wessels, M. R. (2006). Enhancement of streptolysin O activity and intrinsic cytotoxic effects of the group A streptococcal toxin, NAD-glycohydrolase. *Journal of Biological Chemistry*, *281*(12), 8216-8223.

[59] Velarde, J. J., O'Seaghdha, M., Baddal, B., Bastiat-Sempe, B., & Wessels, M. R. (2017). Binding of NAD+-glycohydrolase to streptolysin O stabilizes both toxins and promotes virulence of group A Streptococcus. *MBio*, *8*(5), 10-1128.

[60] Velarde, J. J., Piai, A., Lichtenstein, I. J., Lynskey, N. N., Chou, J. J., & Wessels, M. R. (2022). Structure of the Streptococcus pyogenes NAD+ glycohydrolase translocation domain and its essential role in toxin binding to oropharyngeal keratinocytes. *Journal of Bacteriology*, *204*(1), e00366-21.

[61] Magassa, N. G., Chandrasekaran, S., & Caparon, M. G. (2010). Streptococcus pyogenes cytolysin-mediated translocation does not require pore formation by streptolysin O. *EMBO reports*, *11*(5), 400-405.

[62] Nozawa, T., Iibushi, J., Toh, H., Minowa-Nozawa, A., Murase, K., Aikawa, C., & Nakagawa, I. (2021). Intracellular group A Streptococcus induces Golgi fragmentation to impair host defenses through streptolysin O and NAD-glycohydrolase. *MBio*, *12*(1), 10-1128.

[63] Zhu, L., Olsen, R. J., Lee, J. D., Porter, A. R., DeLeo, F. R., & Musser, J. M. (2017). Contribution of secreted NADase and streptolysin O to the pathogenesis of epidemic serotype M1 Streptococcus pyogenes infections. *The American journal of pathology*, *187*(3), 605-613.

[64] Nasser, W., Beres, S. B., Olsen, R. J., Dean, M. A., Rice, K. A., Long, S. W., ... & Musser, J. M. (2014). Evolutionary pathway to increased virulence and epidemic group A Streptococcus disease derived from 3,615 genome sequences. *Proceedings of the National Academy of Sciences*, *111*(17), E1768-E1776.

[65] Zhu, L., Olsen, R. J., Nasser, W., Beres, S. B., Vuopio, J., Kristinsson, K. G., ... & Musser, J. M. (2015). A molecular trigger for intercontinental epidemics of group A Streptococcus. *The Journal of clinical investigation*, *125*(9), 3545-3559.

[66] Gordon, G., Dale, B. A. S., & Lochhead, D. (1994). An outbreak of group A haemolytic streptococcal puerperal sepsis spread by the communal use of bidets. *BJOG: An International Journal of Obstetrics & Gynaecology*, *101*(5), 447-448.

[67] Mahida, N., Beal, A., Trigg, D., Vaughan, N., & Boswell, T. (2014). Outbreak of invasive group A streptococcus infection: contaminated patient curtains and cross-infection on an ear, nose and throat ward. *Journal of Hospital Infection*, *87*(3), 141-144.

[68] Waddington, C. S., Snelling, T. L., & Carapetis, J. R. (2014). Management of invasive group A streptococcal infections. *Journal of Infection*, *69*, S63-S69.

[69] Inkster, T., Wright, P., Kane, H., Paterson, E., Dodd, S., & Slorach, J. (2012). Successive outbreaks of Group A streptococcus (GAS) in care of the elderly settings; lessons learned. *Journal of Infection Prevention*, *13*(2), 38-43.

[70] Seale, A. C., Davies, M. R., Anampiu, K., Morpeth, S. C., Nyongesa, S., Mwarumba, S., ... & Berkley, J. A. (2016). Invasive group A Streptococcus infection among children, rural Kenya. *Emerging infectious diseases*, *22*(2), 224.

[71] Di Muzio, I., d'Angelo, D. M., Di Battista, C., Lapergola, G., Zenobi, I., Marzetti, V., ... & Altobelli, E. (2020). Pediatrician's approach to diagnosis and management of group A streptococcal pharyngitis. *European Journal of Clinical Microbiology & Infectious Diseases*, *39*, 1103-1107.

[72] Abd El-Ghany, S. M., Abdelmaksoud, A. A., Saber, S. M., & Abd El Hamid, D. H. (2015). Group A beta-hemolytic streptococcal pharyngitis and carriage rate among Egyptian children: a case-control study. *Annals of Saudi medicine*, *35*(5), 377-382.

[73] Banigo, A., Moinie, A., Bleach, N., Chand, M., Chalker, V., & Lamagni, T. (2018). Have reducing tonsillectomy rates in England led to increasing incidence of invasive Group A Streptococcus infections in children?. *Clinical Otolaryngology*, *43*(3), 912-919.

[74] Watts, V., Balasegaram, S., Brown, C. S., Mathew, S., Mearkle, R., Ready, D., ... & Lamagni, T. (2019). Increased risk for invasive group A streptococcus disease for household contacts of scarlet fever cases, England, 2011–2016. *Emerging Infectious Diseases*, *25*(3), 529.

[75] Mahida, N., Prescott, K., Yates, C., Spencer, F., Weston, V., & Boswell, T. (2018). Outbreak of invasive group A streptococcus: investigations using agar settle plates detect perineal shedding from a healthcare worker. *Journal of Hospital Infection*, *100*(4), e209-e215.

[76] Oliver, J., Thielemans, E., McMinn, A., Baker, C., Britton, P. N., Clark, J. E., ... & Crawford, N. W. (2019). Invasive group A Streptococcus disease in Australian children: 2016 to 2018–a descriptive cohort study. *BMC public health*, *19*, 1-10.

[77] Nanduri, S. A., Metcalf, B. J., Arwady, M. A., Edens, C., Lavin, M. A., Morgan, J., ... & Beall, B. (2019). Prolonged and large outbreak of invasive group A Streptococcus disease within a nursing home: repeated intrafacility transmission of a single strain. *Clinical Microbiology and Infection*, *25*(2), 248-e1.

[78] Allen, L. B., Allen, M., Lesa, R. F. A., Richardson, G. E., & Eggett, D. L. (2011). Rheumatic fever in Samoa: Education as prevention. *Pacific Health Dialog*, *17*(1), 107-18.

[79] Centers for Disease Control and Prevention Respiratory Hygiene/Cough Etiquette in Healthcare Settings. [(accessed on 10 February 2020)]; Available online: https://www.cdc.gov/flu/professionals/infectioncontrol/resphygiene.htm

[80] Hammond-Collins, K., Strauss, B., Barnes, K., Demczuk, W., Domingo, M. C., Lamontagne, M. C., ... & Tepper, M. (2019). Group A streptococcus outbreak in a Canadian Armed Forces training facility. *Military medicine*, *184*(3-4), e197-e204.

[81] May, P. J., Bowen, A. C., & Carapetis, J. R. (2016). The inequitable burden of group A streptococcal diseases in Indigenous Australians. *Medical Journal of Australia*, *205*(5), 201-203.

[82] Dooling, K. L., Crist, M. B., Nguyen, D. B., Bass, J., Lorentzson, L., Toews, K. A., ... & Van Beneden, C. (2013). Investigation of a prolonged group A streptococcal outbreak among residents of a skilled nursing facility, Georgia, 2009–2012. *Clinical infectious diseases*, *57*(11), 1562-1567.

[83] Krishna, V., Sankaranarayan, S., Sivaraman, R. P., & Prabaharan, K. (2014). Streptococcal toxic shock syndrome. *The Indian Journal of Pediatrics*, *81*, 946-948.

[84] Vincent, M. T., Celestin, N., & Hussain, A. N. (2004). Pharyngitis. *American family physician*, *69*(6), 1465-1470.

[85] Cunningham, M. W. (2000). Pathogenesis of group A streptococcal infections. *Clinical microbiology reviews*, *13*(3), 470-511.

[86] Kwiatkowska, R. M., Manley, P., Sims, B., Lamagni, T., Ready, D., Coelho, J., ... & Outbreak Control Team. (2018). Outbreak of group A Streptococcus emm94. 0 affecting people who inject drugs in southwest England, April 2017. *American Journal of Infection Control*, *46*(2), 238-240.

[87] Chochua, S., Metcalf, B. J., Li, Z., Rivers, J., Mathis, S., Jackson, D., ... & Beall, B. (2017). Population and whole genome sequence based characterization of invasive group A streptococci recovered in the United States during 2015. *MBio*, *8*(5), 10-1128.

المكورات العنقودية المقيحة: عوامل الضراوة وتدابير الوقاية

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المستخلص. تُعرف المكورات العنقودية المقيحة (GAS) باسم ستربتوكوكوس بايوجينس، وهي مسببات مرضية بكتيرية هامة خاصة بالبشر، يمكن أن تسبب مجموعة واسعة من الأعراض، من عدوى موضعية بسيطة إلى عدوى شديدة وقد تكون مميتة. عادةً ما تنتشر البكتيريا المسببة لعدوى GAS عبر الرذاذ التنفسي، أو من خلال لمس قروح جلدية ملوثة، أو من خلال ملامسة أشياء أو مواد ملوثة. كما أن الانتقال عبر الغذاء هو احتمال آخر، لكن يحتاج الأمر إلى مزيد من التحقيق لتحديد مدى أهمية هذه الطرق في العدوى. تم اكتشاف أن أمراض GAS شائعة جداً في المجموعات المغلقة، والمناطق ذات الدخل المنخفض في الدول المتقدمة، والدول النامية. العديد من الإفرازات الخارجية التي تنتجها أو تُطلقها سلالات S. pyogenes تُعتبر عوامل ضراوة لأنها تساعد في تعزيز المرض و/أو بقاء الممرض في العائل. تشمل عوامل الضراوة التي تُطلق أو تُفرز من سطح البكتيريا: بروتياز السيستين ستربتوكوكالي (SpeB)، وبروتياز C5a من ستربتوكوكوس(ScpA)، وستربتوليزين O (SLO)، وبروتياز غلاف خلايا(SpyCEP) S. pyogenes، والتي تمت مراجعتها في هذه المقالة. يُعتبر SpeB البروتياز السيستيني الرئيسي المفرز من GAS، حيث يقوم بتقطيع أو تكسير بروتينات مصل العائل، بما في ذلك الفراغات الخلوية الخارجية، والأجسام المضادة، ونظام المتمم، وحتى بروتينات سطح GAS والمفرزة. يُعتبر إنزيم ScpA، وهو بروتياز محدد جداً، يقوم بتقطيع الكيميائي C5a المشتق من المتمم. يتم تشفير جين بروتياز C5a (scpA) نحو الطرف ٣' من مجموعة mga، وهو محفوظ جداً بين أنماط GAS الجينية. يرتبط ستربتوليزين-O بالكوليسترول في أغشية الخلايا، مما يتسبب في انحلال العدلات المتعددة الأشكال (PMNs) والليزوزومات الخاصة بها بسرعة، مما يُطلق محتوياتها السامة التي قد تؤثر سلبًا على الخلايا المجاورة SpyCEP هو بروتياز سيرين مكشوف على السطح يُعطل الكيميائيات. أُرجع انتشار عدوى GAS إلى الازدحام وزيادة مستوى التفاعل الاجتماعي في هذه البيئات. يجب أن تكون تحسين ظروف المعيشة والنظافة الشخصية من الأهداف الرئيسية لاستراتيجيات الوقاية والسيطرة. في البيئات عالية المخاطر، يجب إعطاء الأولوية للالتزام بتدابير الوقاية والسيطرة على العدوى.

الكلمات المفتاحية: GAS، ستربتوكوكوس بايوجينس، عوامل الضراوة، المكورات العقدية المقيحة.