

## ***Streptococcus pyogenes* evades adaptive immunity through specific IgG glycan hydrolysis**

*Streptococcus pyogenes* (GAS) is a pathogen causing a variety of diseases in humans, with severities varying from mild to life-threatening. The defence is primarily mediated by IgG antibodies directed toward GAS antigens, although the pathogen is able to resist this adaptive response by producing an endoglycosidase, called EndoS, which diminishes IgG function. The specific action of EndoS has only ever been documented in vitro, but this article aims to demonstrate the function of EndoS in natural GAS infections in vivo, using targeted mass spectrometry. Studying the effects of EndoS in evading the immune response could be important in the development of a future vaccine or in the treatment of severe GAS infections.

EndoS is expressed during acute infection and cleaves the Fc N-glycan on IgG antibodies with high specificity, disabling their effector functions, such as activation of the complement system. GAS strains without expression of EndoS demonstrated decreased resistance to phagocytosis and indicated a decreased virulence in mouse models. Furthermore, the effect of EndoS is primarily localized to the site of infection, but in more severe cases, a systemic effect on the IgG pool is detectable. The amount of secreted EndoS corresponded with the amount of glycan hydrolysis of IgG (IgG<sub>GH</sub>) in plasma. Interestingly, patients with more severe infections, such as septic shock, demonstrated increased amounts of IgG<sub>GH</sub>, which could be contributed to these strains' increased expression or decreased degradation of EndoS. This implies a great variability between strains, which affects severity.

One strength of the study is their use of selected reaction monitoring, which is a type of targeted mass spectrometry, to quantify the EndoS-mediated IgG glycan hydrolysis. It has an exceptional accuracy and sensitivity, which was appropriate for this study. One weakness is their small population, which was only 54 patients who were seeking for a sore throat, of which only 5 was treated with antibiotics, as well as 4 patients with GAS sepsis and necrotizing fasciitis.