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VIEWPOINT

# Malice in Chains

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Infectious diseases physicians encounter few clinical syndromes matching the toxic force of fulminant invasive group A streptococcal disease (iGAS) and many of us are haunted by at least one unforgettable case [1]. The best reassurance we can offer the public, and ourselves, is that these cases are very rare. However, contemporaneous iGAS outbreaks in the northern and southern hemispheres now lay bare the fragility of this reassurance [2, 3]. Although a clear majority of iGAS cases respond to antibiotics and aggressive supportive care, the most severe iGAS conditions are prominent causes of death and disability due to sepsis. How this common mucosal pathogen invades the bloodstream or deep tissues of (sometimes) previously healthy individuals is but one unsettling enigma. To wit—how do we explain deadly polyclonal outbreaks of a penicillin-susceptible pathogen in the year 2023? And how, despite nearly a century of directed efforts, do we still not have a vaccine?

*Streptococcus pyogenes*, the classical Lancefield group A *Streptococcus* (GAS), is a highly coevolved, human-restricted pathogen, with a remarkably diverse clinical portfolio spanning superficial, locally invasive, and disseminated acute infections, to postinfectious syndromes with chronic disease consequences. Centuries before Theodor Billroth described streptococci "arranged in pairs, sometimes in chains" in 1874, the GAS clinical spectrum was well captured by Thomas Syndenham and others under the umbrella term "scarlatina" (scarlet fever). Fatal scarlet fever epidemics [4] made GAS an early immunization target; in 1796, Erasmus Darwin (Charles' grandfather) wrote, "No one could do an act more beneficial to society, or glorious to himself, than by teaching humanity how to inoculate this fatal disease [scarlet fever]; and thus to deprive it of its malignity" [5]. Yet unrelentingly, humans still experience more than 750 million cases of GAS pharyngitis or impetigo each year, with at least 500 000 annual deaths from iGAS and rheumatic heart disease (RHD).

Although no group is exempt, iGAS is most common in the very young, very old, and (very) pregnant (puerperal sepsis). In the United States, the most severe iGAS syndromes of septic shock, necrotizing fasciitis, and streptococcal toxic shock syndrome (STSS) have case fatality rates of 29% to 45% [6]. Rapid bacterial spread and high toxicity reflect a robust array of GAS virulence determinants that impair or degrade key host defense factors such as antimicrobial peptides, complement proteins, chemokines, and immunoglobulins, frustrating efficient opsonophagocytic clearance by neutrophils and macrophages. Pore-forming streptolysin toxins and proteases cause

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host cell death and tissue damage, while its numerous superantigens can trigger polyclonal T-cell activation and cytokine storm in STSS. Epidemiologists, clinicians, and scientists can agree—GAS is a formidable pathogen.

What drives epidemic surges of iGAS? While a reliable correlate of human immune protection against GAS has not been established [7], strains with distinct versions of the immunodominant surface M protein (encoded in >200 corresponding *emm* genotypes) or a new superantigen repertoire can spread through naive populations. The current outbreak, however, is notably placed within a succession of epidemic iGAS waves from emerging dominant clones within the M1/*emm1* background. In the mid-1980s, a hypervirulent M1T1 GAS clone arose and disseminated globally producing a resurgence in iGAS infections. Molecular epidemiology revealed M1T1 had acquired a bacteriophage-encoded DNAse that allows escape from neutrophil extracellular traps, another phage harboring potent superantigen pyrogenic exotoxin A (SpeA), and recombination events increasing expression of streptolysin O and a cytotoxic $NAD^+$ glycohydrolase. Since 2015, a new sublineage ($M1_{UK}$) has emerged, bearing mutations that boost SpeA expression 10-fold further, now representing approximately 90% of invasive M1 isolates in England [8]. So far this season (19 September 2022 to 15 January 2023), there have been 1675 notifications of iGAS in England (47% M1), 21% of these cases in children younger than 15 years (58% M1). Tragically, there have been 211 iGAS deaths across all age groups in England during this period, 27 in children younger than 15 years [9].

Rising iGAS in the United Kingdom, with evidence of outbreaks in Ireland, the Netherlands, Sweden, Australia, and the United States, has fueled speculation of a potential biological linkage to the coronavirus disease 2019 (COVID-19) pandemic. A loaded terminology of "immune debt" postulates an increased risk of iGAS secondary to social distancing measures suppressing GAS infections over the prior two seasons. Alternatively, the more controversial concept of "immune exhaustion" ponders whether postacute effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection might include a window of impaired defense to new pathogen challenge. Certainly, the heavy concurrent viral burden of this season's "tripledemic"—a confluence of influenza, respiratory syncytial virus, and COVID-19—likely predisposes to bacterial superinfection, just as the 1990s saw clusters of GAS necrotizing fasciitis complicating primary varicella in its prevaccine era.

GAS was bad before the pandemic, is bad now, and will remain bad until we have a vaccine to reduce the enormous public health burden of life-threatening fast (iGAS) and slow (RHD) streptococcal diseases. GAS poses unique challenges for vaccine development, including a nonimmunogenic hyaluronic acid capsule mimicking a common human tissue component, *emm*-type diversity, and concerns that indiscriminate antigen selection could provoke autoimmunity and RHD. Recently, the World Health Organization and several private and public funders have sponsored a series of initiatives, including the Strep A Vaccine Global Consortium (SAVAC), to navigate these obstacles and address critical knowledge gaps [10]. Candidate formulations with strong protective efficacy in animal models have, or will shortly, enter human clinical trials. Optimistically, attention to the current iGAS surge may help galvanize these translational efforts and public resolve to finally deliver a GAS vaccine.

## Notes

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