The Epidemiology of Group A Streptococci: A Need to Understand the Significance of the Fertile Fields

Edward L. Kaplan
Department of Pediatrics, Amplatz Children’s Hospital, University of Minnesota Medical School, Minneapolis

(See the Major Article by Stockmann et al, on pages 479–87.)

Anyone who has lived on a farm understands the implications of fertile soil. Not only are there obvious advantages for the cultivated crops, but a favorable environment for unwanted weeds is a persistent and recurring thorn in the side of the farmer! If the field is fertile, almost any plant will colonize it and grow luxuriously.

Perhaps comparison of the epidemiology of group A streptococcal (Streptococcus pyogenes; GAS) colonization and infection in humans with that of unwanted weeds is stretching the point a little. But there are similarities. Since more than half a century ago, when the pioneering work by Rebecca Lancefield differentiated the various serologically distinct groups of beta-hemolytic streptococci [1], and a bit later, when it became obvious that GAS were important human pathogens [2], clinician-scientists, basic scientists, and public health authorities have sought to understand the epidemiology of this unique organism. There have been many enlightening attempts to understand the propensity of GAS to select “fertile fields” for infection. Yet, much remains to be learned. Where does the organism hide while waiting to “attack”? Why are humans (and perhaps only certain humans) its only recognized naturally occurring animal host? How do the answers to these questions impact not only its selection of when to attack the fertile “soil,” but also how do these variables affect strain virulence (ability to thrive in the field)? Our ultimate goal is to protect the host, and to accomplish that, we need this information.

Innovative clinicians, epidemiologists, and laboratory scientists have sought a more complete understanding. Some significant advances—too numerous to detail here—have resulted. Notable examples include the carefully conducted sentinel epidemiologic and clinical studies at the Warren Air Force Base by Rammelkamp and colleagues during the late 1940s and early 1950s [3], as well as the observations by Stollerman and others that epidemiologically linked several specific serotypes of GAS to rheumatic fever (and earned these types the moniker “rheumatogenic” [4], although they could not pinpoint the “rheumatogenic” factor[s]). In the late 1960s and 1970s, significant differences between some GAS strains that had the propensity to infect/colonize the pharynx/tonsils and other strains that caused superficial skin infections (pyoderma) were noted in careful studies from a number of laboratories around the world. Other epidemiologic investigations implied that the sequelae after GAS infections of the upper respiratory tract were different from those after GAS infections of the skin [5]. Despite these and similar studies, there continues to be a need to more thoroughly understand both the responsible streptococcal strains and the human host in these different situations.

The reemergence of serious GAS infections in the mid-1980s renewed enthusiasm to address remaining unanswered epidemiological questions. Outbreaks and clusters of both suppurative and nonsuppurative GAS sequelae became frequently reported in the 1980s and 1990s. The increased interest in refining and expanding current understanding of the incompletely defined factors contributing to the “streptococcal fertility” of the human host has had positive results. The opportunity—perhaps an obligation—to gain new knowledge about the responsible strains and their hosts, as well as their epidemiology, has been facilitated by innovative laboratory techniques in molecular biology. Analytical techniques such as characterizing GAS strains by sequencing the emm gene, first reported in 1996 [6], and later by sequencing the genome itself [7] (which were not possible at the time of the past classic studies) offered advantages and led to new approaches to understand GAS epidemiology.
We know quite a bit about basic GAS epidemiology from studies from around the world during the last half century. This is true for both populations and for individuals. One example of a complete, and therefore useful, population epidemiological study was the comprehensive report by Anthony and colleagues from prospective 2-year evaluations [8]. The data revealed both the movement of newly introduced strains into throat and cutaneous sites in a well-defined population and the resulting influence on the population as a whole [8]. Basic studies of the host immune response reflected by serial streptococcal antibody titers were helpful in understanding the streptococcal dynamics. At the present time, however, because of refined molecular laboratory techniques there is the capacity to increase the resolution and resulting data from such well-designed studies. Now, one can make the case that without using such techniques, relatively limited understanding will result.

Another essential approach in epidemiological studies is the concomitant study of the host immune protective response(s). Not only is this approach essential for understanding the epidemiology and pathogenesis of GAS infections and their sequelae, but since renewed efforts are again being made to design and produce a cost-effective and population implementable GAS vaccine, defining the normal and abnormal qualitative and quantitative host immune responses is obligatory. Illustrative of this need are the past findings by Lancefield of the persistence of arguably protective antibodies against one of the best recognized virulence factors of GAS, the M protein (“type specific antibody”), for 32 years [9], recently confirmed by a report of 46 years of persistence of antibody to M-5 GAS [10], could be very important if the M protein antibody (or any other yet to be studied antibody) is important in influencing either natural GAS infection or vaccine-induced immunity (as has been observed). In view of reports suggesting that natural infection may not be subsequently protective against heterologous M types [11] and perhaps other immunity-stimulating antigens, future epidemiological studies must be prospective, long term, and intensive. As reported from the laboratory of Martin from New Zealand and from Stevens’ laboratory from the United States [12, 13], even strains of the same M type result in production of different antibodies in some instances. While many hypotheses have been offered to explain this, essential knowledge arguably is still limited.

The report by Stockmann and colleagues in this issue of Clinical Infectious Diseases is an example of an attempt to increase available epidemiologic information [14]. The outbreak of rheumatic fever in the intermountain west region of the United States, beginning in 1985 and continuing after the turn of the century [15, 16], suggested a streptococcal epidemiological analogy to the ancient legend of the mythical Phoenix [17]: the streptococcus (probably an M/emm 18) arose with enhanced vigor! In their report, Stockmann and colleagues have attempted to follow up the rheumatic fever outbreak by describing clinical manifestations of GAS infections during the subsequent decade. The list, obtained from insurance records, describes a variety of specific infections, but, as is understandable from the methods used, it leaves the clinical, public health, and scientific communities wondering about 2 essential aspects concerning these complications: the influence of the human host immune response and the host’s status before and after infection, as well as the correlation with the responsible types/strains of GAS causing the various infections.

These examples strongly suggest that less than comprehensive GAS epidemiological studies of what is clearly a dynamic epidemiology ultimately may make only limited contributions. Yet, such studies of what renders the host a “fertile field” for either GAS infection or spread in a population are difficult to properly perform and are expensive. Obtaining frequent and regular serum samples as well as bacteriologic cultures is not easy either in convincing subject participation (especially in children who are the source of most streptococcal infections) or in gaining institutional review boards’ approval. The fact that natural GAS infections are specific only for the human does not make the task easier. Furthermore, it is unnecessary to detail current funding problems for such studies.

As we consider solutions for this problem, it is evident that unless detailed studies take into consideration both the human host and GAS, the resulting conclusions are not likely to be helpful either to physicians, to basic scientists, or to epidemiologists or public health authorities. The streptococcal “fertile field” will then remain an enigma.

Note

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