Epidemiology and Prevention of Group A Streptococcal Infections: Acute Respiratory Tract Infections, Skin Infections, and their Sequelae at the Close of the Twentieth Century

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Infections of the upper respiratory tract and skin due to group A *Streptococcus* are common, and the organism is highly transmissible. In industrialized countries and to some extent in developing countries, control efforts continue to emphasize that group A streptococcal pharyngitis should be properly diagnosed and appropriately treated. In developing countries and in indigenous populations where the burden of group A streptococcal diseases appears greatest, the epidemiology is less completely defined and may differ from that in industrialized countries. There is a need for accurately collected epidemiological data from developing countries, which may also further clarify the pathogenesis of group A streptococcal infections and their sequelae. While proper treatment of group A streptococcal pharyngitis continues to be essential in all populations, it may be appropriate in developing countries to consider additional strategies to reduce rates of pyoderma.

The spectrum of diseases caused by group A β-hemolytic *Streptococcus* is broad, ranging from simple and uncomplicated pharyngitis and pyoderma to severe invasive infections and the poststreptococcal nonsuppurative sequelae of acute rheumatic fever and acute glomerulonephritis. During the 20th century the more severe consequences of group A streptococcal infections have become relatively uncommon in industrialized countries, but the incidence of group A streptococcal pharyngitis has not decreased. The beginning of this decline in sequelae preceded the availability of antibiotics and was attributed mainly to improvements in standards of living [1, 2]. Since the 1940s, further reductions in the incidence of these infections have been thought to have been influenced (but not fully explained) by more accurate diagnosis of streptococcal infections, perhaps combined with the availability of specific antimicrobial therapy; both have been temporally related to improved access to health care [3].

By contrast, the impact of serious group A streptococcal diseases in many developing and even indigenous populations in industrialized countries is much greater. Rates of acute rheumatic fever in many developing countries are at levels similar to those seen in industrialized countries 50–100 years ago [1, 4]. High levels of exposure to group A streptococci throughout childhood as a result of influences such as overcrowded housing, limited access to medical services, and inadequate environmental hygiene and sanitation may explain a substantial proportion of the apparently increased rates of group A streptococcal diseases in developing countries.

Epidemiology in Industrialized Countries

Current understanding of the epidemiology of group A streptococcal infections comes largely from studies in industrialized countries, where pharyngitis and tonsillitis are very common in children aged 5–15 years, whereas streptococcal pyoderma is less common and mostly seen in children aged <5 years. Dingle and colleagues found that in families followed prospectively for extended periods, the average child had experienced one group A streptococcal upper respiratory tract infection by 5 years of age [5]. By 13 years of age, the average was 3 documented episodes per child; the range was from 1 to 8 distinct group A streptococcal infections during that period.

Group A streptococci are highly transmissible, and their pattern of spread in families and communities is dynamic; predominant serotypes are constantly being replaced by others [6]. An example of the frequency of group A streptococcal infections in children is shown in table 1, which documents the isolations of group A streptococci from three siblings closely followed for 4 years. Spread among the three, prolonged persistence and even the presence of non–group A organisms were documented.

Among the best examples of group A streptococcal transmissibility are the classic ''barracks'' studies from the Warren Air

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Table 1. Recovery of β-hemolytic streptococci from the upper respiratory tracts of three siblings living in the same home (March 1972–March 1976).

	Group/serotype of isolates recovered		
Culture date (mo/d/y)	Female (1970)	Male (1966)	Female (1964)
3/28/72	A (M-4)		
9/26/73			A (T-3/13)
10/31/73		A (T-3/13)	
11/1/73	A (T-3/13)		
5/15/74		A (M-5)	
5/17/74	A (T-11/27)		
6/3/74		A (M-4)	
8/19/74		A (M-4)	
11/4/74		A (T-8/25/I-19)	
11/26/74			A (T-8/25/I-19)
11/28/74		A (T-8/25/I-19)	
5/30/75		A (T-5/27/44)	
6/2/75			B
7/17/75		A (T-28)	
12/23/75		A (T-28)	
12/29/75			B
2/2/76		A (T-28)	
3/4/76		A (T-28)	
3/22/76			A (M-3)

NOTE. Table is reproduced with permission from [7].

Force Base in Wyoming. Acquisition rates were related to the distance of beds from the nearest ''colonized'' barracks mate and ranged from >60 acquisitions per 100,000 man-weeks when the distance was between 0 and 5 feet to <20 per 1,000 man-weeks when the distance was ⩾30 feet [8]. This example of ''crowding'' is important when considering the epidemiology of group A streptococcal respiratory tract infections in socially and economically disadvantaged populations.

Although environmental factors such as crowding certainly contribute to the risk of acquisition of group A *Streptococcus* and the development of subsequent suppurative or nonsuppurative complications, they are clearly not the sole determinants. In studies carried out during 2 decades in Rochester, New York, Hall [9] clearly documented that while the incidence of streptococcal sore throats remained relatively constant (with expected yearly fluctuations), the incidence of acute rheumatic fever and acute poststreptococcal glomerulonephritis fell precipitously. Outbreaks of acute rheumatic fever in the United States during the latter part of the 1980s and early 1990s occurred in middle-class populations with ready access to medical care [10]. These outbreaks were attributed to the concomitant appearance of mucoid strains of group A *Streptococcus* in the upper respiratory tracts of children in that community [11] and were associated most frequently with strains of M serotypes 1, 3, 5, 6, and 18 [12]. These observations cannot be fully explained by social and economic factors and suggest that the introduction into a population of certain strains with a capacity to cause acute rheumatic fever (''rheumatogenicity'') may substantially influence the epidemiology of the sequelae of group A streptococcal infections.

The group A streptococcal upper respiratory tract ''carrier'' state has further confused the relationship of the epidemiology of these infections to their suppurative and nonsuppurative sequelae; data from industrialized countries have clarified somewhat our understanding of the role of upper respiratory tract carriage [13]. Studies have documented that as many as one-half of individuals presenting with signs of an upper respiratory tract infection and the presence of group A *Streptococcus* in the upper respiratory tract are in this unique carrier state; these children are of little or no threat to themselves (for sequelae) or to their close contacts (for spread) and, therefore, in theory, require less medical and public health attention [14]. However, it is very difficult, if not impossible, to differentiate consistently the group A streptococcal carrier from an individual with bona fide group A streptococcal infection on the basis of presenting signs and symptoms. The laboratory can be helpful only in retrospect, since 3–6 weeks are required after the infection to demonstrate a rise in streptococcal antibody titers. Although group A streptococcal carriers are found in developing countries, carriage rates in some developing countries may be less than those in more affluent societies [15–17].

Although penicillin has been the antibiotic of choice to treat group A streptococcal infections for >50 years, to date there has never been a clinical isolate of group A *Streptococcus* that is resistant to penicillin. Although much has been written about tolerance to penicillin, this has not been shown conclusively to be of clinical significance. Resistance to the sulfa drugs and tetracyclines quickly became a problem following their introduction into clinical practice. The only other group of antibiotics to which resistance has developed to any important level has been the macrolides [18]. This was a major problem in Japan in the 1960s and 1970s, and recently has been shown to be a problem in some European countries [19]. However, in most parts of the world the macrolides remain clinically effective for treatment of group A streptococcal upper respiratory tract infections in individuals who are allergic to penicillin.

Epidemiology of Group A Streptococcal Infections and Their Sequelae in Developing Countries

Unlike in industrialized countries, few comprehensive and prospective studies have been carried out in developing countries to clarify the epidemiology of group A streptococcal infections in these populations. However, the data that are available suggest that some of the basic epidemiological features of group A streptococcal diseases in developing countries may differ from those in better-studied, more affluent populations. For example, epidemics of acute rheumatic fever occur in military populations and in the wider community in the United States [10, 20], but epidemics have rarely, if ever, been reported from developing countries. This does not mean that they do

not occur; it may reflect the inadequacy of epidemiological studies in these countries.

The dynamics of streptococcal acquisition may also vary in different environments. Classic descriptions of the transmission and endemicity of group A streptococcal infections in industrialized countries with temperate climates rely primarily on the concept of pharyngeal infection, carriage, and droplet spread [21]. An encounter with a potentially infecting strain of group A *Streptococcus* may be relatively uncommon [22, 23]. This contrasts with the situation in developing countries and/or other indigenous populations in tropical climates; where pyoderma is prevalent, the majority of children in a community may be infected with group A streptococci at any one time, and multiple different strains of group A streptococci may be circulating in the community [6]. Multiple strains may even be isolated from the same individual [24]. Further observations in some of these populations raise questions about the nature of the primary streptococcal infections leading to rheumatic fever.

For example, in aboriginal communities of northern Australia, where the highest published incidence of acute rheumatic fever in the world has been reported [25], the prevalence of pyoderma (commonly secondary to scabies infestation) among children may be $\geqslant$70% throughout the year [26]. These children often harbor multiple, different serotypes of group A *Streptococcus* in their lesions [27]. Individual communities have up to 14 genetically different group A streptococcal strains circulating at any one time [28]. Yet in these communities, throat-carriage rates for group A *Streptococcus* are consistently $<$5% and often $<$2% [26].

The incidence rates of bona fide group A streptococcal pharyngitis in these communities are not precisely defined, although anecdotal reports suggest that in some remote communities presentations with sore throat are not as common as in urban settings. Thus, in Australian aboriginal communities with high rates of pyoderma, the primary source of group A streptococcal infection and transmission may not be the throat; the skin sores of children (and many adults) could contribute substantially to community spread.

Such observations raise the intriguing question of how this apparently low prevalence of group A streptococci in the upper respiratory tract and a high incidence of pyoderma can be correlated with high rates of acute rheumatic fever in the same communities, in light of the generally accepted dogma that acute rheumatic fever follows only group A streptococcal infection of the throat, not of the skin [29]. There are a number of theoretical possibilities that require consideration. Perhaps the low throat-carriage rates of group A streptococci in this population do not reflect the true incidence of group A streptococcal pharyngitis (either symptomatic or asymptomatic) and, as generally accepted, the group A streptococcal strains associated with pyoderma lesions play no role in acute rheumatic fever pathogenesis.

A second possibility is that some group A streptococcal strains isolated from pyoderma lesions may have the potential to cause acute rheumatic fever (either de novo or acquired by horizontal transfer of genetic material, as appears to occur in some strains [30]) and that they lead to rheumatic fever, either directly by skin infection or by subsequently infecting the throats of children. This latter possibility would seem unlikely in light of data published by Bisno and colleagues suggesting that so-called skin strains do not cause acute rheumatic fever when isolated from the throats of rheumatics [31]. However, in New Zealand, where high incidence rates of acute rheumatic fever are found in the Maori and Pacific Islander populations [32], group A streptococcal isolates recovered from the throats of patients with rheumatic fever belonged largely to serotypes associated with skin rather than throat infection in that population [33]. Moreover, during a recent 4-year period in Tunisia, more M-typable strains of group A streptococci from throats of patients with acute rheumatic fever came from known pyoderma-associated and nephritis-associated serotypes (M types 2, 9, 11, 33, and 49) than from known rheumatic fever–associated serotypes [34].

Others have found isolates of M serotypes conventionally associated with pyoderma in the throats of patients with rheumatic fever [35, 36]. A case of acute rheumatic fever has been described following group A streptococcal infection of an infected wound with a T-agglutination pattern (T3/13/B3264) that is commonly associated with pyoderma and has been associated with rheumatic fever elsewhere [37, 38]. With newer molecular techniques available for typing strains of group A *Streptococcus,* more data can now be obtained to clarify this possibility.

A third possibility is raised by a hypothesis less related to a specific site of infection. It suggests that the peculiar age distribution of patients with acute rheumatic fever can be explained by the necessity for ''priming'' the immune system by repeated group A streptococcal infections [23]; this would be compatible with multiple episodes of streptococcal pyoderma during early childhood.

Aside from generally higher rates of pyoderma and impetigo, there are other aspects of group A streptococcal pharyngeal infection that may differ between developing and industrialized countries. Markowitz, among others, has noted that data from some developing countries indicate that a lower percentage of children with pharyngitis have throat cultures positive for group A *Streptococcus* than in the United States [39]. There is also evidence that group A streptococcal pharyngitis is more often mild or subclinical in developing countries. A 3-year prospective study in Egypt found no occurrences of typical exudative pharyngitis, despite group A streptococcal pharyngitis attack rates (determined by culture and immune response) equivalent to those found in North American studies [40]. Another prospective study in India found that, of 53 children with group A streptococci isolated from the pharynx, 54% had serological evidence of infection, yet none had manifested symptoms or signs of pharyngitis [16]. Asymptomatic infection due to group A *Streptococcus* is well described and may be common in

developing countries. Moreover, the observation that many patients with symptomatic pharyngitis in some developing countries do not present to health care providers (because of economic, cultural, or other factors) needs to be considered.

In tropical regions, throat-isolation rates of groups C and G streptococci are higher than those for group A [1, 39]. Groups C and G streptococci can cause invasive disease and pharyngitis [41]. Group C *Streptococcus* can cause acute poststreptococcal glomerulonephritis [42]. Both may express M protein [43, 44], and there is evidence of horizontal M-protein gene transfer between group A and group G *Streptococcus* [45, 46]. It is unclear whether these other serogroups of β-hemolytic streptococci may alter the epidemiology and recovery of group A streptococci or to what extent they may have the potential to cause suppurative or nonsuppurative complications. More data from both laboratory and clinical studies are needed.

Prevention

Public health programs for control of group A *Streptococcus* in developing countries have tended to focus on the establishment of registers for acute rheumatic fever/rheumatic heart disease and on improvement of compliance for those receiving secondary prophylaxis regimens [3, 4, 47, 48]. This has represented a major step forward in control of acute rheumatic fever and rheumatic heart disease but has done little to reduce the incidence of first attacks of rheumatic fever or the overall number of people requiring secondary prophylaxis [3]. The lack of implementation of primary prevention of rheumatic fever in the developing world has occurred for a number of reasons. These include the lack of financial and medical resources, the scarcity of laboratory facilities necessary to reduce the overuse of penicillin and other antibiotics (in the absence of proper diagnosis), and difficulties with providing adequate professional education for health care workers.

Approaches to primary prevention of acute rheumatic fever in industrialized countries have varied [49] and have included mass antibiotic prophylaxis in military populations [50] and various combinations of screening surveillance of children with sore throats [51–53]. Public health prevention programs in indigenous populations in industrialized countries have resulted in some success. However, these have also been accused of not being cost-effective [54] and resulting in the overuse of penicillin [55]. A program in an Australian aboriginal community that involved screening with use of throat swabs, in combination with penicillin treatment of group A streptococcal carriers, could not be sustained over the long term [56, 57].

Two recent examples from developing countries illustrate the complexity of primary prevention programs, especially where epidemiological data are incomplete. A policy of empirically treating all sore throats in children with intramuscular penicillin G benzathine, introduced in Costa Rica during the 1970s, was temporally associated with a reduction in the incidence of acute rheumatic fever [58]. However, the major part of the decline occurred prior to the increased use of penicillin G benzathine. This suggests that other factors may have contributed to the reduction in new cases of acute rheumatic fever. It is not clear to what extent living conditions changed in Costa Rica during the 1970s, but it is likely that medical services improved, as this program coincided with the establishment of a national health plan. Improved quality and availability of medical care have been shown elsewhere to result in reduced rates of acute rheumatic fever [59].

A more comprehensive acute rheumatic fever control program in the French Caribbean involved the establishment of a register for acute rheumatic fever/rheumatic heart disease and an extensive education campaign about the nature and treatment of primary group A streptococcal infections, including both pharyngitis and pyoderma [60]. The consequent reduction in incidence of acute rheumatic fever was impressive and offers hope that group A streptococcal control programs can be effective without specifically addressing poverty and living conditions. However, it also suggests that until additional studies have clarified the relative importance of throat and skin infections in the pathogenesis of acute rheumatic fever in these regions, prevention programs may need to address all group A streptococcal infections, not only those of the upper respiratory tract.

The Future: Research and Prevention

There is a clear need for well-planned, prospective, longitudinal studies to understand more completely the epidemiology of group A *Streptococcus* in developing countries and to implement more effective public health prevention programs. The problem of the inability to M-serotype many isolates from regions of endemicity [61, 62] is being addressed by employing molecular techniques (e.g., PCR) for typing systems [28, 63]. The existing network of streptococcal reference laboratories could make these techniques available to researchers in developing countries by typing isolates collected during properly planned, prospective studies, helping with data analysis, and possibly assisting in the training of laboratory personnel in those countries. This could be part of an international effort to standardize new approaches to typing in the same way that M typing is standardized; at present a number of different molecular techniques are used, and it is often difficult to compare results between laboratories, even when the same technique is used. Furthermore, there is the distinct need to correlate molecular features with the biological properties of specific serotypes that have been classified by conventional serological techniques.

There is also a need for continuing laboratory research to better understand the pathogenesis of acute rheumatic fever and acute poststreptococcal glomerulonephritis. This is essential to the development of a cost-effective group A streptococcal vaccine(s). Additional information about the significance of a genetic marker for determining susceptibility to acute rheu-

matic fever and a laboratory diagnostic test specific for acute rheumatic fever would have obvious benefits for public health control of the disease [64].

Because such information is not available presently, there is an immediate need to make sensible interim recommendations for both practitioners and public health authorities about the treatment and prevention of group A streptococcal infections in developing countries and in indigenous populations. A rational approach to the public health management of sore throats is required. A reliable clinical algorithm for the identification of those patients with sore throat who are most likely to have group A streptococcal pharyngitis obviously would be helpful for those many areas where laboratory confirmation of group A streptococcal infections is not feasible. Attempts are being made to accomplish this, but problems remain in developing an algorithm with adequate sensitivity, specificity, and ease of use by health care workers with limited training [65, 66].

Further definitive recommendations about primary prevention programs will have to await the availability of more representative and reliable epidemiological data. For example, where the prevalence of group A streptococcal pyoderma is high and there is a high incidence of acute rheumatic fever, the relationship between pyoderma and acute rheumatic fever should be further investigated. This will require large-scale, long-term, prospective surveys in which populations undergo regular throat and skin swabbing and isolates undergo molecular typing, so that new streptococcal acquisitions can be correlated with new cases of acute rheumatic fever.

The importance of pyoderma in acute poststreptococcal glomerulonephritis and also invasive group A streptococcal infections should be further assessed. Such studies could also be an important stimulus for efforts to reduce pyoderma rates. Community programs to reduce rates of pyoderma [26, 67] could be a rational first step, but these should only be undertaken as part of more comprehensive strategies that also stress the importance of careful diagnosis and appropriate treatment of pharyngitis.

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