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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1058-4838/99/2802–0007$03.00
Streptococcus care [10]. These outbreaks were attributed to the concomitant suggest that some of the basic epidemiological features of States during the latter part of the 1980s and early 1990s oc- tries to clarify the epidemiology of group A streptococcal infec-

fever and acute poststreptococcal glomerulonephritis fell pre-

Unlike in industrialized countries, few comprehensive and

expected yearly ¯uctuations), the incidence of acute rheumatic

tract infection and the presence of group A Streptococcus in

upper respiratory tract infections in individuals who are allergic to penicillin. 3, 5, 6, and 18 [12]. These observations cannot be fully ex-

plaineda 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 sub-

stantially 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 se-

quela; data from industrialized countries have clarified some-

what 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 ret-

rospect, 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 coun-

tries, 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 respira-

tory tract infections in individuals who are allergic to penicillin.

Table 1. Recovery of β-hemolytic streptococci from the upper res-

piratory tracts of three siblings living in the same home (March 1972–

March 1976).

<table>
<thead>
<tr>
<th>Culture date (mo/d/y)</th>
<th>Group/serotype of isolates recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female (1970)</td>
</tr>
<tr>
<td>3/28/72</td>
<td>A (M-4)</td>
</tr>
<tr>
<td>9/26/73</td>
<td></td>
</tr>
<tr>
<td>10/31/73</td>
<td>A (T-3/13)</td>
</tr>
<tr>
<td>11/1/73</td>
<td>A (T-3/13)</td>
</tr>
<tr>
<td>5/15/74</td>
<td>A (T-11/27)</td>
</tr>
<tr>
<td>5/17/74</td>
<td>A (M-4)</td>
</tr>
<tr>
<td>8/19/74</td>
<td>A (M-4)</td>
</tr>
<tr>
<td>11/28/74</td>
<td>A (T-5/27/44)</td>
</tr>
<tr>
<td>5/30/75</td>
<td>B</td>
</tr>
<tr>
<td>6/2/75</td>
<td></td>
</tr>
<tr>
<td>7/17/75</td>
<td>A (T-28)</td>
</tr>
<tr>
<td>12/23/75</td>
<td>A (T-28)</td>
</tr>
<tr>
<td>12/29/75</td>
<td></td>
</tr>
<tr>
<td>2/2/76</td>
<td>A (T-28)</td>
</tr>
<tr>
<td>3/4/76</td>
<td>A (T-28)</td>
</tr>
<tr>
<td>3/22/76</td>
<td>A (M-3)</td>
</tr>
</tbody>
</table>

NOTE: Table is reproduced with permission from [7].
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 industri-
alized 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 multi-
ple 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 Austra-
lia, 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 ≥70% throughout the year [26]. These chil-
dren 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 pharyn-
gitis 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
related 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 infec-
tion 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 popula-
tion do not reflect the true incidence of group A streptococcal
pharyngitis (either symptomatic or asymptomatic) and, as gen-
erally 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 popula-
tion [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 pyo-
derma-associated and nephritis-associated serotypes (M types
2, 9, 11, 33, and 49) than from known rheumatic fever–asso-
ciated serotypes [34].

Others have found isolates of M serotypes conventionally
associated with pyoderma in the throats of patients with rheu-
matic fever [35, 36]. A case of acute rheumatic fever has been
described following group A streptococcal infection of an infec-
ted wound with a T-agglutination pattern (T3/13/B3264) that
is commonly associated with pyoderma and has been asso-
ciated 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 ex-
plained 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 prospec-
tive 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 pros-
pective 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 supplicative or nonsupplicative 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-
mictive 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.

References


