International Congress Series 1289 (2006) 281–284

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Critical issues in prevention and control of rheumatic fever and rheumatic heart disease

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Abstract. The evidence base for public health and therapeutic interventions to prevent and control acute rheumatic fever (ARF) and rheumatic heart disease (RHD) still has some big gaps. Resolving critical issues in the pathogenesis of ARF should accelerate vaccine development and provide reassurances about vaccine safety. The basis of the genetic restriction of ARF predisposition and of the "immunogenic" determinants within group A streptococci (GAS) are critical to define. Also important is whether other bacteria such as groups C and G streptococci can be rheumatogenic and whether skin streptococci can cause ARF, either directly or via secondary throat colonization. Benzathine penicillin remains the mainstay of secondary prevention by preventing recurrent ARF and progression of RHD. However, there remain major issues of quality, supply, dosing, optimal timing of dosing and how best to incorporate secondary prophylaxis into primary care with either vertical or horizontal programs. Alternative secondary prophylaxis regimens remain to be developed.
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Keywords: Acute rheumatic fever; Rheumatic heart disease; Pathogenesis; Group A streptococcus; Streptococci

1. Introduction

There are still big gaps in the evidence base for public health and therapeutic interventions to prevent and control acute rheumatic fever (ARF) and rheumatic heart disease (RHD). While it is hoped that a rheumatic fever vaccine will eventually provide primary prevention of ARF [1–4], the actual basis of the pathogenetic processes resulting

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0531-5131/ © 2005 Published by Elsevier B.V.
doi:10.1016/j.ics.2005.11.023

in ARF remain poorly defined. This is an impediment to vaccine development and to resolving continuing concerns about vaccine safety and the potential for vaccines to actually cause ARF.

2. Pathogenesis of acute rheumatic fever

It is generally accepted that ARF results from infection with a "rheumatogenic" group A streptococcus (GAS) in a genetically susceptible human host [5].

2.1. Genetic susceptibility

Unraveling the human genetic predisposition to ARF would enable primary and secondary prevention programs to selectively target those at risk of developing ARF following GAS infection. It is estimated that between 3% and 15% of any population may be genetically susceptible, but this remains speculative [6]. Issues to resolve include:

1. How genetically restricted is the propensity for an individual to develop ARF?
2. Does this propensity differ between ethnic groups?
3. Is this genetic restriction of potential for ARF absolute?
4. Can a useful and universal marker for this predisposition be developed?
5. Is the D8/17 B-cell alloantigen such a marker?

2.2. Rheumatogenicity

It is generally accepted that only certain GAS can result in ARF. M types of GAS associated with ARF include M types 1, 3, 5, 6, 14, 18, 19 and 24 [7]. However, this association has been almost entirely from studies in the USA and the diversity of *emm* types elsewhere in the world is only now being studied [8–10]. Indeed, the number of reported *emm* types has doubled in the last few years [9,11]. Nevertheless, while recent studies in rats supports a role of M protein components in ARF pathogenesis [12], it remains possible that non-M-protein antigens may be crucial, at least in part [13]. Essentially, the molecular basis of rheumatogenicity remains elusive:

1. How restricted are the GAS that have the ability to cause ARF?
2. What makes these particular GAS rheumatogenic?
3. Is this rheumatogenicity really M-protein related?
4. Can other bacteria such as groups C and G streptococci also be rheumatogenic [14]?
5. Can the "rheumatogenic element" be horizontally transferred between GAS and even to other bacteria such as GGS and GCS [15,16]?

2.3. The immune response in ARF

Molecular mimicry between streptococcal antigens and human tissue is thought to be responsible for the immune mechanisms, which results in ARF [5,6]. As well as the responsible streptococcal antigen(s) remaining to be determined, which are the cross-reactive host tissue antigens, also remains uncertain. Both cardiac myosin and laminin are of interest but still lack definitive support. Most recent studies have focused on a primary cellular inflammation being responsible for the tissue damage seen in ARF and RHD, but

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