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Group A streptococci in the 1990s

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The last decade has witnessed a remarkable change in the epidemiology of group A streptococcal infections. There has been a marked increase globally in the reporting of invasive infections caused by *Streptococcus pyogenes*, Lancefield group A streptococci. Many of these cases were deep-seated infections associated with shock and multi-organ failure and are defined as streptococcal toxic shock syndrome. In addition, reports of streptococcal sequelae, in particular, acute rheumatic fever, have re-emerged and remain a serious health threat in developed countries. It appears that these infections are related to the type distributions of the organism among the general population, with the re-emergence of more 'virulent' strains, such as the M1 serotype which in earlier decades was primarily seen in cases of either superficial disease or scarlet fever. Population-based surveillance studies have clearly indicated the importance and relevance of type identification for epidemiological purposes. There have also been suggestions that certain extracellular products and toxins play a major role in the so-called 'increased virulence' of the organism; these include cell surface molecules such as the M protein, opacity factor, the hyaluronic acid capsule, C5a peptidase and streptococcal inhibitor of complement (SIC), in addition to secreted proteins, pyrogenic exotoxins, cysteine proteinase, streptolysins O and S, hyaluronidase, streptokinase and other enzymes. All these factors, and events during the last decade, strongly emphasize the need for a better understanding of the epidemiology, pathogenesis, treatment and prevention of group A streptococcal infections.

Introduction

Before the introduction of antimicrobials, serious infections caused by Lancefield group A streptococci (GAS) or *Streptococcus pyogenes* were common. Before World War II this organism was responsible for as many as half of postpartum deaths and was the major cause of death in burns patients. With the use of penicillin, the group A streptococcus was believed to be virtually eliminated as a pathogen. Over the last four decades, the industrialized world has witnessed a decline in the incidence of these diseases. In the 1970s, there was optimism that serious GAS disease had been almost completely eradicated in developed countries, and notification of specific diseases, for example scarlet fever, was abolished in many European countries. In addition, in many countries, routine prophylactic treatment of army recruits with penicillin was abandoned.[1]

In the mid to late 1980s, however, concern about GAS disease was heightened in many countries as outbreaks of rheumatic fever occurred in different areas, in addition to reports of systemic disease with severe complications. This resurgence resembled the nineteenth and early twentieth century 'epidemics' of scarlet fever, which was regarded as one of the most frightening diseases of the pre-antibiotic era.[2,3] This resurgence occurred not only in developing countries, but also in populations that had ready access to medical care within industrialized countries.

Numerous reports in the literature have documented changes in the epidemiology of diseases caused by GAS, particularly in Northern Europe and North America.[4–6] Such changes have been particularly noted in previously healthy individuals as well as in those with predisposing conditions such as immunosuppression, carcinomas and varicella. Understanding these changes in epidemiology and virulence is important for the recognition and control of infection and also for gaining valuable information concerning pathogenesis.

Despite the advent of antimicrobials, the understanding

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of GAS epidemiology and pathogenesis is still incomplete and the clinical and public health management of GAS infections and their sequelae remain problematic. GAS infections remain a significant public health problem at the close of the twentieth century.

Infections caused by *S. pyogenes*

GAS can thrive in almost any body tissue but the upper respiratory tract and skin lesions serve as the primary focal sites of infection and principal reservoirs of transmission. GAS cause a variety of human diseases, including both suppurative and non-suppurative complications of these infections. Infections may occur both endemically or as epidemics and range from simple pharyngitis to severe systemic diseases. The types of infection can be subdivided into four main groups: superficial, deep, toxin-mediated and immunologically mediated diseases. Examples of these infections are summarized in Table I. The main non-suppurative complications (streptococcal sequelae) are acute post-streptococcal glomerulonephritis (APSGN) and acute rheumatic fever (ARF), which are both immunologically mediated. ARF usually follows throat infection by GAS; its major clinical manifestations are arthritis, carditis, chorea, erythema marginatum and subcutaneous nodules.[7] Arthritis occurs in approximately 75% of ARF patients and generally involves large joints, knees, ankles, elbows and wrists. Clinical manifestations of ARF occur approximately 3 weeks after a respiratory infection by GAS. APSGN also usually occurs 3 weeks after throat or skin infection by GAS of specific nephritogenic serotypes. Although the general underlying mechanism may be similar, these two sequelae of GAS differ in their pathogenesis, clinical manifestations, epidemiology and potential morbidity.[8–10]

The mechanisms underlying immunity and susceptibility to GAS disease are not well understood. For example, there is no definitive explanation as to why GAS pharyngitis is primarily a childhood disease or why 'life-threatening' invasive infections so often occur in apparently healthy young adults. These infections are still significant and serious health problems in many countries worldwide.

Biology of *S. pyogenes*

The streptococcus was first described in 1879 by Louis Pasteur, who saw streptococci under the microscope as 'chains of beads' in a sample from a patient dying of puerperal sepsis, but the generic name *Streptococcus* was first proposed by Rosenbach in 1884. In 1903 Schottmüller reported that numerous organisms produced distinct changes in media containing blood, and those producing clear zones of lysis around the colony were called *Streptococcus haemolyticus*, because of the classic β haemolysis they produced. This early work formed the basis for the biochemical and serological typing schemes that followed in the early 1900s.[11]

Dr Rebecca Lancefield made a major contribution to our knowledge of this organism, from the 1920s through to the 1970s, with the discovery of the streptococcal group polysaccharide and the cell wall M protein. These antigenic molecules are the basis for not only the pathogenic characterization of the organism but also the phenotypic schemes used extensively throughout the world for typing these organisms. During the early 1930s, Dr Fred Griffith, the founder of the UK Streptococcus Reference Laboratory, worked extensively on the 'other' cell wall protein, the T protein. Even though Dr Griffith and Dr Lancefield were thousands of miles apart, they worked very closely in the development of the classic serotyping schemes for group A streptococci.[11–14]

Serological grouping provided the first precise method for identifying the major human pathogen of the genus *Streptococcus* (Lancefield group A streptococcus). Several other tests, in addition to Lancefield grouping, are useful for subdividing and identifying GAS and the other human pyogenic streptococci of Lancefield groups B, C and G that are often encountered in a clinical diagnostic laboratory (Table II).[15,16]

Serological classification of group A streptococci

GAS are serologically classified, according to the schemes first described by Griffith[14] in 1934 and Lancefield in 1962,[13] into specific types based upon the identification of the

Table I. Diseases caused by *Streptococcus pyogenes*

Category of disease	Examples of infections
Superficial diseases	pharyngitis, skin and soft tissue infections, impetigo, erysipelas, vaginitis, post-partum infections
Deep infections	bacteraemia, necrotizing fasciitis, deep soft tissue infections, cellulitis, myositis, puerperal sepsis, pericarditis, meningitis, pneumonia, septic arthritis
Toxin-mediated	scarletina, toxic shock-like syndrome
Immunologically mediated	rheumatic fever, post-streptococcal glomerulonephritis, reactive arthritis

Table II. Biochemical characterization of the human pyogenic streptococci of Lancefield groups A, B, C and G

Streptococcus sp.	Haemolysis	Lancefield group	Bacitracin sensitivity (0.1 unit disc)	Pyrrolidonyl-arylamidase	Alkaline phosphatase	Ribose	Vogues–Proskauer reaction	Hippurate hydrolysis
S. pyogenes	+	A	+	+	+	–	–	–
S. agalactiae	v	B	–	–	+	+	+	+
S. equisimilis	+	C	–	v	+	+	–	–
Streptococcus spp.	+	G	–	v	+	+	–	–

+, 85–100% positive reactions; v, 16–84% positive reactions; –, 0–15% positive reactions.

T and M cell wall protein antigens. Conventional typing is based upon the antigenic specificity of these surface-expressed T and M proteins.[17] The T protein forms the basis of the agglutination typing system but its function is unknown. The M protein is the basis of the precipitation typing system and has major significance in the pathogenicity of the organism. When M protein is absent, the organism cannot survive in normal human blood and antibody to the M protein is type specific. Ninety-three different M types have now been validated and internationally recognized[19] and only a single M-type antigen is usually expressed by each strain.

Approximately 50% of GAS strains also produce an apoproteinase, an enzyme that causes mammalian serum to increase in opacity; this reaction is called serum opacity factor and the enzyme responsible is referred to as opacity factor (OF).[17,18] The OF reaction has proved useful in the routine serological identification of GAS. Antibody to OF is specific in its inhibition of the opacity reaction of the M type producing it and this characteristic has proved extremely useful as a supplementary aid to the typing scheme. Table III describes the common reactions observed amongst GAS currently isolated within the UK and the relationship of T, M and OF antigens.

Table III. Some common GAS M types and their related T and OF antigens (bold denotes the most common M types observed within the UK from 1998 to the end of June 1999)

	Opacity factor	
T pattern	positive	negative
1	68	**1**
2	**2**	
3/13/B3264	73, **77**, 81, 85, 90	**3**, 83
4	**4**, 60, 63	24, 26
6	–	**6**
5/27/44	82	**5**, 91
11	**11**, **78**, **89**	–
12	**22**, 62, 76	**12**
28	**28**, 87	–
8/25/IMP19	**75**, 79, **84**	

Serological typing is a specialized technique used in only a few international Reference Centres worldwide. Other phenotypic methods, such as phage typing, bacteriocin typing, pyrolysis mass spectrometry and multilocus enzyme electrophoresis, have also been described[17] but have found limited use.

Most epidemiological studies of GAS disease classify the organisms by M type; however, it is sometimes difficult to identify M protein types in this way owing to the unavailability of typing reagents and difficulties in their preparation and maintenance. It is also believed that many GAS isolates are not typeable, either because of the lack of M protein expression or the unavailability of specific antisera. Hence there has recently been interest in the development of alternative methods utilizing molecular technology.[20–23]

Molecular approaches to typing GAS

In the early 1980s, there was complacency about the necessity for GAS serotyping and many reference laboratories decreased their in-house production of M typing sera. This practice and opinion changed because of the resurgence of invasive disease in the mid to late 1980s. Typeability rates reflected the range and availability of sera, so molecular approaches were considered. Many of the molecular methods that have been documented do not correlate with the classical M typing system. An example is *Vir* typing using PCR primers to the entire virulence-regulating gene, the *mga* gene (see section on virulence factors), which was developed in Australia.[24,25] Other methods included the use of labelled oligonucleotide probes targeting specific areas of the gene encoding M protein, the *emm* gene, for example oligonucleotide typing or dot blotting[22] and the PCR *emm* gene ELISA.[26] The major disadvantage of these methods is that many probes are required to cover the full range of GAS types. At least 35 different *emm* type probes would be required. Other subtyping methods, including multilocus enzyme electrophoresis, ribotyping, pulsed field

gel electrophoresis and, more recently, fluorescent amplified fragment length polymorphisms (FAFLP) and multilocus sequence typing (MLST), are useful for examining clusters and undertaking population genetic studies.[23,27,28]

The current 'gold standard' molecular methodology is based upon *emm* sequence typing as developed by the Centers for Disease Control (CDC).[19,20] The major international Reference Centres in the UK, USA, Czech Republic, Canada and New Zealand are currently evaluating this method. The definition of an *emm* type sequence is based upon the identity of >160 bases at the 5′ terminal end of the hypervariable portion of the *emm* gene which must share at least 95% homology. Most strains of different serotypes show <80% homology to their nearest 'neighbour' and few strains will fall within the 80–95% range. The 5′ end *emm* sequences are listed at http://www.cdc.gov/ncidod/biotech/infotech_hp.html. A few oddities have been described; for example, the strains with the *emm*27 and *emm*77 genes show >95% homology. However, M typing sera may differentiate these.

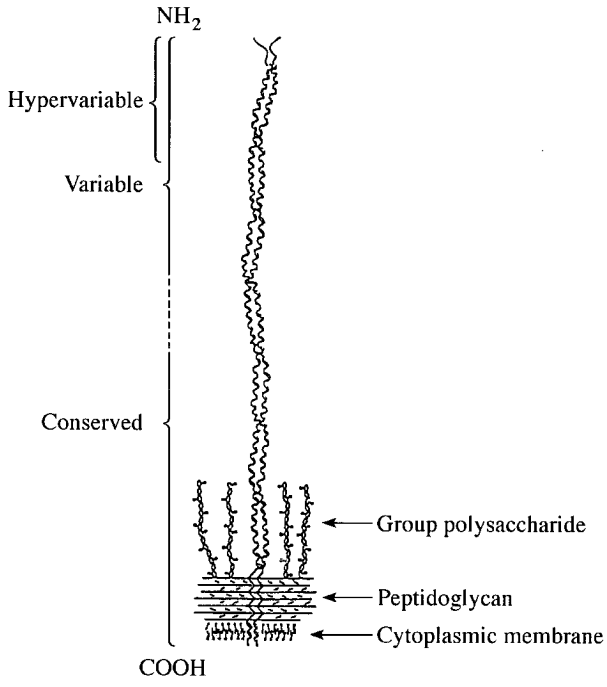

Figure 1. Diagrammatic representation of the M protein molecule on the cell surface of GAS.

Virulence factors of group A streptococci

In addition to the major virulence factor, the M protein,[29] GAS produce many other extracellular substances and possess several surface factors which also have a role in pathogenesis.[30,31] The genes encoding these factors and many more have now been sequenced and include genes for erythrogenic toxins,[31] C5a peptidase,[32] streptococcal superantigen,[33] cytolysins,[34] the hyaluronic acid capsule,[35] the M and M-like proteins[36,37] and, more recently, the SIC protein (streptococcal inhibitor of complement).[38] The entire genome sequence for *S. pyogenes* will be completed by Dr Ferretti's team in Oklahoma City, by the end of 1999 (J. J. Ferretti, personal communication). Streptococcal toxic shock syndrome (STSS) has been most commonly associated with strains of a specific M type (M1 or M3) and such strains produce pyrogenic exotoxins A, B, C, D or F.[39] Though the pathogenesis of STSS has not been defined, it is clear that all these toxins are superantigens and capable of inducing production of tumour necrosis factors α, and β, interleukin 1 (IL-1), IL-6, gamma interferon and IL-2 by human monocytes and lymphocytes. Shock and organ failure may be the consequence of massive induction of the cytokine cascade.[29]

M protein and other surface virulence proteins

The M protein has always been considered to be the major virulence factor of GAS as it confers resistance to phagocytosis and protects the organism from phagocytosis by polymorphonuclear leucocytes. M proteins are dimeric, α-helical coiled coil protein molecules attached to the cell surface at their carboxy-terminal end.[29] The amino-terminal end is a hypervariable region and is the region responsible for type specificity (Figure 1).[29] As they are definitive type-specific serological markers, most anti-M protein antibodies produced after infection with GAS are opsonic and therefore protect against future infections with GAS of the same type.[29] So, a shift to a predominance of certain serotypes, for example, M1, M3 and M18 (particularly within the USA), which were uncommon among invasive disease isolates before the 1980s, may have resulted in highly susceptible populations because of the low prevalence of type-specific M antibodies to these serotypes.[16,40] Some M types have also been linked to specific clinical diseases, so the changing epidemiology of GAS diseases may be related directly to a changing distribution of serotypes.[40] This highlights and reflects the changes in and the importance of serotype distribution studies among populations.

DNA sequencing data have revealed that M protein and immunoglobulin G (IgG) receptor genes share a high degree of homology, indicating that they have evolved from a common ancestral gene. They are now considered as one gene family, the M and M-like (*emm* gene) family. These genes are often closely linked on the streptococcal chromosome and they are controlled by the same regulatory gene, the *Mry* or *Vir*R regulon, located upstream of the *emm* gene cluster.[36,37] These genes constitute a pathogenicity island[41] which in effect is a gene locus (*mga* regulon) containing multiple genes involved in virulence (*vir* or *mga* regulon, *emm* gene cluster, the core *vir* regulon). In strains of the M1 serotype, there is an insertion sequence (IS) between two of the genes in the *mga* regulon, namely

the genes encoding protein SIC and the C5a peptidase. This sequence (IS1562) comprises 1483 nucleotides and is flanked by terminal inverted repeats but lacks target site duplication. It contains an open reading frame coding for protein homologous to transposons in other bacterial species.[42]

The streptococcal *emm*-like genes are clustered together at the *vir* locus of the chromosome and are divided into the *mrp*, *emm* and *enn* gene groups on the basis of differences in conserved 5′ and 3′ regions and relative positions within this region. The variable 5′ sequences of the majority of the *emm* genes have been elucidated. The sequence diversity of *emm* genes varies: class I M proteins (OF-negative strains) exhibit four different gene arrangements while class II M proteins (OF-positive) exhibit only one pattern. Recent data have also shown that many different M types could be correlated with hybridization to *emm* allele-specific oligonucleotides.[22] This technology is extremely useful and could be applied in almost any laboratory that has access to molecular techniques. However, it will not allow identification of new *emm* genes. In addition, these systems will not identify any potential hybrid *emm* genes that may arise through interstrain gene transfer.[43,44] Thus, new techniques based upon rapid sequence analysis of *emm* gene alleles have been described as a practical and useful tool for typing GAS that correlates well with M type expression.[20] Further, knowledge about the presence of specific *emm* genes among invasive GAS isolates could perhaps facilitate the development of anti-streptococcal vaccines.

Other significant virulence determinants include the hyaluronate synthase and UDP-glucose dehydrogenase surface proteins that bind mammalian proteins (lysozyme, fibronectin and myosin). It has been speculated that the ADP-ribosylating activity of glyceraldehyde-3-phosphate dehydrogenase could promote 'communication' between the host and pathogen during GAS disease.[45] Another cell-bound streptococcal component that interferes with the immune system of the host is C5a peptidase. It cleaves and inactivates the chemotactic component C5a of the complement system and so limits the recruitment of polymorphonuclear leucocytes to the site of the infection. The structural gene for C5a is located downstream, adjacent to the *emm* gene cluster.[32,37]

Other important extracellular factors include the cytolysins, streptolysins O and S,[34] spreading factors such as hyaluronidase,[35] deoxyribonuclease, streptokinase and cysteine protease, streptococcal pyrogenic exotoxins (SPEs) A, B, C, D and F (mitogenic factor).[30] Several streptococcal extracellular components, as well as cell-wall associated components, have been recognized as superantigens; these include SPE A, B, C, F and streptococcal superantigen, SSA.[30,33] The SPEs share several biological activities, such as induction of fever, alteration of immune response, depression of the reticuloendothelial system and superantigenicity. SPE B cleaves the interleukin 1α precursor to produce the active form of interleukin 1α. Evidence from epidemiological studies and *in vivo* experiments have shown that antibodies against SPE B are protective. Several publications suggest that SPE B contributes to the virulence associated with GAS; however, little is known about its regulation. Nucleotide sequence data (as part of the GAS genome sequencing project in Oklahoma) revealed the presence, upstream of the *speB* gene, of a gene, designated *rgg*, that was predicted to encode a polypeptide similar to previously described regulatory factors. To assess its role in the production of SPE B, the *rgg* gene was insertionally activated in a strain of GAS, which resulted in a marked decrease of SpeB production; however, the production of other extracellular products (for example, streptolysin O, streptokinase and DNase) was not affected.[46] As a result of the genome sequencing database at the University of Oklahoma, several important and novel streptococcal superantigen genes (*speg*, *speh* and *spej*) have also been identified.[47]

More recently, Akesson and colleagues identified a novel GAS extracellular protein, produced by M1 strains, that inhibits human complement. The SIC protein is an important factor which is incorporated into the membrane-attack complex (C5b–C9) and inhibits target cell lysis by an undetermined mechanism.[38] The gene encoding this protein is highly polymorphic and is useful in molecular characterization studies.[48] The observation that the *sic* gene is much more variable than all other genes examined, in particular, for M1 isolates, suggests that *sic* sequencing could be used as a rapid typing approach to differentiate GAS that are thought to be epidemiologically linked. The data provide a valuable insight into the molecular basis of infections and epidemics caused by M1 and also new information about pathogen emergence and re-emergence. Other recent publications have reported the usefulness of Fluorescent amplified fragment length polymorphism (FAFLP) analysis to subtype clinical invasive and superficial isolates of M1.[28]

Invasive diseases caused by GAS and current epidemiology

Given the diversity of the structure and function of M protein it is not surprising that GAS of certain M types, in particular M1 and M3, are strongly associated with invasive infections. In the USA, clinical isolates examined by the CDC during the 1970s and 1980s showed a doubling in the prevalence of M1 and M3 during the 1980s; this is also true for the 1990s.[32,40] These results are in concordance with those described by other countries, in particular the UK and other areas of Europe.[5,49] They are also consistent with the view that the increased incidence of invasive GAS disease is a result of the increased prevalence of virulent serotypes. Certainly, the famous cluster of infections with invasive GAS that occurred in Gloucestershire, UK, in May 1994 heightened the awareness of this type of infec-

tion even more.[50] Following, this 'unusual' cluster of necrotizing fasciitis cases in one small part of the UK, the Public Health Laboratory Service (PHLS) decided to reassess their surveillance strategies for severe GAS disease, and many countries followed this example. At that time, a PHLS Action Group was formed and the main recommendation was that an Enhanced Surveillance System for invasive GAS disease should be established for England and Wales.[51]

Although several hospital-based case series had been reported previously, primarily based upon specific studies in localized regions, there had not been any specific prospective studies until the publication in 1996 of a study by Davies and colleagues in Ontario, Canada.[52] This report was based upon a 2 year study from 1992 to 1993 of an analysis of 323 cases of invasive disease in Canada. Studies from different parts of the world subsequently appeared in the literature. For example, in Sweden, a retrospective study of invasive disease in Stockholm during 1983–1995 was undertaken, with the average disease incidence being 2.3 cases/100,000 population. The incidence varied between 3.7 in 1988 and 1.3 in 1993. Their review of (M1) cases showed cyclic increases of infection during 1986–1990 and 1993–1995; the overall case fatality rate was 11%.[53]

In the USA, population-based surveillance was undertaken in metropolitan Atlanta during 1994–1995. A total of 183 cases were documented with an annual incidence of 5.3/100,000.[54] Surveillance studies in other areas of the USA followed[55,56] and also in other countries, for example Canada,[57] Israel,[58] Japan,[59] Australia[60] and France.[61]

Surveillance of GAS in England and Wales

At the time of the Gloucestershire cluster of necrotizing fasciitis, approximately 550 bacteraemia cases caused by GAS were being reported to the PHLS each year and there had been little variation during previous years. The numbers of reports increased during the Enhanced Surveillance and has remained stable (Figure 2).

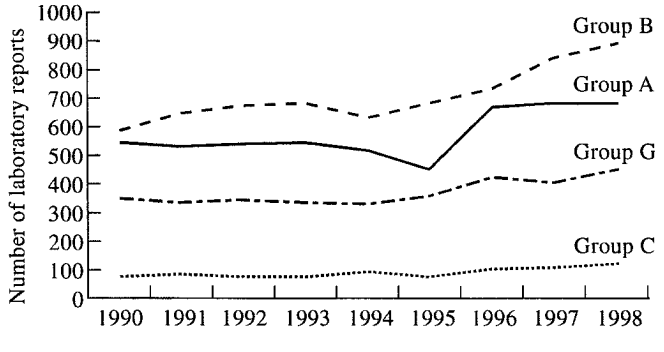

Figure 2. Bacteraemia in England and Wales: laboratory reports 1990–1998 to the PHLS Communicable Disease Surveillance Centre. Pyogenic streptococci of Lancefield Groups A, B, C and G.

The PHLS surveillance commenced in July 1994 for a period of 3 years. The main objectives were: to gain a clearer understanding of the changes in the epidemiology of GAS invasive disease; to be able to detect outbreaks or clusters of disease in a timely manner; to determine patterns of M types, genotypes, virulence factors and the manifestations of clinical disease; to obtain population-based data on the incidence of disease; to define risk factors and clinical characteristics; and also to try and develop preventative measures and recommendations for treatment strategies from the data obtained. The surveillance included all patients presenting with severe invasive disease as defined by the isolation of a GAS from a normally sterile site which included blood, CSF, joint aspirates, abscesses, and pericardial, pleural or peritoneal fluid. Also included were cases with the isolation of GAS from other sites such as wound swabs from an affected site, urine, sputum, high vaginal swabs (HVS) and throat swabs in the absence of other pathogens together with one or more of the following: sudden death, shock with a systolic blood pressure of $<$90 mmHg, disseminated intravascular coagulation (DIC) and/or system failure.[49,51] Full epidemiological, clinical and microbiological data were obtained for all isolates during the surveillance period by a simple questionnaire and typing data from the PHLS Streptococcus and Diphtheria Reference Unit (SDRU).

During the Enhanced Surveillance, isolates from more than 1900 cases of invasive disease were received by SDRU for serotyping. Overall, the questionnaire response rate was excellent at 95%. Periodic reports of the Surveillance were documented in the PHLS Communicable Disease report.[51] The age of patients varied from $<$1 year to $>$100 years, with almost equal numbers of males and females. The overall mortality rate was 27%, with a much higher rate among the elderly (the mortality rate for those aged $\geqslant$65 years was approximately 43%).[49] Most isolates were from blood and the remainder from other sterile sites. Hence, most patients were bacteraemic; other diseases included septic arthritis, STSS and necrotizing fasciitis. Approximately 17% of cases were admitted to intensive therapy units; most required artificial ventilation. Some presented with septic shock, DIC and/or system failure (mainly renal failure). Some patients had undergone some form of therapeutic surgical intervention, which included debridements and amputations. Skin trauma was reported as the main predisposing factor. Other factors included diabetes, recent childbirth, immunosuppression, the use of non-steroidal anti-inflammatory drugs, varicella infection and alcohol abuse. The data indicated that only approximately 5% of cases were nosocomially acquired.[49]

The overall M typeability rate was high (95%), with approximately half of the isolates belonging to one of three predominant serotypes, i.e. M1, M3 and R28.[49] There appeared to be a higher risk of fatality associated with isolates belonging to particular M types, notably M1, M3 and M5. The proportion of M1 isolates was quite similar to

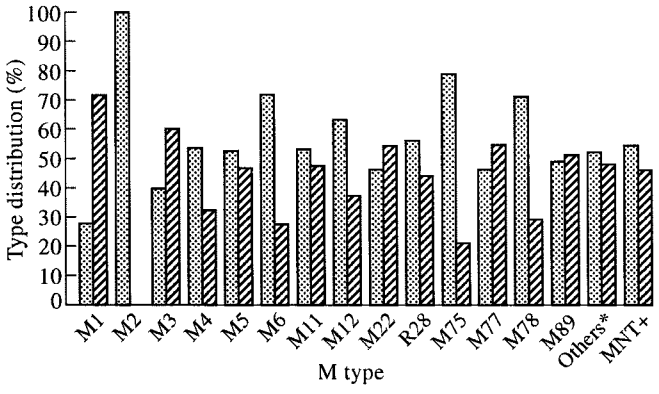

Figure 3. GAS isolate referrals from UK laboratories to the PHLS Streptococcus and Diphtheria Reference Unit, Respiratory and Systemic Infection Laboratory, from January to June 1999. Stippled bars, superficial sites; hatched bars, sterile sites; *, other M types; +, M-non-typeable.

that in data reported from Canada, USA and Europe.[52,55,57] As the numbers of M1 isolates increased, the number of severe and fatal invasive disease cases appeared to increase.[49] The elderly and those patients with underlying conditions were at high risk for severe manifestations of GAS disease, in particular STSS and necrotizing fasciitis.

During 1998 and the first half of 1999 (January–June), M1, M3 and R28 were still prevalent from throat and invasive infections and, interestingly, M84 emerged as a predominant type in 1998 and then 'disappeared' during the first half of 1999, with the emergence of M89 in 1999 (Figure 3). Invasive infections caused by other types, such as M2, M4, M5, M6, M11, appeared to be declining but were prevalent among superficial diseases such as pharyngitis.

Several incidents of disease among close contacts and residents within closed institutions have emphasized the high risk of transmission and that immediate control strategies should be initiated. Therefore, it is crucial that clinicians should always be aware of the severity of these infections. A Working Group was formed in the USA and concluded overall that no definitive recommendations could be made regarding chemoprophylaxis for household contacts of persons with invasive disease.[62] More data are required to assess the risk of subsequent cases and to determine an optimal regimen for chemoprophylaxis. Until such data are available, clinicians should base decisions regarding chemoprophylaxis on their assessment of the risk associated with each individual case.[62]

Treatment strategies

It is critically important to establish a diagnosis of GAS infection early on during the course of the disease. However, diagnosis is difficult during the early stages and delays in treatment may be associated with increased mortality and morbidity. This is particularly important in patients with necrotizing fasciitis. Early clues to diagnosis of necrotizing fasciitis are: increasing pain, often disproportionate to discernible signs at the site of infection; confusion; fever; a marked left shift in the white cell blood count; elevated muscle enzymes in serum; and evidence of renal failure which may precede hypotension. Cutaneous findings include: diffuse erythema; bullae filled with fluid; and necrosis of the skin. The presence of bullae should prompt surgical exploration of the deeper soft tissues because necrotizing fasciitis and myositis are frequently associated with this presentation. Treatment should include aggressive surgical debridement and antibiotics as necessary, together with fluid replacement, circulatory support, intensive care monitoring, ventilation and dialysis.[63]

The recognition of the possible pathogenic role of streptococcal extracellular products (toxins) has led to the reassessment of non-surgical treatment strategies and the introduction of new modes of therapy for these patients.

Many clinicians have noted the disappointing response to penicillin in some patients, despite the susceptibility of the organism to penicillin *in vitro*. Clindamycin appears to be more effective for invasive GAS disease, presumably because it acts by binding to the ribosome and inhibiting protein synthesis, irrespective of the growth phase of the bacteria. Therefore, many centres use clindamycin in addition to penicillin for the treatment of invasive GAS disease.[39,63]

The other mode of therapy undergoing extensive evaluation is the use of intravenous immunoglobulin, as pools of human immunoglobulin are likely to contain antibodies to the streptococcal toxins that may neutralize the effects of the toxins. Scientists in Sweden collected plasma samples from patients with STSS and treated them with immunoglobulin. The results showed that stimulation of T cells by streptococcal culture supernatants could be inhibited by the immunoglobulin itself or by the patient's plasma after immunoglobulin infusion, although the same patient's pretreatment plasma was ineffective.[64] These data are somewhat encouraging; however, a randomized large controlled multicentre study is essential to determine whether treatment with either clindamycin or immunoglobulin improves the outcome of severe GAS disease.

Another possible strategy is development of an active M-protein vaccine; work along these lines is currently in progress at the Rockefeller University, New York, USA, where genetically engineered mucosal vaccines using live vectors targeting the conserved region of the M protein are being investigated. One of the major challenges in the development of GAS M-protein-based vaccines is the multiplicity of M types expressed by the organisms. Another approach by Dale and colleagues is the development of a hexavalent GAS vaccine containing protective M protein peptides from types 24, 5, 6, 19, 1 and 3, that has been designed in such a way that each M protein

fragment is immunogenic and evokes protective antibodies.[65]

Conclusions

Some groups have proposed that specific strains within dominant serotypes have gained invasive capabilities and are disseminating worldwide. Host factors also play a significant role; production of antibodies to type-specific M protein during infection confers immunity. As host resistance increases, new types may emerge. The variation in the clinical manifestations of severe GAS disease does suggest that there are differences in the pathogenic mechanisms of the organism. More information needs to be gathered concerning pathogenesis. Continued epidemiological and microbiological surveillance of GAS disease among populations is very important in order to assess the situation with GAS globally and also to improve therapeutic and preventative strategies for these infections which will be with us for many years to come.

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