

## Pyogenic Streptococci – Danger of Re-emerging Pathogens

IZABELA SITKIEWICZ\* and WALERIA HRYNIEWICZ

Department of Epidemiology and Clinical Microbiology, National Medicines Institute, Warsaw, Poland

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### Abstract

$\beta$ -hemolytic, pyogenic streptococci are classified according to type of major surface antigen into A (*Streptococcus pyogenes*), B (*Streptococcus agalactiae*), C (multiple species including *Streptococcus dysgalactiae*) and G (multiple species including *Streptococcus canis*) Lancefield groups. Group A *Streptococcus* causes each year hundreds of thousands deaths globally as a result of infections and post-infectious sequelae. An increasing number of severe, invasive infections is caused by selected, specialized pathogenic clones. Within the last 50 years, an increasing number of human infections caused by groups B, C and G *Streptococcus* (GBS, GCS, GGS) has been observed worldwide. GBS was first identified as animal pathogen but the spectrum of diseases caused by GBS quickly shifted to human infections. Groups C and G *Streptococcus* are still regarded mostly as animal pathogens, however, an increased number of severe infections caused by these groups is observed. The increasing number of human infections caused worldwide by GCS/GGS can be a sign of similar development from animal to human pathogen as observed in case of GBS and this group will gain much more clinical interest in the future. The situation in Poland regarding invasive infections caused by pyogenic streptococci is underestimated.

**Key words:** *Streptococcus* sp., GAS, GBS, GCS, GGS

### Background

In the antibiotics era and with the development of vaccines, it was believed that bacterial infections could be easily managed, and prevented thanks to vaccination. However, the spread of antibiotic resistance and lack of vaccines for multiple pathogens have become a public health problem. Lack of efficient tools to combat infections promotes the emergence of strains that are more pathogenic, more difficult and expensive to eradicate.

Streptococci are major human and animal pathogens, divided into more than 40 species and multiple groups whose taxonomy changed several times over the years (Kohler, 2007). This mini review will concentrate on  $\beta$ -hemolytic group of pyogenic streptococci and is intended to give a broad overview of the group, stress common aspects of their pathogenicity and point out the health cost of infections and economic aspects.

### Classification of *Streptococcus*

*Streptococcus* is a genus that groups catalase negative, gram-positive cocci. Due to single and parallel division plane, they form chains composed of two or more cells. First classifications of streptococci, in addition to cell type and biochemical properties, were

based on the type of hemolysis:  $\alpha$  – reduction of hemoglobin, resulting in greenish zone around colonies;  $\beta$  – complete lysis of erythrocytes and  $\gamma$  – lack of visible hemolysis.

The pioneering work of Rebecca Craighill Lancefield in the early 1930s (Lancefield and Todd, 1928; Lancefield, 1933) systematized the classification of streptococci based on the presence and type of surface antigen: cell wall carbohydrate or lipoteichoic acids. The Lancefield classification differentiates well the  $\beta$ -hemolytic group and subdivides it further into groups labeled with capital letters from A through W. Some streptococci that exhibit  $\alpha$  or  $\gamma$  hemolysis, for example *Streptococcus pneumoniae*, do not encode Lancefield antigen. Major human streptococcal pathogens belong to so called “pyogenic” division of  $\beta$ -hemolytic streptococci and are classified as Lancefield groups A, B, C and G. For current and historic overview of classification of all streptococci see recent publications (Hardie and Whaley, 1997; Facklam, 2002; Kohler, 2007).

### Group A *Streptococcus* – a major player

*Streptococcus pyogenes* belongs to Lancefield group A and is often called group A *Streptococcus* or simply GAS. Only a few other species such as *Streptococcus dysgalactiae* subsp. *equisimilis*, *Streptococcus*

\* Corresponding author: I. Sitkiewicz, Department of Epidemiology and Clinical Microbiology, National Medicines Institute Chelmska 30/34, 00-725 Warsaw, Poland; e-mail: [isitkiewicz@cls.edu.pl](mailto:isitkiewicz@cls.edu.pl)

*castoreus*, *Streptococcus anginosus*, *Streptococcus constellatus* subsp. *constellatus* and *Streptococcus orisratti* can in very rare cases contain group antigen A (Kohler, 2007).

*S. pyogenes* is a causative agent of common suppurative, superficial infections of mucosal surfaces, skin and skin structures. The most common examples of GAS infections are streptococcal pharyngitis/tonsillitis, scarlet fever, impetigo, erysipelas, cellulitis, abscesses of various localization and pyoderma. However, in some cases these infections can lead to post-streptococcal non-suppurative sequelae as rheumatic fever, rheumatic heart diseases and glomerulonephritis. GAS is also able to cause severe, invasive, life threatening infections as streptococcal toxic shock syndrome (STSS), necrotizing fasciitis (NF), rare cases of meningitis and pneumonia, puerperal sepsis and septicemia (for a review see (Cunningham, 2000) and references therein). Factors that predispose to invasive GAS infections are often related to immunological defects, metabolic diseases as diabetes, previous viral infections (chicken pox and influenza) and skin injuries (lesions, surgery, injecting drug use) (Lamagni *et al.*, 2008).

GAS is recognized as one of the most important bacterial pathogens. Based on WHO data (Carapetis *et al.*, 2005), it is estimated that GAS infections were in 2002 amongst the deadliest, just behind HIV, tuberculosis, malaria, pneumococcus, hepatitis B, *Haemophilus influenzae* type b, measles and rotavirus. Carapetis and co-workers (Carapetis *et al.*, 2005), based on systematic analysis of GAS epidemiological data, estimate that GAS causes 616 million new cases of pharyngitis each year and number of existing cases of pyoderma is estimated to exceed 110 millions. In addition, the number of severe cases (both invasive infections and post-streptococcal sequelae) is estimated as at least 18.1 million of existing cases, with 1.78 million new cases each year that result in over half a million deaths each year globally.

Classification of GAS is based on the type of major surface antigen: protein M (serotyping) (Cunningham, 2000). In the past, M type of the strain was determined using immunological reactions; recently most of the laboratories use sequencing of variable region of the gene encoding M protein (*emm* typing) (Johnson *et al.*, 2006). So far, over 150 M general serotypes (not including individual alleles of *emm* gene within each serotype) have been described (<http://www.cdc.gov/ncidod/biotech/strep/strepblast.htm>).

The geographical distribution of M types varies, the most prevalent types in high income countries belong to M12, M1, M28, M4 and M3. Moreover, in these countries over 90% of all strains belong to 25 serotypes while remaining 10% groups over 145 se-

rotypes (Steer *et al.*, 2009). The distribution of strains in regions as Africa or Pacific region is remarkably different and 25 most prevalent serotypes contribute only 60% of all isolated serotypes (Steer *et al.*, 2009). Serotypes isolated from invasive cases in Poland are very diverse on the molecular level but the majority of strains belong to serotype M1 (Szczyba *et al.*, 2006). Currently, there is no commercially available vaccine that could prevent GAS infection. GAS is universally sensitive to penicillin and in cases of immediate allergy to penicillin, GAS infections are usually treated with macrolides as erythromycin. However, the increasing number of macrolide resistant strains in many parts of the world including Poland (Szczyba *et al.*, 2004) can make the treatment more expensive and less efficient. Antibiotic treatment of invasive diseases is very often unsuccessful due to very rapid onset of the disease that results in death rate as high as 50%. Based on success of pneumococcal vaccine (Whitney *et al.*, 2003; Pletz *et al.*, 2008; Isaacman *et al.*, 2010) it seems that the future direction in management of GAS is elaboration of vaccine. Because infection with certain M type does not protect from infection with other M types, formulation of currently tested vaccine is based on multiple M proteins (McNeil *et al.*, 2005).

**GAS virulence factors.** Group A *Streptococcus* encodes a set of sophisticated virulence factors that are involved in multiple aspects of pathogenesis, from adhesion to intimate modulation of human immune system.

Initial contact between GAS and human host cells is achieved via interactions between bacterial adhesins and cell receptors as integrins, fibrinogen, collagen and extracellular matrix proteins (fibronectin, laminin, vitronectin) (Cunningham, 2000; Nobbs *et al.*, 2009). Each strain of GAS encodes multiple, usually highly polymorphic, surface proteins that allows complex binding of host proteins (Nobbs *et al.*, 2009).

The major adhesin and virulence factor of GAS is M protein. The protein has a very characteristic coiled coil structure with conserved cell wall anchored C terminus and hyper variable N terminal part (Cunningham, 2000; Bisno *et al.*, 2003). Sequencing of the fragment encoding first 50 aa with 10 aa signal peptide is a base of molecular *emm* typing to determine serotype (Beall *et al.*, 1996). M and M-like proteins are also involved in interaction between pathogen and immune system (Perez-Caballero *et al.*, 2004). They disrupt the classic complement cascade by binding of C4b factor and are able to disrupt the alternative cascade by binding factor H and factor H-like protein 1 (FHL-1) (Perez-Caballero *et al.*, 2004). M proteins also acts as anti-phagocytic factor by physical blocking of complement binding (Carlsson *et al.*, 2005) and is a potent

inducer of inflammation upon binding Toll-like receptor 2 (Pahlman *et al.*, 2006).

As a next step after initial contact, bacterial cells are released from the site and spread through tissues thanks to activity of multiple lytic enzymes. Host tissues are degraded by SpeB protease (Bohach *et al.*, 1988; Chiang-Ni and Wu, 2008), host protease – plasmin, activated by streptokinase produced by GAS (Bergmann and Hammerschmidt, 2007) and hyaluronidase (Hynes *et al.*, 2000).

In addition to host tissue degradation, GAS produces set of factors, including multiple proteases, involved in modulation of human immune response. SpeB protease cleaves component C3b of the complement and immunoglobulins (Collin and Olsen, 2003; Chiang-Ni and Wu, 2008); ScpA protease cleaves human C5a complement component and slows influx of inflammatory cells to the site of infection (Ji *et al.*, 1996); Mac/IdeS protease cleaves human IgG and blocks phagocytosis (Lei *et al.*, 2001; von Pawel-Rammingen *et al.*, 2002); SpyCEP protease cleaves chemokines as IL-8, granulocyte chemotactic protein 2, growth-related oncogene alpha, macrophage inflammatory protein 2-alpha and growth-related protein beta (Edwards *et al.*, 2005; Sumbly *et al.*, 2008; Kurupati *et al.*, 2010); SIC blocks C5b-C9 complement complex (Akesson *et al.*, 1996). GAS also developed strategy to evade response of innate immune system by production of DNAses that allow to escape neutrophil extracellular traps (Sumbly *et al.*, 2005a; Buchanan *et al.*, 2006).

Third large group of GAS virulence factors is composed of multiple toxins as pore forming streptolysins S and O (Nizet, 2002), and superantigens that are also factors interacting with immune system (Fraser *et al.*, 2000). Superantigens bind directly to MHC-II receptors and activate T-cells what leads to the uncontrolled release of pro-inflammatory cytokines (Fraser *et al.*, 2000).

**Selection of highly virulent clonal lineages.** One of the most important aspects of multiple M types is non-random association of M type with manifestation of the disease. For example serotype M12 predominantly causes throat infections (Luca-Harari *et al.*, 2009), while M3s are causing relatively more severe infections with higher mortality (Davies *et al.*, 1996; Daneman *et al.*, 2007), M18 serotype is correlated with rheumatic fever (Smoot *et al.*, 2002a; Smoot *et al.*, 2002b), and M28 serotype with puerperal sepsis (Green *et al.*, 2005a; Green *et al.*, 2005b).

The severity of the disease is associated with the emergence of particular lineages within certain serotypes that evolved as a result of acquisition of new genes/virulence factors that improve their fitness. The first well documented example of hyper virulent GAS clone is MIT1 lineage (Cleary *et al.*, 1992). Strain

classified as MIT1 are the most frequent isolated strains from severe invasive GAS infections (Aziz and Kotb, 2008). The unique features of MIT1 clone are related to the presence of 36 kb genomic island, prophages, acquisition of *speA2* allele encoding superantigen SpeA and *sdal* encoding DNase (Aziz *et al.*, 2005; Sumbly *et al.*, 2005b). The activity of Sda1 in particular was shown as major factor responsible for selection of highly virulent line (Walker *et al.*, 2007).

Similar selection of virulent clone can be observed in case of M3 strains (Beres *et al.*, 2002; Beres *et al.*, 2004) where the process is also driven by acquisition of phage encoded new virulence factor – phospholipase A2 named SlaA (Sitkiewicz *et al.*, 2006).

### **Group B Streptococcus** – *Streptococcus agalactiae* (GBS)

*Streptococcus agalactiae* is classified as Lancefield group B (GBS). GBS is a major bovine pathogen that is one of the causes of bovine mastitis. Bovine infections still have big economic impact, as GBS might infect over 40% of the herd and influence milk quality and quantity (Keefe *et al.*, 1997). GBS infecting humans was first isolated and described in 1930s in vaginal samples and samples from puerperal sepsis (Lancefield and Hare, 1935). Today, GBS colonizes gastrointestinal tract and genitourinary tract of about 30% of healthy individuals, without any symptoms (Badri *et al.*, 1977; Foxman *et al.*, 2006; van der Meer-Marquet *et al.*, 2008).

Until mid 1960s, human infections caused by GBS were described infrequently. However, from late 1960s to 1970s GBS became predominant pathogen in neonates and children younger than 3 months (Phares *et al.*, 2008). In children, GBS causes two major types of infections named early – and late onset disease. Early onset disease is caused by direct vertical transmission from colonized birth canal, usually develops within first few days of live and manifests as pneumonia, meningitis and/or sepsis. Fatality of early onset disease can be as high as 50% (Shet and Ferrieri, 2004). Late onset disease can develop up to third month of live and direct mode of transmission is still unknown. The late onset disease manifests as sepsis, meningitis or osteomyelitis. In addition, GBS is able to cause infections of amniotic fluid during pregnancy and cause septic abortions (Daugaard *et al.*, 1988; McDonald and Chambers, 2000). Following recommendations issued first by Centers for Disease Control in the United States (CDC, 2010) and later in many countries including Poland (Kotarski *et al.*, 2008), the number of neonatal cases dropped in USA from 1.7 per 1000 live births in 1993 to 0.34 per 1000 live births in 2005. Unfortunately, antibiotic (penicillin)

prophylaxis in pregnant individuals responsible for dramatic drop in early onset cases does not prevent late onset of the disease (Phares *et al.*, 2008).

Like GAS, GBS is able to cause invasive diseases in non-pregnant individuals. The surveillance data shows that on the contrary to decline in neonatal infections, number of adult infections, especially among people older than 65 years, is high (25.3 cases per 100 000) (Phares *et al.*, 2008). Adult infections in non-pregnant individuals are very often correlated with underlying medical conditions as diabetes mellitus, heart disease, cancer, obesity, neurologic disorders, immunosuppressive diseases *etc.* According to surveillance studies, 88% of adult cases have at least one underlying medical condition (Phares *et al.*, 2008). Unfortunately, the success of penicillin treatment in GBS infection prevention and treatment delayed the development of GBS vaccine

**GBS virulence factors.** GBS virulence factors are less described than those of GAS, but similar classes of virulence factors can be distinguish in both pathogens. GBS encodes multiple adhesins responsible for interaction with eukaryotic cells: fibrin, fibrinogen and laminin binding proteins (Maisey *et al.*, 2008); Srr (serine rich proteins) proteins that allow binding to keratin (Samen *et al.*, 2007); surface pilli-like structures (Lauer *et al.*, 2005); and large Alp/Rib family of adhesins that groups  $\alpha$ C (ACP),  $\beta$ C (BCP), epsilon/Alp1, Alp2, Alp3, and Rib proteins (Bolduc *et al.*, 2002; Baron *et al.*, 2004; Creti *et al.*, 2004). GBS also encodes pore forming toxins as hemolysin (Nizet, 2002). Production of hemolysin is correlated with the production of orange pigment protecting GBS from free radicals. Second pore forming toxin is called CAMP factor (Lang and Palmer, 2003) but its role in pathogenesis process remains unclear (Hensler *et al.*, 2008). Finally, GBS produces set of factors that are involved in modulation of immune response as ScpB protease, homolog of GAS ScpA, that cleaves C5a component of complement (Bohnsack *et al.*, 1997) and abolishes the activity of polymorphonuclear leukocytes (Takahashi *et al.*, 1995). In addition, ScpB influences adhesion by cutting host proteins (Cheng *et al.*, 2002). CspA encoded by GBS has similar sequence and function to SpyCEP (Harris *et al.*, 2003). It cleaves fibrinogen and extracellular matrix proteins, but also degrades chemokines as growth-related onco-genes alpha, beta and gamma, granulocyte chemo-tactic protein 2 and neutrophil-activating peptide 2, but on the contrary to GAS it does not cleave interleukin 8 (Bryan and Shelver, 2009).

**Clonal structure of GBS population.** Similarly to GAS, infections with GBS exhibit non random association with serotype, neonatal infections are predominantly caused by serotypes Ia and III, while infections in non pregnant adults are caused more frequently by

serotypes Ib, II and V, with small percentage of infections caused by serotype III (Shet and Ferrieri, 2004).

Multiple studies on population structure of GBS conducted worldwide show that GBS infecting and colonizing humans has a highly clonal structure (Bohnsack *et al.*, 2008; Springman *et al.*, 2009). The clonal structure was also detected in Poland (Sadowy *et al.*, 2010). Based on MLST (*multi locus sequence typing*) analysis, one particular clonal complex (CC 17) distinguished within serotype III is associated with neonatal invasive disease (Luan *et al.*, 2005; Jones *et al.*, 2006). Interestingly, analysis of population structure clearly shows the emergence of highly virulent human-associated CC17 complex from the bovine-associated CC67 (Sorensen *et al.*, 2010).

### **Groups C and G *Streptococcus* – an underestimated problem**

Groups C and G *Streptococcus* (GCS and GGS) are pathogens of animal origin, many are still classified as opportunistic pathogens. Similarly to GAS and GBS they can be carried by humans and are able to cause similar diseases as GAS, such as pharyngitis or impetigo. Human infections related to animal origin are often milk-borne and can have outbreak characteristics with severe complications as glomerulonephritis (Bordes-Benitez *et al.*, 2006).

The classification of C and G groups of streptococci has changed over the last 40 years, and often various species designations are used by different authors. Bergey's Manual of Determinative Bacteriology from 1974, lists four species of group C Streptococcus: *Streptococcus equisimilis*, *Streptococcus dysagalactiae*, *Streptococcus equi* and *Streptococcus zooepidermicus*. However, some *S. equisimilis* strains contain the group G antigen. More recently, the introduction of subspecies was proposed to better distinguishes between Lancefield groups (Vandamme *et al.*, 1996). *S. equi* was subdivided into *S. equi* subsp *equi* (GCS) and *S. equi* subsp *zooepidermicus* (GCS); and *S. dysagalactiae* was subdivided into *S. dysagalactiae* subsp *dysagalactiae* (GCS or rarely group L) and *S. dysagalactiae* subsp *equisimilis*. (GCS/GGS and rarely GAS or group L). The other species classified as GCS is *Streptococcus canis*.

Until the 1970s only rare cases of GCS/GGS invasive infections were described. For example, among 150 000 blood cultures obtained at the Mayo Clinic from 1968 to 1977, only 8 revealed signs of GCS infection (Mohr *et al.*, 1979). Multiple case reports from 1980-90s showed that most infected patients have some underlying diseases such as cardiovascular disease or malignancy, similar to GAS and GBS. In the case of GCS, the most common clinical manifestations were bacteremia and endocarditis, but also puerperal

sepsis, pleuropulmonary infections, skin and soft-tissue infection, central nervous system infection, urinary tract infection, intra-abdominal abscess, epidural abscess, and dialysis-associated infection (Quevedo *et al.*, 1987; Salata *et al.*, 1989; Bradley *et al.*, 1991; Marchandin *et al.*, 2007).

In last 20 years an increase in number of human, invasive and often fatal diseases caused by GCS and GGS has been observed and GCS and GGS are being recognized as an important and emerging pathogens (Brandt and Spellerberg, 2009). According to epidemiological data from 2003–2004, burden and death rate parallels that of GAS (XVII Lancefield International Symposium on Streptococci and Streptococcal Diseases, presentation 013.3 “Genotypic analysis of invasive, *emm*-typeable *Streptococcus dysgalactiae* subsp. *equisimilis* and *Streptococcus canis*” Sakota V. *et al.*) (Efstratiou, 1989; Efstratiou, 1997; Ikebe *et al.*, 2010).

### GAS, GBS, GCS and GGS epidemiology in Poland

Based on published epidemiological data, increasing number of severe infections caused by pyogenic streptococci is observed worldwide. In addition, selection of highly virulent clones and dangerous shift from zoonotic infections to humans should be carefully monitored. Therefore, there is constant need of surveillance to trace of sources of infections, clonality and antibiotic resistance spread.

The situation in Poland regarding invasive diseases caused by pyogenic streptococci is greatly underestimated. National Institute of Public Health (PZH) collects epidemiological data about infections in Poland ([http://www.pzh.gov.pl/oldpage/epimeld/index\\_p.html](http://www.pzh.gov.pl/oldpage/epimeld/index_p.html)). Until 2008 only cases of scarlet fever and erysipelas caused by GAS and cases of bacterial non meningococcal meningitis (presumably caused by GBS) were required by law to be reported to the authorities. According to legislation changed in 2008, the reported data includes other invasive infections caused by GAS. Cases of invasive GBS infections in non pregnant adults and infections caused by GCS and GGS are not reported. Collection of strains causing invasive infections is not required by law. However, the material is often sent to reference and academic centers for microbiological evaluation.

Knowledge about infections caused by GAS and GBS in Poland and clonal structure of populations is mostly related to the ongoing activity of two research groups (Szczyba *et al.*, 2004; Szczyba *et al.*, 2006; Skoczynska *et al.*, 2007; Brzywczy-Wloch *et al.*, 2008; Strus *et al.*, 2009a; Strus *et al.*, 2009b; Brzywczy-Wloch *et al.*, 2010; Sadowy *et al.*, 2010). The rate of infections caused by GCS and GGS in Poland is currently not recognized.

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