Case Report

Microbiology & Infectious Diseases

Invasive Group A Streptoccoacal Infection, Host Factors and Bacterial Determinants

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Case Presentation

An eleven year old previously healthy girl developed symptoms of low grade fever and malaise for 2 days. She was unable to go to school. On the 3rd day of illness, she also developed right arm, left leg and thigh pain and was unable to walk.

She was taken repeatedly by parents to ambulatory services and was told she had a viral illness. On the night of that day, the parents called 911 when she was found to have blue extremities. On arrival to a peripheral hospital, she was febrile and hypotension. Her extremities were blue with poor perfusion. The hypotension was refractory to multiple fluid boluses (90ml/kg of normal saline was given) and also to epinephrine. She developed a short period of cardiac asystole after her intubation, which recovered with 20 seconds of chest compression. Afterward, she was started on three inotropic agents in addition to antibiotics; ceftriaxone, clindamycin and vancomycin. Given her critical condition, she was transferred to the Hospital of Sick children.

Upon arrival at the Emergency Department of the Hospital of Sick Children, she looked unwell and appeared pale with diffuse edema. Her temperature was 40°C axillary, and her blood pressure continued to be low. At this time she started to develop a widespread petechial and pupuric rash on the upper and lower limbs along with scattered blisters.

Here limbs continued to be under perfused, cold and blue. Capillary refill was more than 6 seconds in the upper limbs and absent in her lower limbs. Overall, poor skin perfusion was evident in most body areas. In some limbs shearing of skin upon handling was apparent. There was evidence of arthritis in multiple joints primarily in the elbows and knees, and the abdomen was markedly distended. Multiorgan failure soon ensued with severe rhabdomyolysis, coagulopathy (DIC), cardiac dysfunction and renal failure.

A turbid fluid was obtained from multiple joints and was processed for microbiological identification to further direct her therapy. The clinical and the available laboratory features were consistent with sepsis and toxic shock syndrome with sever purpura fulminans. At this stage, meropenem was added to vancomycin and clindamycin.

Within few hours of her presentation, severe compartment syndrome developed necessitating an urgent fasciotomies to all limbs. Blood culture and synovial aspirates showed a growth of group A streptococcus, therefore, antibiotics were discontinued and penicillin was started. While she continued to receive intensive care, her extremities continued to show evidence of progressive ischemia. She developed irreversible tissues damage. Finally, decision was made to amputate her right lower limb and left upper limb. Yet, she continued to develop diffuse ischemic ulcers and wounds in her remaining limbs.

Introduction

Group A Streptococcus (GAS), also known as Streptococcus pyogenes, causes a broad range of infections and complications. These range from superficial infections such as pharyngitis or impetigo to life-threatening conditions such as bacteremia, necrotizing fasciitis (NF), and toxic-shock syndrome (TSS). GAS is also associated with sequelae including rheumatic fever and post-streptococcal glomerulonephritis.

There is a general increase in the incidence of invasive Group A Streptococcus (iGAS) disease worldwide. Data from Public Health of Ontario in Canada showed a significant increase in the reported cases from 2005 to 2014 from 3.1 cases per 100,000 population in 2005 to of 5.4 cases per 100,000 population in 2014. Overall, incidence rates of iGAS in Ontario have been similar to the Canadian incidence rates over this time period [1] (Figure 1A).

The incidence of iGAS disease tends to follow a seasonal pattern, with higher case counts in the winter and early spring months. The overall incidence rate is higher in males than females.

iGAS is relatively high among infants less than one year of age. In the same report, incidence rate in this age group was 10.6 cases per 100,000 population in 2014, lowest among those between 10 and 19 years of age; and then increases steadily with age. The majority of iGAS cases (79.2%) were reported among those 30 years of age and older [1] (Figure 1B). Similar data has been reported in USA [2] (Table 1).

Determinants and pathogenesis of invasive GAS disease

The pathogenic mechanisms underlying invasive GAS are poorly understood.

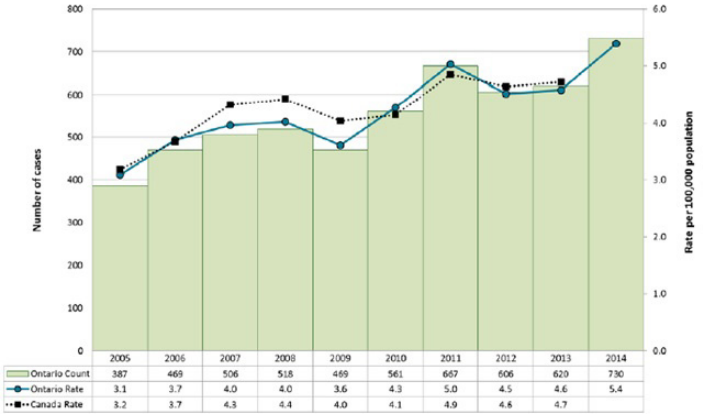

Figure 1A: Incidence of GAS disease, invasive (iGAS): Ontario and Canada, 2005-14.

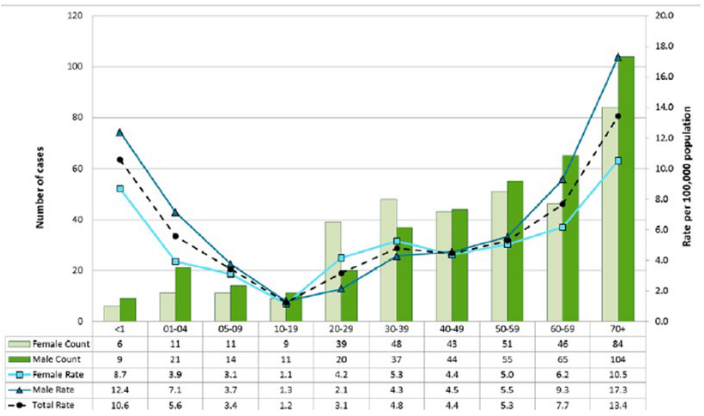

Figure 1B: Incidence of GAS disease, invasive (iGAS) by age and sex: Ontario, 2014B.
Adopted from Public Health of Ontario, Reportable Disease Trends in Ontario, 2014.

A highly complex interaction between the human defense mechanisms and specific virulence factors of the organism does exist. The increased severity of invasive GAS infections has resulted in a search for new virulence factors and host determinants that may amplify the potential of this organism for producing disease.

Age (years)	Cases No.	Cases (Rate*)	Deaths No.	Deaths (Rate*)
< 1	18	(4.4)	2	(0.49)
1	17	(4.2)	0	(0.00)
2-4	38	(3.1)	0	(0.00)
5-17	83	(1.5)	3	(0.05)
18-34	226	(2.8)	9	(0.11)
35-49	319	(4.7)	26	(0.39)
50-64	455	(6.8)	49	(0.73)
65-74	233	(8.5)	24	(0.88)
75-84	136	(10.4)	24	(1.83)
≥ 85	97	(15.6)	24	(3.85)
Total	1,622	(4.8)	161	(0.48)

* Per 100,000 population for ABCs areas

Table 1: Incidence of GAS disease, invasive (iGAS) in USA by age.
Adopted from Centers for Disease Control and Prevention. 2015. Active Bacterial Core Surveillance Report, Emerging Infections ProgramNetwork, Group A Streptococcus-2015.

Bacterial Determinants

Virulence factors

A number of different constituents and products of group A Streptococcus have been identified as virulence factors.

This article will focus on the M protein and the pyrogenic exotoxins.

M protein

M protein is an important cell-surface protein and one of the major virulence and immunological determinants of GAS [3] (Figure 2). The main function of the M protein is to protect the organism from phagocytosis by polymorphonuclear leukocytes (PMNs) [4,5]. More than 80 different M protein types have been described and added to the current typing protocols. The number of nontypeable M proteins is increasing and new M types are constantly emerging [4]. M protein is encoded by emm gene, a coiled-coil gene inside the bacterial cell consisting of four regions of repeating amino acids (A to D), this gene expresses a high level of heterogeneity [4].

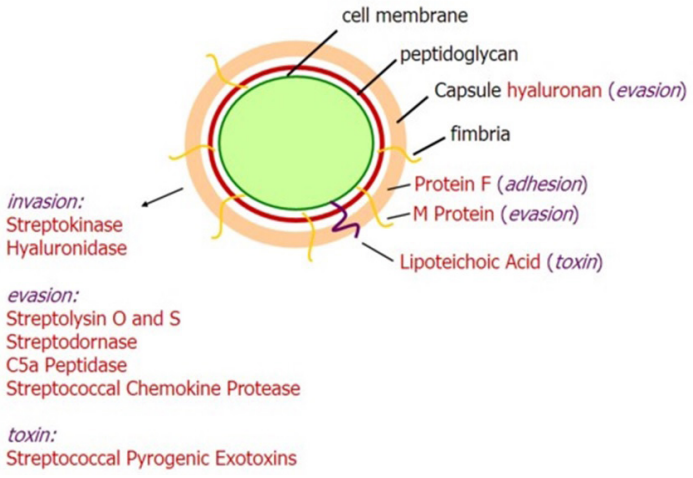

Figure 2: GAS virulence factors.

Emm sequence typing is the most widely used method for defining (GAS) strains [4] which assists in determining potential linkages among cases and identifying new strains that may be associated with more severe illness.

Pyrogenic exotoxins

These are family of proteins that function immunologically as superantigens (SAgs). They are chromosomally encoded and many of them are phage mediated [6]. Several streptococcal pyrogenic exotoxins (spe) have been identified; the three most important exotoxins are type A, B, and C. These three types of pyrogenic exotoxins have the ability to induce lymphocyte blastogenesis, potentiate endotoxin-induced shock, induce fever, and suppress antibody synthesis [4,7]. It was observed that contemporary strains carried (spe A) genes were subtly different from those carried by historical strains [6].

Strains capable of producing speA and speB have been associated with severe cases of scarlet fever and streptococcal toxic shock syndrome [4,8,9]. Interestingly, certain SAg gene profiles were closely associated with the particular emm type [10].

Molecular characterizations of invasive GAS

There is no single invasive clone responsible for severe disease [11]. Different studies have been done in different parts of the world to characterize the invasive clones of GAS. In most of the studies, a number of different clones have been identified in variable frequency. In most of the time, the invasive diseases have been attributed to the isolated strains. Surprisingly, there is evidence that the identified emm types undergo some changes with time, and new clonal properties are continuously emerging. The extent to which this might contribute to the severity of GAS is not completely understood.

Nevertheless, a more consistent pattern has been observed in most of the available studies and reports. In one report of 5400 cases of invasive GAS infection, emm types 1, 3, and 12 were independent risk factors associated with mortality [4,12].Moreover, the association between M1 and the production of exotoxin A has been well established [11]. The emergence of highly virulent and successful Streptococcus pyogene clones has been attributed to their modified genetic profile i.e. their emm type and SAgs profile. We here present some pooled data from Canada and USA.

Canada

In their annual summary, the National Laboratory Surveillance of Invasive Streptococcal Disease in Canada, 2015, reported that emm1 continues to be the most prevalent in Canada, decreasing from 27.6% in 2014 to 18.0% in 2015. This was followed by emm 12 and emm 3 (8%). As reported emm 3 has reported a significant increase from 2.2% in 2014 to 8.0% in 2015. Other reported emm type was emm81 (7.4%). In contrast, emm89 which has been predominant in the previous years, has reported a decline from 9.6% in 2014 to 6.6% in 2015 indicating the ongoing shift of serotypes with time [13] (Figure 3).

USA

In the Active Bacterial Core Surveillance (ABCs) Report, Emerging Infections Program Network, Group A Streptococcus-2015. Published by the Centers for Disease Control and Prevention, 2015 (CDC), the three most common emm types have consistently been emm 1, 89 and 12 [2] (Table 2).

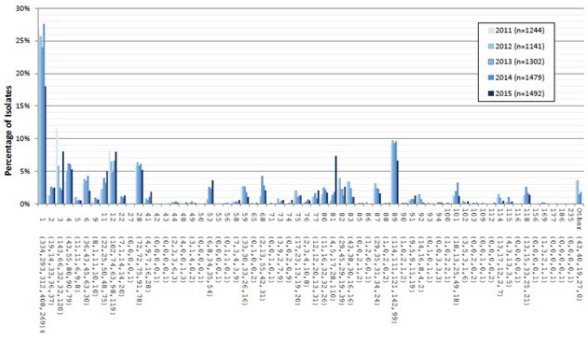

Figure 3: (iGAS) emm types in all combined age groups, 2011 – 2015. Adopted from National Laboratory Surveillance of Invasive Streptococcal Disease in Canada - Annual Summary 2015.

ABCs Area	Most common *emm* types*	% of area isolates
California	82, 1, 92, 89, 49, 12	68.0
Colorado	1, 82, 12, 89, 92, 28	76.6
Connecticut	1, 11, 89, 28, 12, 81	70.2
Georgia	1, 89, 12, 28	64.5
Maryland	1, 89, 3, 4, 75, 77, 28	72.9
Minnesota	1, 89, 12, 28, 4, 3, 77	75.5
New Mexico	59, 89, 1, 12	67.1
New York	1, 89, 12, 28	70.8
Oregon	1, 92, 89, 12, 83, 28, 82	67.0
Tennessee	1, 82, 77, 89, 28	71.7
Total	1, 89, 12, 82, 28	57.1

*Requires ≥3 or more isolates and ≥ 5% of isolates typed

Table 2: GAS emm types in different resgioens in USA , 2015 Adopted from CDC. 2015. ABC Surveillance Report, Emerging Infections Program Network, Group A *Streptococcus*-2015.

Geographical distribution

It is believed that the distribution of M types may not be uniform in all regions [6,14,15]. Andrew C et al. Conducted a systematic review in 2009 to identify the global distribution of GAS emm types, and assessed the possibility of implications of the study findings for the development of vaccines to the prevalent Strains [3]. In their study Andrew C et al. have divided the world regions in to high–income countries (Europe, North America, Australia, New Zealand, and Japan, Hong Kong), and low in-come countries, Africa and Pacific (including the Indigenous Australians) [3].

On a global scale, the overwhelming burden of GAS disease is found in low-income countries, where more than 95% of the estimated of invasive GAS disease occur and more than 95% of the estimated deaths due to rheumatic heart disease occur [3].

In high-income countries, 25 emm types accounted for more than 90 % of all isolates. There were obvious similarities in emm type distribution between those regions, emm1 and emm12 were the two most common emm types in high-income countries, Asia, and Latin America, and the second and third most common emm types in the Middle East, accounting for between 26.1% and 40.0% of all isolates in these regions.

By contrast In Africa and the Pacific region a higher diversity of emm types was reported, no dominant emm types have been noted, 26 emm types only accounted for 62.5% and 61.8% of all isolates, respectively . Moreover, many of the common emm types in other parts of the world were less common (including emm1, 4, 6, and 12) [3]. emm1 was ranked fifth in Africa and 13th in the Pacific region.emm12 did not appear in the 25 most common sequence types in the Pacific region [3].

The author concluded that epidemiology of GAS infections in Africa and the Pacific region seems to be different from that in other regions. He also concluded that this information has an implication for the development of GAS vaccines. On the basis of the available data, current formulation of the experimental multivalent emm vaccine would provide good coverage in high-income countries, particularly USA, Canada, and Europe, but poor coverage in Africa and the Pacific, and only average coverage in Asia and the Middle East [3].

Host determinants

Multiple host factors appear to play roles in the occurrence of invasive GAS disease, an underlying illness like diabetes mellitus, and cancer were the most common conditions predisposing to invasive GAS infection. Previous skin lesions in particular chickenpox are an independent risk factor for an invasive disease [11].

Other risk factors include: alcoholism, drug abuse, large family and living condition. Living in relatively crowded conditions may facilitate the spread of the organism [15].

Family with more than one child at home has a higher risk of sever disease. This fact can be explained by higher incidence of the asymptomatic carrier among children population. The reasons one person will remain asymptomatic carrier while another will develop severe and sometimes lethal disease is not fully understood. One of the major host factors that thought to play a significant part in determining the outcome of infection by toxigenic strains of S. pyogenes, is the host predisposition to the toxic effects of superantigens [6].

SAgs are classically presented to the host T-Cell by HLA class II, a process that ultimately leads to a T-cell proliferation and cytokines production. The magnitude of T cell response to SAgs and hence the outcome of the disease clinically is influenced by the HLA class II polymorphisms i.e. at a subisotype level [6]. Kotb et al. found that specific human leukocyte antigen (HLA) class II haplotypes conferred strong protection from severe systemic disease, whereas others increased the risk of severe disease. Patients with the DRB1*1501/DQB1*0602 haplotype mounted significantly reduced responses and were less likely to develop severe systemic disease [16]. In contrast, T cell response was greater in response to (spe A) presented by HLA-DQA1*01 than by HLA-DQA1*03 or *05. [6].

Further studies of GAS epidemiology and pathogenesis are required to determine the reasons for acquiring severe invasive GAS diseases in specific hosts. This knowledge will allow a more accurate definition of the risk factors for these infections and may lead to development of effective intervention strategies [11].

Future Vaccine

Typing of emm genes has important implications for vaccine development. Information regarding the geographic distribution of M types will assist in directing vaccine development to prevalent strains. Several vaccine candidates have shown promises; however, only one vaccine, a 26-valent M-protein-based vaccine, has recently reached clinical trials [3]. The emm serotypes in the proposed 26-valent vaccine accounted for 79 percent of isolates, for 85 and 88 percent of isolates implicated in necrotizing fasciitis and streptococcal toxic shock syndrome, respectively, and for 79 percent of deaths [9].

Serotypes for this vaccine were chosen if they were known to be common causes of invasive GAS disease or uncomplicated pharyngitis in the USA, or if they were associated with rheumatic fever in classic studies from the USA in the mid-20th century [3]. The authors calculated that the proposed vaccine could prevent up to 50 and 63 percent of invasive GAS infections among [9,17-19].

Conclusion

Clonal properties like some emm types or SAg genes were associated with different disease presentations. Based on the available data emm 1, 3, and 12 seem to be isolated more frequently in cases of invasive GAS diseases. Toxigenic strains capable of producing speA and speB have been associated with more sever diseases. Other, yet unidentified factors may also play an important role [14]. Host immunogenetics and environmental factors also influence the outcome of invasive streptococcal infection. The exact host –organism interaction is not fully understood and remains an area of extensive research. Further molecular and epidemiological data are required to postulate a host-organism relationship.

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