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Invasive Group A Streptococcal (GAS) Disease in Virginia

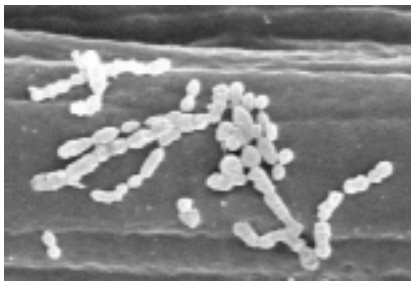
Introduction

Streptococci are spherical or ovoid, Gram-positive, nonmotile bacteria that are grouped based on antigenic differences in their cell wall carbohydrates (Lancefield groups). While some streptococci form part of the normal flora of humans, *Streptococcus pyogenes* [Group A streptococci (GAS)] is an important bacterial pathogen of humans.[1] This article reviews some of the clinical characteristics and the descriptive epidemiology of GAS disease as well as some of the interventions that have been developed to reduce the impact of these infections.

GAS Infections

Diseases caused by GAS can be classified as non-invasive or invasive. The most common non-invasive GAS infections include pharyngitis ("strep throat"), scarlet fever, and superficial skin infections (e.g., impetigo and cellulitis/erysipelas).[2]

Invasive GAS infections occur less frequently and result when bacteria enter normally sterile sites (e.g., blood, pleural fluid, peritoneal fluid, spinal fluid, joint fluid), usually via breaks in the skin. *S. pyogenes* owes its success as a pathogen to its ability to colonize and multiply rapidly, as well as its wide array of virulence factors that facilitate invasion, inhibit phagocytosis, and provide immunologic disguise. The organism can also produce exotoxins, or 'superantigens', that evoke a massive but detrimental immune response.[1] In particular, M-1 and M-3 serotypes of GAS are more likely to cause serious invasive infections such as:



- bacteremia;
- myositis;
- necrotizing fasciitis (NF);
- pneumonia;
- postpartum sepsis (puerperal fever); and,
- streptococcal toxic shock syndrome (STSS).[1]

The overall case-fatality rate (CFR) for invasive GAS infections is approximately 15%;[3] CFRs for some syndromes (e.g., STSS) can be as high as 30-80%.[4]

In addition, serious, non-suppurative illness can occur one to three weeks after GAS infection. For example, acute rheumatic fever (ARF) is a sequela of GAS pharyngeal infections and can result in permanent damage to the heart valves. Although the pathogenesis of ARF is unknown, an abnormal or enhanced immune response seems essential. Unfortunately, since streptococcal pharyngitis infections may re-occur, persons with a history of rheumatic fever require life-long antibiotic prophylaxis to prevent recurrence of ARF.[5]

Another sequela of pharyngeal GAS infections, as well as of GAS infections of the skin, is acute glomerulonephritis (AGN) resulting from deposition of antigen-antibody-complement complexes on the basement membrane of kidney glomeruli. The antigen may be streptococcal in origin, or it may be host tissue with antigenic determinants similar to those of streptococci (i.e., with cross-reactive epitopes for endocardium, vascular smooth muscle, etc.). Fortunately, recurrences of AGN are uncommon, and prophylaxis following an initial attack is unnecessary.[5]

Risk Factors for Invasive GAS

Asymptomatic carriage of *S. pyogenes* in the respiratory tract has been shown to occur, and may be as high as 15-20% in healthy children. The organism is transmitted mainly through person-to-person contact via droplets of saliva or nasal secretions.[1] Although healthy people may develop invasive GAS infection, chronic illnesses such as cancer, diabetes, immunosuppression, or heart, lung or kidney disease place people at higher risk. Conditions that increase the risk of developing necrotizing fasciitis include cuts, burns, penetrating injuries, surgical procedures, chickenpox, and blunt trauma. While there have been no reports of casual contacts of a person with invasive GAS disease developing *S. pyogenes* infections, household contacts, especially those with underlying chronic illnesses, have occasionally developed severe disease. For GAS, a household contact is defined as a person who spent a total of 24 hours or more in the same household as the index patient during the seven days prior to the onset of the case patient's symptoms.[6] It is important to distinguish household contacts from other close contacts such as

residents of long term care facilities and children in day-care centers and schools since the risk among household contacts is higher.

Epidemiology of Group A Streptococcal Disease

Nationwide

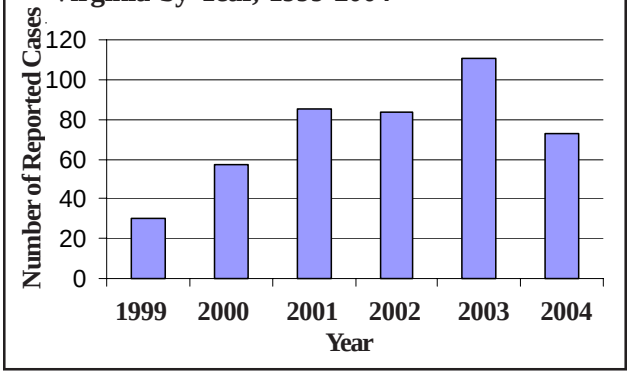
Invasive GAS infections are relatively rare. Based on 2002 data, the Centers for Disease Control and Prevention (CDC) estimates the overall rate of invasive GAS in the U.S. to be 3.2 cases per 100,000 persons. An estimated 9,000 cases of invasive disease occurred in 2002, with 12% of the cases occurring as STSS and NF. Disease incidence was highest among children less than one year of age (6.9/100,000 persons) and adults greater than 65 years of age (8.9/100,000 persons). Currently, 10 states (including Virginia) actively conduct population-based surveillance for GAS.[6] As a result of this surveillance, knowledge of the impact of GAS infections has been improving.

Virginia

The Virginia Board of Health's *Regulations for Disease Reporting and Control* list invasive Group A streptococcal infections as a notifiable condition (12 VAC 5-90-80). Furthermore, initial isolates from invasive Group A streptococcal infections should be submitted to the Virginia Division of Consolidated Laboratory Services (DCLS). For this article, cases of GAS infection reported to local health departments by healthcare providers and directors of healthcare facilities and laboratories in Virginia from 1999 through 2004 were reviewed. A case of invasive GAS disease was defined as: 1) the isolation of GAS from a normally sterile site including, but not limited to, blood and cerebrospinal fluid; 2) streptococcal toxic shock syndrome (STSS); or, 3) a streptococcal infection with necrotizing fasciitis (NF). Reports of GAS isolated from nonsterile sites, such as the pharynx or skin, were not counted as cases.

A descriptive analysis of cases was performed using *Epi Info 6* and *Microsoft Excel (2000)*. Population estimates for each year in Virginia were obtained from the U.S. Census Bureau.

Figure 1. Invasive GAS Cases Reported in Virginia by Year, 1999-2004



Since 1999, when invasive GAS disease became a notifiable condition in Virginia, 440 cases of invasive GAS have been reported to the Virginia Department of Health (Figure 1). The average annual number of reported cases of invasive GAS disease for the six-year period was 73, with a low of 30 (0.4/100,000 persons) in 1999 and a high of 111 in 2003 (1.5/100,000 persons). The overall crude annual incidence for the six-year period was 1.0/100,000 persons. However, the number of cases reported in 1999 was relatively low, likely related to an incomplete reporting year.

The incidence of invasive GAS infection by age-group was bimodal, with the greatest risk occurring in persons less than one year of age (2.08/100,000 persons); the risk in persons fifty years of age and older (2.05/100,000 persons) was similar (Figure 2). Persons 10-19 years of age had the lowest incidence of invasive GAS infection (0.27/100,000 persons).

The average annual incidence of invasive GAS among Blacks was 1.1/100,000 persons and among Whites was 0.9/100,000 persons (risk difference statistically significant at $p<0.05$). Overall, males accounted for 50.1% of the cases.

Invasive GAS disease also followed a seasonal trend. The largest proportion of cases of GAS occurred in the winter and spring months during the six-year period (Figure 3).

The majority of invasive GAS cases was reported from the Northwest region of Virginia (119 cases, 1.9/100,000 persons) while the lowest number of cases was reported from the Northern region (16 cases, 0.1/100,000 persons).

Over the six-year period the overall case-fatality ratio (CFR) for invasive GAS infections in Virginia was 7.5%, representing 33 deaths. The largest number of deaths from invasive GAS infection occurred in 2001 (11 deaths) compared to one death in 1999. Most deaths occurred in persons older than 50 years of age (19 deaths); however, persons one to nine years of age had a higher CFR (11.6%), followed by those less than one year of age (8.3%). The lowest CFR was observed in persons 30-39 years of age (4.2%).

Public Health Response

Reported Cases

Reporting cases of invasive Group A streptococcal infections to the health department, including details on the site of infection, is an important step in controlling this disease since it enables local health department staff to investigate possible sources of the infection and interrupt further transmission. The investigation involves contacting the patient and/or the patient's family to obtain information on risk factors and underlying conditions, as well as to identify anyone in close contact with the patient who has an underlying chronic condition that could increase the risk of developing an invasive GAS infection. As necessary, the patient also receives health education with an emphasis on precautions for preventing spread of the organism (e.g., frequent handwashing, appropriate wound care).

Figure 2. Incidence of Invasive GAS Cases in Virginia by Age Group, 1999-2004

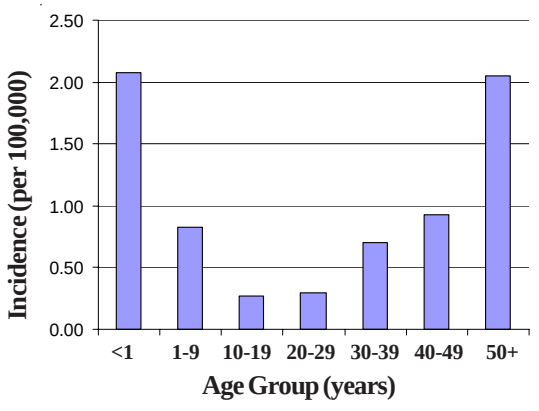
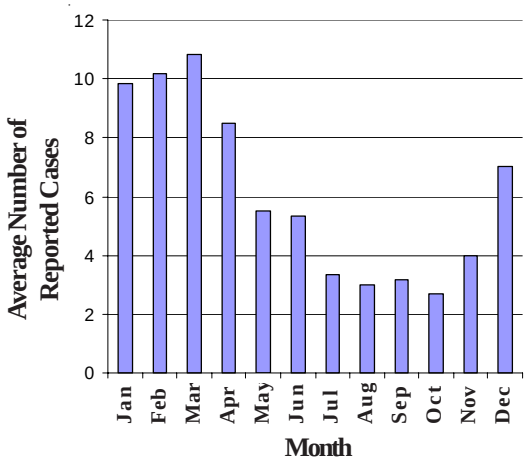


Figure 3. Average Invasive GAS Cases Reported in Virginia by Month, 1999-2004



Management of Household Contacts

All household contacts of cases should be under surveillance for clinical manifestations of pharyngeal and invasive GAS infection (e.g., fever, sore throat and localized muscle pain). Studies indicate that a heightened suspicion of subsequent GAS disease (e.g., pharyngitis, impetigo, scarlet fever, cellulites, pyoderma) should be maintained for 30 days after the diagnosis is made in the index case.[6]

No controlled trials have evaluated the effectiveness of chemoprophylaxis in preventing invasive GAS disease among household contacts of persons with invasive GAS infections. Since overly-broad use of antimicrobial therapy increases the risk of undesirable effects (e.g., adverse drug reactions, antimicrobial resistance), routine chemoprophylaxis for all household contacts is not recommended. Instead, the CDC recommends that healthcare providers should target chemoprophylaxis to household members of cases who are greater than 64 years of age or those who are at increased risk for sporadic invasive GAS infection. However, since the source of GAS infection in a household is not necessarily the person with invasive GAS infection (i.e., asymptomatic carriers) healthcare providers may choose to prescribe chemoprophylaxis for all members of the household if there is at least one person in the household who is at high risk.[6] As a result, Virginia's guidelines for the control of GAS infections encourage chemoprophylaxis for all household members if there is anyone in the household at risk for developing invasive GAS disease. The routine use of cultures to identify colonized household members is not recommended.[6]

Recommended Regimens for Chemoprophylaxis Against GAS Infection

The CDC recommends any one of the following regimens for chemoprophylaxis of asymptomatic carriers:

1) Benzathine penicillin G (BPG) plus rifampin - BPG: 600,000 U IM in one dose for patients weighing <27 kg or 1,200,000 U IM in one dose for patients weighing ≥27 kg; Rifampin: 20 mg/kg/day orally (max. daily dose: 600 mg) in two divided doses for four days. This regimen is not recommended for pregnant women due to the teratogenic effect of rifampin in laboratory animals. Alternative contraceptive measures should be used while on rifampin due to the effect rifampin may have on the efficacy of oral contraceptives.
2) Clindamycin: 20 mg/kg/day orally (max. daily dose: 900 mg) in three divided doses for 10 days.
3) Azithromycin: 12 mg/kg/day orally (max. daily dose: 500mg) in a single dose for five days.[6]

It is important to note that all regimens are acceptable for nonpregnant persons who are not allergic to penicillin. Orally administered clindamycin is just as effective at eradicating pharyngeal carriage of GAS as BPG plus rifampin; orally administered azithromycin is 95% effective at eradicating pharyngeal carriage of GAS based on studies in school-aged children.[6]

Clusters of GAS

If two or more cases of GAS are identified within a definable population during a six-month period, there may have been a common source of infection (e.g., a healthcare worker in a facility). If a cluster of cases is suspected, the local health department must be informed. Health department staff may be of assistance in investigating and controlling a potential outbreak and facilitating delivery of clinical isolates to DCLS for further characterization (e.g., pulsed field gel electrophoresis [PFGE] DNA fingerprinting). Identification of two or more cases infected with bacterial strains indistinguishable by PFGE should lead to enhanced surveillance and to an investigation of possible epidemiological links between cases. Screening cultures (anus, skin lesions, throat, and vagina) may be indicated to identify sources; chemoprophylaxis options may be considered. Efforts to reinforce infection control methods (e.g., standard precautions such as handwashing/alcohol-based hand rubs, glove use) may also be required.[6]

Conclusions

Invasive Group A streptococcal infections continue to be a relatively rare but serious health problem in Virginia. Timely reporting to the local health department of any suspected or known cases of invasive GAS infections can improve the public health response and help to reduce the morbidity and mortality from these infections in Virginia.

For more information about this condition, go to the VDH website at www.vdh.virginia.gov/epi/strepf.htm.

Submitted by: Blythe Allen-Dickerson, MD, MPH, Preventive Medicine Resident

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Cases of Selected Notifiable Diseases Reported in Virginia*

Total Cases Reported, February 2005

Disease	State	Regions NW	N	SW	C	E	Total Cases Reported Statewide, January - February This Year	Last Year	5 Yr Avg
AIDS	40	0	10	1	9	20	108	63	99
Campylobacteriosis	26	4	7	8	0	7	35	51	33
E. coli O157:H7	0	0	0	0	0	0	0	0	2
Giardiasis	32	3	9	9	8	3	62	42	37
Gonorrhea	664	51	62	101	200	250	1,427	1,335	1,431
Hepatitis, Viral									
A	7	3	1	1	0	2	8	8	14
B, acute	18	0	1	6	8	3	33	12	16
C, acute	0	0	0	0	0	0	0	3	1
HIV Infection	51	2	10	4	13	22	100	104	113
Lead in Children†	26	3	6	6	8	3	44	67	60
Legionellosis	3	0	1	1	1	0	3	3	2
Lyme Disease	1	0	1	0	0	0	2	0	1
Measles	0	0	0	0	0	0	0	0	0
Meningococcal Infection	1	1	0	0	0	0	2	2	6
Mumps	0	0	0	0	0	0	0	0	0
Pertussis	25	3	7	8	3	4	27	12	6
Rabies in Animals	21	7	5	4	0	5	46	66	61
Rocky Mountain Spotted Fever	0	0	0	0	0	0	0	0	0
Rubella	0	0	0	0	0	0	0	0	0
Salmonellosis	40	8	11	5	6	10	72	91	68
Shigellosis	3	0	3	0	0	0	10	14	46
Syphilis, Early§	14	1	4	0	2	7	25	14	32
Tuberculosis	22	2	12	0	0	8	24	14	18

Localities Reporting Animal Rabies This Month: Alexandria 1 raccoon; Arlington 1 raccoon; Bedford 1 cat; Caroline 1 fox; Culpeper 1 fox; Fairfax 1 raccoon; Isle of Wight 1 skunk; James City 1 raccoon; King William 1 raccoon; Northampton 1 raccoon; Northumberland 1 dog; Page 1 cat; Patrick 1 raccoon; Prince William 1 raccoon, 1 skunk; Rappahannock 1 horse; Rockingham 1 cow, 1 raccoon, 1 skunk; Wythe 1 cow, 1 skunk.
Toxic Substance-related Illnesses: Adult Lead Exposure 4; Asbestosis 2; Mercury Exposure 1; Mesothelioma 1; Pneumoconiosis 7.
*Data for 2005 are provisional. †Elevated blood lead levels ≥10µg/dL. §Includes primary, secondary, and early latent.

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