

GROUP A STREPTOCOCCAL (GAS) INFECTION

INVASIVE GROUP A STREPTOCOCCAL DISEASE

Revised 9/9/2011

Group A streptococci (strep) bacteria are closely associated with the upper respiratory tract which is the usual portal of entry. Group A strep are considered to be part of the colonizing flora of the upper respiratory tract. It is estimated that between 5%-15% of normal individuals harbor the bacterium, usually in the respiratory tract, without signs of disease.

Microbiology

Streptococcus pyogenes (Group A streptococcus) is a Gram-positive, nonmotile, nonsporeforming coccus that occurs in chains or in pairs of cells. Individual cells are round-to-ovoid cocci, 0.6-1.0 micrometer in diameter. Streptococci divide in one plane and thus occur in pairs or (especially in liquid media or clinical material) in chains of varying lengths. The metabolism of *S. pyogenes* is fermentative; the organism is a catalase-negative aerotolerant anaerobe (facultative anaerobe), and requires enriched medium containing blood in order to grow. Group A streptococci typically have a capsule composed of hyaluronic acid and exhibit beta (clear) hemolysis on blood agar.

Streptococcus pyogenes produces a wide array of **virulence factors** and a very large number of diseases. Virulence factors of Group A streptococci include:

- (1) M protein, fibronectin-binding protein (Protein F) and lipoteichoic acid for adherence;
- (2) hyaluronic acid capsule as an immunological disguise and to inhibit phagocytosis; M-protein to inhibit phagocytosis
- (3) invasins such as streptokinase, streptodornase (DNase B), hyaluronidase, and streptolysins;
- (4) exotoxins, such as pyrogenic (erythrogenic) toxin which causes the rash of scarlet fever and systemic toxic shock syndrome.

The **cell surface structure of Group A streptococci** is among the most studied of any bacteria. The cell wall is composed of repeating units of N-acetylglucosamine and N-acetylmuramic acid, the standard peptidoglycan. Historically, the definitive identification of streptococci has rested on the serologic reactivity of "cell wall" polysaccharide antigens as originally described by Rebecca Lancefield. Eighteen group-specific antigens (Lancefield groups) were established. The Group A polysaccharide is a polymer of N-acetylglucosamine and rhamnose. Some group antigens are shared by more than one species. This polysaccharide is also called the C-substance or group carbohydrate antigen.

Group polysaccharide: They have a tough cell wall associated with polysaccharide (carbohydrate) group antigen. The Lancefield serotypes A-H and K-U are based on a cell wall carbohydrate. Typing is usually done only for groups A, B, C and G for which there are simple agglutinating antibodies.

Capsule of hyaluronic acid	
Cell	Cell wall protein antigen: M, T and R
Wall	Group specific carbohydrate = Polysaccharide antigen: Lancefield A to U
	Mucopeptide
Cytoplasmic membrane	
Cytoplasm	

M protein: Some GAS produce a lot of M protein, the colonies are **mat**, they are virulent and fairly insusceptible to phagocytosis by human leukocytes. The M protein is a virulence factor that impairs phagocytosis. Immunity to infection with GAS is related to the presence of anti-M antibodies. There are more than 80 types of M protein. A person may have repeated infections with GAS provided they are from different M types. M proteins have also been found on group G, and group C has a protein homologous to the M protein.

A component of the cell wall of selected type M induces antibodies that react with cardiac muscle tissue and may play a role in the genesis of rheumatic fever.

Some GAS produce relatively little M protein, the colonies are **glossy**, they are much less virulent.

T & R proteins: have no relation with virulence. T protein has been used in epidemiologic investigations since there are specific antibodies.

Toxins & Enzymes

GAS produce more than 20 extracellular products:

- **Streptokinase** (Fibrinolysin): produced by all β hemolytic strains. It transforms human plasminogen into plasmin, a potent proteolytic enzyme that digests fibrin (blood clots). Streptokinase is administered IV for treatment of coronary artery thrombosis (heart attack).
- **Streptodornase:** a deoxyribonuclease that uncoils (depolymerases) DNA molecules.
- **Hyaluronidase:** splits hyaluronic acid, an important component of connective tissue. It helps in the spread of GAS through the tissues. . Hyaluronidases are antigenic and specific.
- **Pyrogenic exotoxins:** There are 3 pyrogenic (capable of inducing fever) exotoxins.
- **Exotoxin A** is produced by GAS carrying a lysogenic phage
- **Exotoxin B** with unclear role
- **Exotoxin C** may contribute to TSS

The exotoxins have been associated with streptococcal toxic shock syndrome and scarlet fever. Most GAS associated with TSS either produce exotoxin A or have the gene for exotoxin A while only 15% of GAS from other patients have exotoxin A gene.

- **Diphosphopyridine nucleotidase:** provides GAS the ability to kill leukocytes
- **Hemolysins:** Complete destruction of hemoglobin is called hemolysis β , incomplete lysis is α hemolysis.
- **Streptolysin:** of interest because of the antibody induced by it. Anti-streptolysin O can be titrated, a high titer meaning a recent infection.
- **Streptolysin S:** is elaborated in the presence of serum (S), responsible for the hemolysis seen on agar plates. It is not antigenic.

Epidemiology

Transmission is by large droplets. Acutely ill patients are the major source of infection while chronic carriers play a minor role. However, there is a large reservoir of chronic carriers which become carriers after infection. Carriers usually have relatively small bacterial loads. They are at little risk for acute disease or

sequelae and are probably a common source of infection for others. The distinction between colonization and infection is unclear for strep A.

Transmission requires a large dose; approximately 100 microorganisms are needed to infect an adult by swabbing the tonsils. Streptococci may survive in dust and blankets but they seem to rapidly lose their infectivity in the environment. Transmission by fomites or from pets appears to be unlikely.

Fewer strains colonize the skin and cause skin infections (impetigo).

School-aged children were most often responsible for introducing a GAS strain into a household. Mothers were more likely to subsequently acquire the bacteria than fathers. Exposure to children and duration of exposure to a GAS-infected person influences the transmission of GAS within households. Infections among children may represent an important reservoir for infections in adults.

Group A strep disease is endemic throughout the world occurring throughout the year with some seasonal fluctuations. Localized outbreaks are observed in closed populations: newborn nurseries, nursing homes, day-care centers, military barracks.

Disease Burden: GAS infection can lead to dramatic, rapidly-progressive syndromes such as necrotizing fasciitis and streptococcal toxic shock syndrome (STSS). The Centers for Disease Prevention and Control (CDC) estimates that the national incidence of invasive GAS disease is 3.3 cases per 100,000 persons annually; this translates to approximately 150 cases in Louisiana each year, resulting in approximately 20 deaths. The overall case-fatality rate of invasive GAS is estimated to be from 10% to 15%; the case-fatality rate for STSS can exceed 60%. Most of these infections are community-acquired.

Strep A pharyngitis is one of the most common acute bacterial infections. With the advent of penicillin, the incidence of rheumatic fever, scarlet fever and other related diseases decreased.

Scarlet fever was responsible for 2000 to 6000 deaths annually in the USA until the 1940s (death rates of 5 to 12 per 100,000). Its incidence slowly declined from 1910 to 1940, well before the introduction of antibiotics. After the introduction of antibiotics, incidence and mortality due to scarlet fever declined sharply.

Acute Rheumatic Fever (ARF): In the 1940s, the yearly incidence of rheumatic fever in the U.S. was approximately 40 per 100,000. Forty years later in the 1980s, incidence was down to 0.2 per 100,000. The decline of ARF is largely due to 1) primary prevention with penicillin treatment of GAS infections and 2) prevention of secondary attacks with prolonged penicillin prophylaxis in patients who had a previous attack.

In the late 1980s there was a resurgence of ARF expressed in a few outbreaks. The reappearance of ARF has sometimes occurred among relatively affluent urban and rural populations.

Glomerulo-nephritis secondary to strep infections is rare nowadays.

In recent years there seems to have been an increase in invasive strep A disease. Since 1980 the number of septicemic deaths has increased in the USA and UK. Several outbreaks of severe GAS have been reported in the late 1980s.

Possible host risk factors for the development of invasive GAS disease include age (the elderly and the very young), HIV infection, diabetes mellitus, malignancy, injecting drug use, cardiovascular disease, corticosteroids use, alcoholism, cigarette smoking and other chronic diseases.

A large proportion of patients with invasive GAS disease had a cutaneous form of the disease and a large portion of those with cutaneous disease reported an open sore, bruise, or burn before the onset of invasive GAS symptoms. This suggests that the skin is an important portal of entry for invasive GAS infection.

Clinical Description

Since the 1980s, a marked increase has occurred in highly invasive group A streptococcal (GAS) infections, in particular streptococcal toxic shock syndrome (STSS) associated with necrotizing fasciitis or myositis. The classical case definition for STSS is similar to staphylococcal toxic shock, caused by *Staphylococcus aureus*, but the outcome is more serious in STSS, with a reported death rate of 30% to 70%. The multiorgan involvement in STSS suggests that a toxin produced by GAS might be involved in pathogenesis.

The most common Group A streptococcal infections are pharyngitis, tonsillitis, scarlet fever, impetigo, pyoderma and cellulitis. Less common syndromes are peritonsillar abscess, mastoiditis, sinusitis, otitis media, erysipela, pneumonia, puerperal sepsis, meningitis, endocarditis, proctitis and vulvovaginitis. The non-infectious (suppurative) sequelae include acute rheumatic fever, acute glomerulo-nephritis and acute endocarditis.

Pharyngitis

It affects the pharynx including the tonsils and possibly the larynx. Symptoms include sore throat, fever, ear pain, abdominal pain, and headache. There may be swollen and perhaps tender lymph nodes in the neck, bright red tonsils, and dark red hemorrhagic petechiae on the soft palate and uvula

Invasive Group A Streptococcal Infections: Streptococcal Toxic Shock Syndrome:

Fulminant, invasive group A streptococcal infections with streptococcal toxic shock syndrome are characterized by shock, bacteremia, respiratory failure and multi-organ failure. Death occurs in about 30% of patients. The infections tend to follow minor trauma in otherwise healthy persons with several presentations of soft tissue infection.

These include:

- 1-necrotizing fasciitis, a progressive infection of subcutaneous tissue with destruction of fascia and fat
- 2-myositis and infections at other soft tissue sites, including tissues around the upper respiratory tract

Bacteremia occurs frequently in patients with these severe group A streptococcal infections.

Scarlet fever: Pyrogenic exotoxins A to C also cause scarlet fever in association with group A streptococcal pharyngitis or with skin or soft tissue infection. The pharyngitis may be severe. The rash appears on the trunk after 24 hours of illness and spreads to involve the extremities. Streptococcal toxic shock syndrome and scarlet fever are clinically overlapping diseases.

Rheumatic fever

This is the most serious sequela of hemolytic streptococcal infections because it results in damage to heart muscle and valves. Certain strains of group A streptococci contain cell membrane antigens that cross-react with human heart tissue antigens. Sera from patients with rheumatic fever contain antibodies to these antigens. The onset of rheumatic fever is often preceded by a group A streptococcal infection one to four weeks earlier, although the infection may be mild and may not be detected. In general, however, patients with more severe streptococcal sore throats have a greater chance of developing rheumatic fever. Typical symptoms and signs of rheumatic fever include fever, malaise, a migratory non-suppurative polyarthritis and evidence of inflammation of all parts of the heart (endocardium, myocardium, pericardium). The carditis characteristically leads to thickened and deformed valves and to small peri-vascular granulomas in the myocardium (Aschoff bodies) that are finally replaced by scar tissue. Erythrocyte sedimentation rates, serum transaminase levels, electrocardiograms and other tests are used to estimate rheumatic activity. Rheumatic fever has a marked tendency to be reactivated by recurrent streptococcal infections, whereas nephritis does not. The first attack usually produces only slight cardiac damage, which, however, increases with each subsequent attack. It is therefore important to protect such patients from recurrent β hemolytic group A streptococcal infections by prophylactic penicillin administration.

Jones criteria for the diagnosis of ARF (AHA)

High probability of ARF =

Criteria: 2 major
or 1 major + 2 minor
AND evidence of preceding strep infection

Major: Carditis, Polyarthritits, Chorea, Erythema marginatum, subcutaneous nodules

Minor: Fever, Arthralgia, previous rheumatic fever or rheumatic heart disease

Evidence of strep infection: positive throat culture, positive rapid strep antigen test, rising titer against ASO or other strep antibody.

Laboratory Tests

Cultures: Streptococci grow poorly on ordinary media and need media enriched with blood, brain or heart infusion, serum or glucose. Standard media used in the USA are Todd-Hewitt broth (enriched and buffered) and 5% sheep blood agar. Plates are incubated at 37°C for 24 hrs. Group A strep have small opaque white colonies surrounded by a wide zone of clear β hemolysis. Some strep have an irregular zone of hemolysis (α hemolysis). Colonies suspected of being Group A strep are subcultured. A bacitracin sensitivity test identify strep A: a bacitracin disk placed on a strep A plate causes a large area of inhibition because of strep A is extremely sensitive to bacitracin.

Rapid diagnostic test for strep A: Most methods are based on identification of a cell wall antigen and detection by latex agglutination or other method. They give a result in 10 to 60 minutes instead of two days for a culture. Their sensitivity is 60% to 85% and specificity 90% to 95%. Patients with the heaviest bacterial load are almost always detected. A throat culture is usually recommended if the rapid test is negative. Such tests do not identify group C or G which are also responsible for pharyngitis. Their cost is about \$2.00 per test versus \$0.20 for a culture plate.

Serologic tests: Although tests are available for group A and B strep, their use is limited because they do not differentiate between present and past infection, unless a rise in titer over a few weeks period is demonstrated. The most commonly used test is the antistreptolysin O (ASO). ASO cannot differentiate reliably between carriage and disease. It may be useful to diagnose rheumatic fever or strep pharyngitis associated glomerulo-nephritis. A single test of ≥ 250 or ≥ 200 U in children is considered elevated.

Treatment

Acute GAS tonsillopharyngitis

Poor compliance with standard antibiotic regimens contributes significantly to treatment failure in acute group A streptococcal (GAS) respiratory tract infection. Patients may fail to complete the recommended 10-day course of treatment, stopping once symptoms have resolved (typically, within 2 to 5 days). Accumulating evidence from a large number of prospective clinical studies suggests that shortened courses of treatment may be as effective as or more effective than conventional regimens. Short-course therapy has the potential to improve patient compliance and so reduce the rate of clinical and bacteriologic failure and the emergence of resistant strains. Other potential benefits include fewer adverse effects, improved patient satisfaction and lower treatment costs.

Patients receiving 10-day courses of antibiotic treatment for acute upper respiratory tract infections rarely complete the full course. Patients usually stop taking a prescribed course of antibiotics once the symptoms have resolved, typically within two to five days, often keeping the remaining antibiotic suspension or tablets to use if symptoms of the infection recur.

The modified Centor score is used to determine the management of people with pharyngitis. Based on five clinical criteria, it indicates the probability of a streptococcal infection.

One point is given for each of the criteria:	Points	Strep Probab	Management
Absence of a cough	1	< 10%	No antibiotic or culture needed
Swollen and tender cervical lymph nodes	2	11-17%	Antibiotic based on culture or RADT
Temperature >38°C (100°F)	3	28-35%	Antibiotic based on culture or RADT
Tonsillar exudate or swelling	4	52%	Empiric
Age less than 15 (-1 pt if age >44)	5	52%	Empiric

Surveillance

Invasive Group A streptococcal infection is a condition reportable within five business days of diagnosis.

Case Definition

1. Invasive group A streptococcal infections

Clinical description: Invasive group A streptococcal infections may manifest as any of several clinical syndromes, including pneumonia, bacteremia in association with cutaneous infection (e.g., cellulitis, erysipelas, or infection of a surgical or nonsurgical wound), deep soft-tissue infection (e.g., myositis or necrotizing fasciitis), meningitis, peritonitis, osteomyelitis, septic arthritis, postpartum sepsis (i.e., puerperal fever), neonatal sepsis and nonfocal bacteremia.

Laboratory criteria for diagnosis: Isolation of group A *Streptococcus* (*Streptococcus pyogenes*) by culture from a normally sterile site (e.g., blood or cerebrospinal fluid, or, less commonly, joint, pleural, or pericardial fluid)

Case classification: Confirmed: a case that is laboratory confirmed

2. Streptococcal toxic-shock syndrome (STSS)

Clinical description: Streptococcal toxic-shock syndrome (STSS) is a severe illness associated with invasive or noninvasive group A streptococcal (*Streptococcus pyogenes*) infection. STSS may occur with infection at any site but most often occurs in association with infection of a cutaneous lesion. Signs of toxicity and a rapidly progressive clinical course are characteristic and the case-fatality rate may exceed 50%.

Clinical case definition: An illness with the following clinical manifestations occurring within the first 48 hours of hospitalization or, for a nosocomial case, within the first 48 hours of illness:

Hypotension defined by a systolic blood pressure less than or equal to 90 mm Hg for adults or less than the fifth percentile by age for children aged less than 16 years.

Multi-organ involvement characterized by two or more of the following:

- **Renal impairment:** Creatinine greater than or equal to 2 mg/dL (greater than or equal to 177µmol/L) for adults or greater than or equal to twice the upper limit of normal for age. In patients with preexisting renal disease, a greater than twofold elevation over the baseline level.
- **Coagulopathy:** Platelets less than or equal to 100,000/mm³ (less than or equal to 100 x 10⁶/L), or disseminated intravascular coagulation, defined by prolonged clotting times, low fibrinogen level and the presence of fibrin degradation products.
- **Liver involvement:** Alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels greater than or equal to twice the upper limit of normal for the patient's age. In patients with preexisting liver disease, a greater than twofold increase over the baseline level.

- Acute respiratory distress syndrome: Defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure or by evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia.

A generalized erythematous macular rash that may desquamate.
Soft-tissue necrosis, including necrotizing fasciitis or myositis, or gangrene.

Laboratory criteria for diagnosis: Isolation of group A Streptococcus.

Case classification

Probable: a case that meets the clinical case definition in the absence of another identified etiology for the illness and with isolation of group A Streptococcus from a nonsterile site.

Confirmed: a case that meets the clinical case definition and with isolation of group A Streptococcus from a normally sterile site (e.g., blood or cerebrospinal fluid or, less commonly, joint, pleural, or pericardial fluid).

Intervention

No case investigation is required unless an outbreak is reported.

Because there is the lack of definitive and consistent guidelines for response to GAS disease in high risk settings (i.e., day care), collection of data on invasive group A streptococcal infections is required to investigate clusters and allow for more efficient and controlled management of the problem.

School and Child Care: Children with streptococcal pharyngitis or skin infection should not return to school or child care until at least 24 hours after beginning microbial therapy. Close contact with other children during this time should be avoided, if possible.

Because information about the epidemiology of GAS in child care centers is limited, there are no published recommendations about prevention strategies following identification of one or more cases of invasive GAS infection in these facilities. In Alabama, a fatal case of invasive GAS infection in a child attending a CCC led to identification of GAS carriage in 25% of all children in six of nine classrooms attending the center. In Sweden, after a child and teacher in a CCC had onset of GAS pharyngitis, GAS infection or carriage occurred in 61% of the children in the center's two classrooms within 16 days of identification of the index case. In the Boston outbreak, few children were infected outside the classroom of patients one and two, possibly reflecting the greater separation between the groups, the ability of four year-old children to control secretions, and/or the role of fomites in transmission. Results of this investigation suggest that age and center characteristics may be important factors in developing prevention strategies.

The role of fomites in transmitting GAS is unclear. Guidelines for sanitation in child care centers state that "toys that are placed in children's mouths...should be set aside to be cleaned with water and detergent, disinfected and rinsed before handling by another child" .

Asymptomatic contacts: Asymptomatic acquisition of GAS may pose some risk of non-suppurative complications; studies indicate that as many as one third of patients with rheumatic fever had no history of recent streptococcal infection and another third had minor respiratory tract infections that were not brought to medical attention. However, cultures of asymptomatic household contacts usually are not indicated except during outbreaks or when the contacts are at increased risk for developing sequelae of infection. Short courses (fewer than 10 days) of antibiotics for contacts are inappropriate. More than half of those contacts who acquire the organism will become ill.

In some circumstances, such as a large family with documented, repeated intra-family transmission resulting in frequent episodes of GAS pharyngitis during a prolonged period, physicians may elect to treat all family members. Throat cultures should be obtained in these circumstances to identify those individuals harboring the organism.

Infected contacts: Contacts of documented cases of streptococcal infection who have recent or current clinical evidence of a streptococcal infection should have appropriate cultures obtained and should be treated if the culture is positive. Rates of GAS acquisition are higher among sibling contacts (25%) than among parent contacts in non-epidemic settings; rates as high as 50% for sibling contacts and 20% for parent contacts have been reported during epidemics.

Chemoprophylaxis:

For children with repeated episodes of documented GAS pharyngitis occurring at short intervals, some experts recommend oral penicillin prophylaxis during the seasons of the year of greatest risk. The dosage is the same as for secondary prophylaxis of rheumatic fever.

Limited data suggest that household contacts of patients with severe, invasive GAS disease, including streptococcal toxic shock syndrome, are at substantially increased risk for the development of severe, invasive GAS disease compared with the general population. However, additional studies are needed to define further the magnitude of the risk, the potential effectiveness of prophylactic antimicrobial agents and the settings in which chemoprophylaxis would be cost-beneficial. As a result, no recommendations for chemoprophylaxis for these household contacts can be made at this time.

Chemoprophylaxis of Recurrences of Rheumatic Fever

- Benzathine penicillin G: 1,200,000 U, q 4 wks, IM
- Penicillin V, 250 mg twice a day, po
- Sulfadiazine, 0.5 g once a day for patients ≤ 27 kg, po
- Sulfisoxazole, 1.0 g once a day for patients >27 kg
- For individuals allergic to penicillin and sulfonamide drugs
- Erythromycin, 250 mg twice a day, po

Secondary Prophylaxis of Rheumatic Fever.

Patients who have a well-documented history of rheumatic fever (including cases manifested solely by Sydenham's chorea) and those who have documented evidence of rheumatic heart disease should be given continuous antibiotic prophylaxis to prevent recurrent attacks (secondary prophylaxis) because asymptomatic and symptomatic GAS infections can result in a rheumatic recurrence. Continuous prophylaxis should be initiated as soon as the diagnosis of rheumatic fever or rheumatic heart disease is made.

Secondary prophylaxis should be long-term, perhaps for life, in patients with rheumatic heart disease (even after prosthetic valve replacement because these patients remain at risk for recurrence of rheumatic fever). The risk of recurrence declines as the interval from the most recent episode lengthens and patients without rheumatic heart disease are at a lower risk of recurrence than those with cardiac involvement. Duration depends on whether residual heart damage (valvular disease) is present or absent. These considerations influence the duration of secondary prophylaxis in adults, but should not alter the practice of secondary prophylaxis in children and adolescents. Secondary prophylaxis in all patients who have had rheumatic fever should be continued for at least five or more years or until the individual is 21 years of age, whichever is longer. Prophylaxis also should be continued if the risk of contact with persons with GAS infection is high, such as for parents with school-age children and teachers. When streptococcal infections occur in family members of rheumatic fever patients, infected persons should be treated promptly with an appropriate antibiotic.

The IM regimen is the most reliable because the success of oral prophylaxis depends primarily on patient compliance, although inconvenience and the pain of injection may cause some patients to discontinue intramuscular prophylaxis. In some countries and in situations where the risk of GAS infection is high, benzathine penicillin G is given every three weeks because of greater effectiveness. In the U.S., administration every four weeks appears adequate in most patients. Oral sulfadiazine is as effective as oral peni-

cillin for secondary prophylaxis, but may not be readily available in the U.S.. Based on extrapolation from data demonstrating effectiveness of sulfadiazine, sulfisoxazole is an appropriate alternative.

Duration of Prophylaxis for Persons Who Have Had Rheumatic Fever: Recommendations of the American Heart Association:

Rheumatic fever without carditis
⇒ 5 years or until age 21 years, whichever is longer
Rheumatic fever with carditis but no residual heart disease (no valvular disease)
⇒ 10 years or well into adulthood, whichever is longer
Rheumatic fever with carditis and residual heart disease (persistent valvular disease)
⇒ At least 10 y since last episode and at least until age 40 y; sometimes lifelong prophylaxis

Allergic reactions to oral penicillin are similar to those with intramuscular penicillin, but they usually are less severe and occur less frequently. These reactions also occur less often in children than in adults. Anaphylaxis is extremely rare in patients receiving oral penicillin. Severe allergic reactions in patients receiving continuous benzathine penicillin G prophylaxis also are rare. Anaphylaxis and death have been reported but usually in patients older than 12 years with severe rheumatic heart disease. Most of these severe reactions may result from vasovagal responses rather than anaphylaxis. Reactions include a serum sickness-like reaction, characterized by fever and joint pains, which can be mistaken for an acute rheumatic fever recurrence.

Reactions to sulfadiazine or sulfisoxazole are infrequent and usually minor; obtaining blood counts may be advisable after two weeks of prophylaxis, since leukopenia has been reported. Prophylaxis with a sulfonamide in late pregnancy is contraindicated because of interference with fetal bilirubin metabolism. Febrile mucocutaneous syndromes (erythema multiforme, Stevens-Johnson syndrome, or epidermal necrolysis) have been associated with penicillin as well as with sulfonamides. When an adverse event occurs with any of these therapeutic regimens, the drug should be stopped immediately and an alternative drug selected. For the rare circumstance where a patient is allergic to both penicillins and sulfonamides, erythromycin is recommended.

Poststreptococcal Reactive Arthritis

Following an episode of acute GAS pharyngitis, a reactive arthritis may develop in the absence of clinical manifestations and laboratory findings that would fulfill the Jones criteria for the diagnosis of acute rheumatic fever. This syndrome has been termed post-streptococcal reactive arthritis (PSRA). In contrast to the arthritis of acute rheumatic fever, the arthritis of PSRA does not respond dramatically to anti-inflammatory agents. Because some patients with PSRA apparently may have silent or delayed-onset carditis, patients should be observed carefully for several months for the subsequent development of carditis. Some experts recommend prophylaxis for these patients for several months to a year if carditis does not develop; if carditis occurs, the patient should be considered to have rheumatic fever and prophylaxis should be continued.

Bacterial endocarditis prophylaxis

Patients with rheumatic valvular heart disease also require additional short-term antibiotic prophylaxis at the time of certain procedures (including dental and surgical procedures), to prevent the possible development of bacterial endocarditis. Patients who have had rheumatic fever without evidence of valvular heart disease do not need prophylaxis for prevention of endocarditis. Penicillin, ampicillin or amoxicillin should not be used for endocarditis prophylaxis in patients who are receiving oral penicillin for secondary rheumatic fever prophylaxis because of relative resistance to penicillins and amino-penicillins of viridans streptococci in the oral cavity in such patients. Erythromycin is the alternative antibiotic recommended for such patients.

Hospital precaution and isolation: Standard precautions.

NECROTIZING FASCIITIS

Necrotizing fasciitis (NF) is a deep-seated soft tissue infection resulting in progressive destruction of subcutaneous tissue, fat and fascia. If not diagnosed and treated in a timely fashion, this infection eventuates in gangrene, with substantial morbidity and mortality. Streptococcal NF has been dubbed the "flesh-eating disease" by the public and lay press and has struck panic into those communities in which cases have appeared in clusters.

NF caused by group A streptococci is the most rapidly progressive and devastating form of the disease. Approximately 50% of adult cases are associated with toxic shock and multiorgan failure and the mortality rate ranges from 30% to 70%. Although NF may be caused by a variety of other aerobic and anaerobic microorganisms, that caused by group A streptococci is most likely to present difficulty in early diagnosis and to result in devastating consequences should the diagnosis be missed.

Epidemiology

The CDC estimates the overall incidence of invasive group A streptococcal infections in the general population to be approximately 3 per 100,000 and only a minority of such infections are NF. The incidence may vary widely by time and place, dependent on the virulence of circulating group A streptococcal strains and the immunity of the local populace to them.

Clinical Presentation

The infection often begins at a site of significant local trauma: surgical incisions or penetrating injuries or minor injuries, such as cuts and burns, or non-penetrating injuries, such as blunt trauma and muscle strain. Secondary infection of varicella lesions is a well-recognized precursor of NF and streptococcal bacteremia in children and occasionally, in adults.

The time elapsed between onset of symptoms and initial visit to a health care provider ranged from hours to seven days (median, 2 days).

The major presenting complaints are:

- Localized pain with or without associated swelling, tenderness, or erythema (87%)
- GI complaints (nausea, vomiting and diarrhea) (53%)
- Influenza-like symptoms of aches, chills and fever (47%)
- Afebrile patients may have received antipyretics, particularly NSAIDs. These findings led to diagnoses of musculoskeletal strain, viral gastroenteritis and influenza.

Suspicion should be increased by fever, tachycardia, GI symptoms (nausea, vomiting, diarrhea), and generalized myalgias and signs suggestive of impending STSS, such as hypotension (systolic blood pressure less than 100 mm Hg), generalized erythematous macular eruption and altered mentation.

Once the diagnosis is seriously considered, antimicrobial therapy should be instituted promptly. Crepitus, or obvious gas in tissues is not a feature of streptococcal NF and indicates that other organisms, most likely anaerobes, are involved. Although there are no controlled studies of the response to therapy, experimental evidence suggests that clindamycin is the agent of choice in streptococcal NF and penicillin as well. Although clindamycin-resistant group A streptococci are exceedingly rare in the United States at the present time, the theoretical possibility of such resistance exists and penicillin and clindamycin are not antagonistic. If the microbiologic diagnosis has not been established, then an expanded-spectrum penicillin or cephalosporin should be added to clindamycin to ensure coverage against gram-negative bacteria. It is imperative to realize, however, that antimicrobials are adjunctive therapy for NF and complete surgical debridement is the sine qua non for cure.

CLINICAL SIGNS OF STREPTOCOCCAL TOXIC SHOCK SYNDROME (STSS)

(Based on the STSS case definition published in JAMA 1993; 269:390-391)

Please enter clinical finding and/or laboratory information on the following components of the STSS definition. Record the HIGHEST or LOWEST value within 48 hours of admission.

(Note: Actual laboratory results are preferred to clinical findings. Where the baseline laboratory values are abnormal, please include baseline value or answer .yes. to criteria if value is twice the baseline value or, for children, twice the 95th percentile for age)

A. Hypotension ☐ Y ☐ N ☐ DK Lowest systolic BP _____ mm Hg

(Systolic BP \leq 90mm Hg)

B. Multisystem involvement

1. Renal impairment ☐ Y ☐ N ☐ DK Highest creatinine _____mg/dL

(Creatinine $>$ 2 mg/dL)

2. Coagulopathy ☐ Y ☐ N ☐ DK Lowest platelets _____ (000)/mm²

(Platelets $<$ 100,000/mm²)

DIC ☐ Y ☐ N ☐ DK

3. Liver involvement ☐ Y ☐ N ☐ DK Highest SGOT (AST) _____ IU/ml

(SGOT or SGPT $>$ 70 IU/ml) Highest SGPT (ALT) _____ IU/ml

(Total bilirubin $>$ 2 mg/dL) Highest Bilirubin _____ mg/dL

4. Adult respiratory distress syndrome ☐ Y ☐ N ☐ DK

Generalized edema ☐ Y ☐ N ☐ DK

Pleural/peritoneal effusion with hypoalbuminemia ☐ Y ☐ N ☐ DK

(hypoalbuminemia = serum albumin $<$ 3 mg/dL)

5. Rash ☐ Y ☐ N ☐ DK

If yes, was it: ☐ Generalized ☐ Focal (location _____) ☐ DK

Rash type: ____ (1 = macular, 2 = papular, 3 = maculapapular, 4 = petechial,

5 = bullous, 6 = vasicular, 7 = other, specify: _____)

6. Soft-tissue necrosis ☐ Y ☐ N ☐ DK If yes, location _____

Surgery ☐ Y ☐ N ☐ DK

If yes, amputation ☐ Y ☐ N ☐ DK or debridement ☐ Y ☐ N ☐ DK

These data were collected by: ☐ physician interview ☐ chart abstraction ☐ other

Your initials: _____