



Health, Healthy Living and Seniors

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Re: Streptococcal Invasive Disease (Group A) Reporting and Case Investigation

Reporting of Streptococcal invasive disease (Group A) (*Streptococcus pyogenes*) is as follows:

Laboratory:

- All specimens isolated from sterile sites (refer to list below) that are positive for *S. pyogenes* are reportable to the Public Health Surveillance Unit by secure fax (204-948-3044).

Health Care Professional:

- Probable (clinical) cases of Streptococcal invasive disease (Group A) are reportable to the Public Health Surveillance Unit using the *Clinical Notification of Reportable Diseases and Conditions* form (<http://www.gov.mb.ca/health/publichealth/cdc/protocol/form13.pdf>) ONLY if a positive lab result is not anticipated (e.g., poor or no specimen taken, person has recovered).
- Cooperation in Public Health investigation (when required) is appreciated.

Regional Public Health or First Nations Inuit Health Branch (FNIHB):

- Cases will be referred to Regional Public Health or FNIHB. Completion and return of the *Communicable Disease Control Investigation Form* is generally not required, unless otherwise directed by a Medical Officer of Health.

Sincerely,

“Original Signed By”

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“Original Signed By”

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The sterile and non-sterile sites listed below represent commonly sampled body sites for the purposes of diagnosis, but the list is not exhaustive. If a site does not appear on this list and/or there is some uncertainty as to whether it is a sterile site for the purposes of diagnosing Streptococcal invasive disease Group A, please contact the regional Medical Officer of Health <http://www.gov.mb.ca/health/publichealth/contactlist.html> .

A. Sterile Sites Include:

1. Blood
2. Beta streptococcal isolate fluid (means the sample was taken from a normally sterile site).
3. Bone
4. Cerebrospinal fluid (CSF)
5. Deep tissue
6. Inner ear drainage
7. Fluid aspiration (e.g., vitreous fluid)
8. Joint
9. Joint fluid
10. **Necrotizing** soft tissue (tissue that is beneath the skin)
11. Paraspinal **or** spinal abscess
12. Placenta/amniotic fluid, **only in death.**
13. Pleural aspirate
14. Pleural fluid
15. Pericardial fluid, deep tissue
16. Specimen taken from surgery (e.g., muscle collected during debridement for necrotizing fasciitis or myositis), bone or joint fluid. This does not include middle ear or superficial wound aspirates.
17. Sub-tendon
18. Surgical tissue
19. **Surgical** wound (surgical site infection)
20. Tendon

B. Not a Sterile Site:

1. Bone chips
2. Cervix
3. Catheter
4. Colostomy
5. Endotracheal secretions
6. Fluid from an eye, ear, pelvic or other abscess.
7. Graft
8. Lung tissue
9. Middle ear or superficial wound aspirates – not Notifiable
10. Miscellaneous fluid

11. Other respiratory secretions include:

- nasal swab
- nasopharyngeal swab
- percutaneous tracheobronchial lavage
- fiberoptic endoscopic sampling.

12. Skin

13. Sputum

14. Superficial tissue

15. Throat

16. Tissue

17. Toe nail

18. Ulcer (reported alone)

19. Urine

20. Vagina

21. Wound (reported alone)

Invasive Group A Streptococcal Disease



Protocol Definitions

Invasive Disease: Infection with isolation of Group A *Streptococcus* (GAS) (specifically *Streptococcus pyogenes*) from a normally sterile site (1, 2).

Normally Sterile Site: Blood, cerebrospinal fluid (CSF), pleural fluid, pericardial fluid, deep tissue specimen taken from surgery (e.g., muscle collected during debridement for necrotizing fasciitis or myositis), bone or joint fluid. This does not include middle ear or superficial wound aspirates (3).

Severe Disease: Streptococcal Toxic Shock Syndrome (STSS), soft-tissue necrosis (including necrotizing fasciitis, myositis or gangrene), meningitis, GAS pneumonia, other life-threatening conditions or death.

Severe Invasive GAS Disease: STSS, soft-tissue necrosis (including necrotizing fasciitis, myositis or gangrene), meningitis, GAS pneumonia, other life-threatening conditions or a confirmed case of GAS disease resulting in death **plus** isolation of GAS organisms from a normally sterile site (3).

Case Definition (1-4)

Confirmed Case of Invasive GAS Disease:

- Laboratory confirmation of infection with or without clinical evidence of severe¹ disease. Laboratory confirmation requires the isolation of GAS from a normally sterile site.

Confirmed Case of Severe Invasive GAS disease:

- Severe¹ disease with isolation of GAS from a sterile site.

Probable Case Definition for Severe Invasive GAS Disease (1, 3):

- Severe¹ disease in the absence of another identified etiology **and** with isolation of GAS from a non-sterile site.

Reporting Requirements and Public Health Follow-up

- Reporting by laboratories (see Table 1) is only required for GAS isolated from sterile sites as defined under Protocol Definitions (see page 1).
- Operators of clinical laboratories in Manitoba that isolate GAS organisms obtained from sterile sites, must submit isolate subcultures to Cadham Provincial Laboratory. Isolates suspected of causing cases of STSS should be identified as such on submission.

1 Severe disease may be manifested by the following conditions:

- a) STSS which is characterized by hypotension (systolic blood pressure ≤ 90 mmHg in adults or < 5 th percentile for age in children) AND at least two of the following signs:
 - Renal impairment: creatinine ≥ 177 $\mu\text{mol/L}$ for adults
 - Coagulopathy: platelet count $\leq 100 \times 10^9$
 - Liver function abnormality: Alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin levels $\geq 2X$ the upper limit of normal
 - Adult respiratory distress syndrome (ARDS)
 - Generalized erythematous macular rash that may desquamate
- b) Soft tissue necrosis including necrotizing fasciitis (NF), necrotizing myositis (NM) or gangrene
- c) Meningitis
- d) Pneumonia
- e) Other life-threatening conditions/death
- f) A combination of the above

N.B. Toxic shock syndrome can also be caused by *Staphylococcus aureus* (*S. aureus*).

Table 1: Reporting Requirements and Public Health Follow-up

Case Definitions	Clinical Status	Laboratory Isolation From		Reportable to Manitoba Health by		Referral From Communicable Disease Control Branch to Regional Health Authority for Public Health Follow-up	Notifiable to Public Health Agency of Canada
		Sterile Site	Non-Sterile Site	Physician or Other Clinician	Laboratory		
Confirmed Case of Invasive GAS Disease	Any	+	N/A	No	Yes	No	Yes
Confirmed Case of Severe Invasive GAS Disease	Severe disease	+	N/A	Yes	Yes	Yes	Yes
Probable Case of Severe Invasive GAS Disease	Severe disease	-	+	Yes	No	Yes	No

Clinical Presentation/Natural History

The clinical presentation of patients with invasive GAS disease is not specific (5). Local pain and tenderness together with swelling and redness, often of abrupt onset, is the most common initial symptom (6, 7). Invasive GAS disease may be preceded by influenza-like symptoms such as sore throat, malaise, fever, headache, myalgia, vomiting and diarrhea (6, 7). Both host and organism factors are likely to affect the severity of the disease (8). The site and size of inoculation may also be important (8).

Invasive GAS infections may present as any of several clinical syndromes, including pneumonia, bacteremia in association with cutaneous infection (e.g., cellulitis, erysipelas, or infection of a surgical or non-surgical wound), deep soft tissue infection (e.g., myositis or necrotizing fasciitis), meningitis, peritonitis, osteomyelitis, septic arthritis, postpartum sepsis (i.e., puerperal fever), neonatal sepsis, STSS or nonfocal bacteremia (2). Skin and soft tissue infections tend to be the most common invasive GAS manifestations (9, 10).

Streptococcal Toxic Shock Syndrome: This disease is the most serious manifestation of invasive GAS disease (11). STSS has the highest case fatality rate when compared with other invasive GAS infections (12). It is characterized by renal impairment, hypotension, abnormal liver function, ARDS, and rapid onset of shock and multi-organ failure (13, 14). Necrotizing Fasciitis (NF) with or without Necrotizing Myositis (NM) is present in about 50 per cent of patients with STSS (15).

Necrotizing Fasciitis: NF is a deep-seated infection of the subcutaneous tissue that results in rapid destruction of fascia and fat, but may spare the skin itself (13). NF may begin in an operative incision or from trivial or unapparent trauma to the skin (4). Initially mild erythema rapidly becomes more extensive and evolves into bullae (blisters) containing yellow or hemorrhagic fluid (4).

Necrotizing Myositis: Streptococcal myositis is an uncommon GAS infection (14, 16), but does occur in patients with NF and STSS (4). Infection occurs after non-penetrating trauma to the skin or presumably when the bacteria are translocated to the deep tissue hematogenously from another site

(4). Distinguishing NF from NM is easily done anatomically from surgical exploration or incisional biopsy (17). The clinical features of NF and NM overlap and patients may have symptoms of both NF and NM (6).

Outcomes:

Sequelae of severe invasive GAS disease may include death, organ system failure, need for extensive surgical debridement and amputation (18). Case fatality rates vary substantially by age and clinical syndrome (19). Mortality rates are higher in individuals five years of age and under and among those 65 years of age and over (20, 21). Twenty per cent of patients with NF die and more than 50 per cent of patients with STSS die (22). The overall case fatality rate for individuals with invasive GAS disease is estimated to be 10-15 per cent (9, 16, 21, 23, 24) in Canada. The case fatality rate is similar to those reported recently in Sweden (10) and the United States (19).

Etiology

Invasive GAS disease is caused by the gram positive, β -hemolytic bacterium, *Streptococcus pyogenes* (*S. pyogenes*) (4). More than 100 distinct M-protein serotypes of *S. pyogenes* have been identified (25). Overall, M1 is the most common M type seen in Canada (26), and is common outside Canada as well (4, 27). Other species of *Streptococcus* displaying the Lancefield Group A antigen exist, but do not cause the same spectrum of disease as *S. pyogenes*. Only *S. pyogenes* is to be considered in the context of this protocol.

Epidemiology

Reservoir: *S. pyogenes* is a bacterium commonly found in the throat and on the skin of individuals who have no symptoms of illness (22). The organism may be found in saliva, even following intense antibiotic therapy (28). Infections in children are an important reservoir for infections in adults (23).

Transmission: Person-to-person transmission of *S. pyogenes* occurs through respiratory droplets (16,

25, 29, 30). The organism may also spread through direct contact in body secretions from an infected patient (16, 18). The portal of entry for invasive GAS infections is often the skin or soft tissue (23, 25), and infection may follow minor or unrecognized trauma (13, 25), without an obvious break in the skin (13). The mechanism by which GAS breaches mucosal barriers is unknown (28). The portal of entry is unknown in almost 50 per cent of invasive GAS cases (25). Isolation of GAS organisms from plastic toys in child care centres has been documented (31, 32). Invasive GAS infection in high school football players has recently been reported and raised concerns about transmission through shared equipment, particularly since the nature of the sport exposes players to forceful skin-to-skin contact and subsequent trauma (33).

Invasive GAS disease may be acquired nosocomially (7, 12, 29), particularly following surgical procedures (29). Many outbreaks have been traced to operating room personnel who are anal, vaginal, skin or pharyngeal carriers (29).

Occurrence:

General: Invasive GAS infections have been described in all parts of the United States, Europe and Australia, and have occurred predominantly in otherwise healthy adolescents and adults (13). The burden of invasive GAS disease; however, is concentrated at the extremes of age (18, 19). Few people who come into contact with GAS organisms will develop invasive GAS disease (22). Invasive GAS disease has been increasing since the mid-1980s (6, 12, 34, 35).

Canada: In 2001, the overall incidence of disease was 2.7 per 100,000 population (3). Higher incidence rates have been reported among children one year of age and under and in the elderly (9, 21). Incidence rates are similar among the provinces for which data exists (16). The highest number of invasive GAS cases tends to occur in the winter (21, 36) and spring months (36). Childhood invasive GAS disease occurs at an incidence rate similar to that of the adult population, but with a lower rate of STSS and lower case-fatality (12).

Manitoba: Data for invasive GAS infections (other than STSS, NF and NM) is likely incomplete as these infections were not reportable to Manitoba Health in the past. There were 11 reported cases of invasive GAS disease in 2002, with two deaths. The years 2003 and 2004 each had six reported cases, with no deaths. Ten cases of invasive GAS disease were reported in 2005. NF was more common than STSS for all four years and there were no reported cases of NM (37). There was no gender predominance.

Incubation: The incubation period for invasive GAS disease is usually short; one to three days (29). However, the incubation period may depend on the route of inoculation (25).

Host Susceptibility and Resistance: Individuals of advanced age as well as individuals with chronic illnesses such as diabetes mellitus, cancer, alcoholism, cardiovascular disease, infection with human immunodeficiency virus, and intravenous drug use are at increased risk of disease (6, 9, 20, 22, 24). Pregnancy and institutional acquisition have also been identified as risk factors (21). However, a significant portion of patients that acquire invasive GAS infection have no underlying disease (6, 7).

Varicella (chickenpox) is the most commonly identified risk factor in children (12, 16, 25, 31, 38-40). Other types of skin disease in children, such as eczema, appear to increase the risk of invasive GAS disease, possibly by providing a portal of entry for the bacteria (5). Underlying illnesses in some children diagnosed with invasive GAS disease include asthma and malignancy (12).

While invasive GAS infections in the postpartum period are rare, obstetric patients are vulnerable due to disrupted cutaneous or mucosal barriers during delivery (41).

Penetrating injuries, minor cuts, burns, splinters, blunt trauma and muscle strain may be more likely to be associated with invasive GAS disease (13, 22).

Communicability: Carriage of GAS organisms may persist for many months, but the risk of transmission to others is low (25). Individuals who carry the bacteria but have no symptoms are much less contagious than individuals with symptomatic infection (4, 22). Patients are considered not to be contagious within 24 hours after initiation of appropriate antimicrobial therapy (25). Antimicrobial regimens that eradicate GAS organisms from the pharynx may not protect against infections occurring through a cutaneous portal of entry (18). Culture results from the site of infection of patients with STSS may remain positive for several days after appropriate antimicrobial agents have been initiated (25).

Diagnosis

Diagnosis of invasive GAS disease is based on the culture of GAS organisms from specimens taken from normally sterile body sites. If NF is suspected, the clinician may take clinical specimens from other non-sterile sites such as a wound (42). For STSS, see the **case definition** as well.

Key Investigations

- All isolates associated with laboratory-reported cases should be sent to Cadham Provincial Laboratory (CPL). Any suspicion of penicillin resistance or STSS should be indicated on the CPL requisition.
- Confirmed Group A streptococcal isolates are sent to the National Centre for Streptococcus (NCS) for M-protein serotyping. NCS is the only laboratory in Canada that performs M-protein serotyping of *S. pyogenes* isolates.
- Probable and confirmed cases of severe invasive GAS infection are referred by Manitoba Health to Public Health for follow-up.

Control

Management of Cases:

Physicians may wish to consult with infectious disease specialists and infection control practitioners. In addition, Routine Practices as defined in the Health Canada Document, *Routine Practices and Additional Precautions for Preventing the Transmission of Infection in Health Care* are recommended (43). Cases with major wounds where drainage cannot be contained by dressings should be placed on Contact Precautions until 24 hours of appropriate antibiotic therapy has been received (11).

Early surgical consultation should be sought if NF is suspected, as exploration of the fascia may be needed to limit progression and avoid mortality (5). Surgery also establishes a definitive diagnosis by providing material for culture, Gram's staining and histopathological examination (15).

Penicillin is the treatment of choice for streptococcal cellulitis and erysipelas (4). Antimicrobial therapy with both penicillin and clindamycin is recommended for cases of NF and STSS (4, 15, 44).

In selected cases, intravenous immunoglobulin therapy (IVIG) is added to antimicrobial therapy to limit morbidity and improve survival (17). More information on this treatment is available from a guideline developed for the Mount Sinai Hospital for the treatment of NF and STSS (44).

Other supportive measures typically used in the management of shock and multi-organ failure, including aggressive fluid resuscitation, are indicated (15).

Management of Contacts:

Limited data exists on the risk of subsequent² invasive infection for contacts of patients with invasive GAS infection (37, 45, 46). The risk of severe invasive infection in contacts has been estimated to be at least 15-fold greater (25, 45) and as high as 200-fold greater (5, 9) than that for sporadic infection in the general population (25), but is still extremely rare (25, 45). Most contacts will have asymptomatic colonization (25). As a result, the efficacy and optimal regimen of

antibiotic prophylaxis for contacts of individuals with invasive GAS infection has not been established (45, 47, 48).

In Manitoba, based upon passive surveillance, no secondary cases of invasive GAS disease have been reported to Manitoba Health since the start of such reporting in 1995.

Definition of Close Contacts:

- A person who spent at least 24 hours in the same household as the index patient during the seven days before the onset of the patient's symptoms (49)
- Non-household persons who share the same bed with the case or had sexual relations with the case (3)
- Persons who have had open skin or direct mucous membrane contact with the oral or nasal secretions of a case (e.g., mouth-to-mouth resuscitation, open mouth kissing, child care contacts) or direct contact of open skin or mucous membrane with an open skin lesion of the case (3, 11, 46)

Close contacts must have been exposed to the case during the period from seven days prior to onset of symptoms in the case to within 24 hours after the case's initiation of antimicrobial therapy (3).

Expert opinion regarding chemoprophylaxis of contacts of individuals with invasive GAS infection varies. Given the relative infrequency of invasive GAS infections, and the lack of a clearly effective chemoprophylactic regimen (4, 18, 47, 49), routine screening for and prophylaxis against streptococcal infection are not recommended for close contacts of cases (4, 48, 49). Similarly, because of the rarity of subsequent cases and the low risk of invasive GAS infections in children in general, routine chemoprophylaxis is not recommended in schools or child care facilities (25). Chemoprophylaxis of contacts may be considered when:

2 Subsequent case – An invasive infection that develops after exposure to a person with a confirmed case of infection (49).

- contacts have open wounds, recent surgery, recent childbirth, current viral infections such as varicella, influenza or immune deficiency diseases (4);
- household includes one or more close contacts at high risk for severe infection or death because of advanced age (> 65 years) or very young age (< one year) (18), or who is in a high-risk group for infection (see **Susceptibility and Resistance**). As the source of GAS in households may not be the person with invasive GAS disease, if an elderly or high-risk member is to receive chemoprophylaxis, all other household members should receive it as well (49).

It is recommended that health care providers routinely inform all household contacts of persons with invasive GAS infection, and stress the importance of seeking immediate medical attention if contacts develop symptomatic illness consistent with GAS infection including pharyngitis, scarlet fever, cellulitis, erysipelas, inflamed joints, bursitis, impetigo, abscess, etc. (11, 49). **Physicians may wish to consult with public health professionals or infectious disease specialists.**

Long-term Care Facility (LTCF) Contacts:

Long-term care facility residents are at risk for outbreaks of GAS infections (8). An outbreak is defined as increased transmission of GAS causing invasive disease in a population (3). Invasive GAS infections in long-term care settings are associated with a high case-fatality rate in debilitated adults (32, 50). Direct contact between residents in a LTCF is a route for transmission of infection that is uncommon in the acute care setting (32). Strain persistence in a facility may be associated with the presence of a chronically colonized resident and poor infection control practices (50). Facility staff may also be carriers, and a source of infection, but this is less common than spread of infection among residents (8, 32, 50).

The following guidelines were adapted from the National Guidelines for the Prevention and Control of Invasive Group A Streptococcal Disease (3).

When a case of invasive GAS infection is diagnosed in a resident of a long-term care facility, an audit and reinforcement of standard infection control procedures with facility staff is recommended (32, 51). The following approach, in consultation with Infection Control or Public Health, may be useful in controlling invasive GAS disease (3, 11, 52):

- Follow reporting requirements for invasive GAS infection.
- Review resident charts for the previous two months for recent cases of infection consistent with GAS disease such as pharyngitis, cellulitis, etc.
- Assess the potential for a source of infection from outside the facility such as regular visits from children who have recently been ill.

If it is determined that there is no excess³ of GAS infection **OR** there is evidence of an outside source of infection for the index case, then active surveillance alone for two to four weeks to ensure the absence of further cases is appropriate (3, 11).

If it is determined there is an excess³ of GAS infection, the following actions should be considered:

- Residents on units where cases have been identified may be screened for GAS (3, 11).
- Colonized residents should receive antibiotic prophylaxis (3, 11, 51).
- Staff should be questioned about possible recent GAS infections, swabbed if history is positive, and treated with appropriate antibiotics if cultures are positive (11, 52).
- Active surveillance for GAS infections (including specimen collection and culture of suspect cases) of residents and staff should be maintained (3, 11, 32) for four to eight weeks (11).

³ Excess is defined as an incidence rate of culture-confirmed GAS infections > one per 100 residents per month or at least two cases of culture-confirmed infection in one month in facilities with less than 200 residents.

Chemoprophylaxis:

There is little published data on the success rate of eradication of GAS carriage in household contacts (52) and the ideal chemoprophylactic regimen has not been determined (5). Generally, cephalosporins appear to be somewhat more effective than penicillin VK (43); however, some experts feel that penicillin should be considered an alternate first line therapy (3). If prophylactic antimicrobial therapy is indicated, the following drug regimens are recommended (3):

Cephalosporins: (First generation such as cephalexin, cephadroxil)

- Children and adults: 25 to 50 mg/kg/day, to a maximum of one g/day, in two to four divided doses x 10 days

Alternative regimens:

Erythromycin:

- Children: 5 to 7.5 mg/kg every six hours or 10 to 15 mg/kg every 12 hours (base) x 10 days
- Adults: 500 mg every 12 hours (base) x 10 days

Clarithromycin:

- Children and adults: 250 mg twice daily x 10 days

First generation cephalosporins are recommended for pregnant and lactating women (3).

Management of Outbreaks:

- All contacts should be managed as per this protocol.

Prevention

- Currently, there are no vaccines approved for use in the prevention of GAS infection in Canada. However, vaccines are under development (3). Clinical trials with StreptAvax (ID Biomedical Corporation), a 26 valent vaccine against 26 serotypes of GAS was tolerated and immunogenic in adult volunteers (51, 53).

- As the risk of acquiring invasive GAS infection is higher in individuals with antecedent varicella infection, the use of varicella vaccine is one strategy for preventing some cases of invasive GAS disease (12, 31, 38).
- With the increasing incidence of invasive GAS disease, physicians should continue to diagnose and treat group A streptococcal infections aggressively (54).
- Educate the public and health care workers about reducing the spread of all types of GAS infection by good hand washing, especially after coughing and sneezing and before preparing foods or eating (22).

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