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1.0 CLINICAL INFORMATION

Invasive Group A streptococcal (invasive GAS) disease is caused by *S. pyogenes,* a Gram-positive coccus. Certain strains of *S. pyogenes* are associated with severe invasive disease. This increases the likelihood that a secondary case from a severe invasive index case will also be more severe. Clinical evidence of severe invasive disease may be manifested as: streptococcal toxic shock syndrome (STSS); soft-tissue necrosis, including necrotizing fasciitis (NF), myositis or gangrene; meningitis; or death directly attributable to GAS in a confirmed case. Invasive GAS disease is confirmed through laboratory testing of specimens taken from normally sterile sites. In the post partum scenario iGAS occurring within 7 days of hospital discharge or giving birth is considered puerperal fever.

Clinical presentation - 48% soft tissue infection; 14% bacteremia without focus; 11% pneumonia; 6% for NF; 13% for STSS.

Case fatality rate (CFR) - overall is 15-20%; the CFR for STSS may be 30-70%. Mortality is reduced by early diagnosis with surgical intervention for NF, antibiotic treatment, supportive management, IVIG for STSS.

Mode of transmission – primarily by large droplet contact of the oral or nasal mucous membranes with infectious respiratory secretions or with exudates from wounds or skin lesions, or by direct or indirect contact of non-intact skin with exudates from skin or wound or infectious respiratory secretions. Transmission by contaminated equipment or patient care products has rarely been reported.

Incubation period – the incubation period for invasive GAS infection has not been determined. The incubation period for non-invasive GAS infection varies according to the clinical syndrome, but is usually 1 to 3 days.

Period of communicability – in untreated cases 10 – 21 days. Transmissibility generally ends within 24 hours of appropriate antibiotic therapy. There are few data on subsequent (i.e. secondary) cases of severe invasive GAS disease. Evidence indicates an increased risk of invasive GAS disease in household contacts of a case. The risk of subsequent infection is household contacts is estimated to range between 0.66 and 2.94 per 1,000. However, this estimate is based on extremely small numbers of subsequent cases. The risk of subsequent infection for non-household close contacts has not been quantified, but there is a reasonable theoretical risk that invasive GAS disease can be transmitted to these persons.

Evidence to-date suggests that the use of prophylaxis in close contacts may prevent severe illness. These guidelines have been prepared to assist in the public health management of close contacts of cases of ***severe*** invasive GAS disease.

2.0 EPIDEMIOLOGY

The majority of cases occur sporadically, but nosocomial, long term care facility (LTCF), daycare/preschool, community, educational facility and household outbreaks have been documented. Invasive GAS is most common during winter months.

Age specific rates are highest in adults ≥ 60 years of age and in children less than 4 years of age. Other risk factors for invasive disease include: HIV/AIDS, cancer, heart and lung disease, diabetes, IDU and alcohol abuse, and varicella infection.

For the most up-to-date iGAS epidemiology in BC, see the Annual Summaries of Reportable Diseases on the BCCDC website.

3.0 CASE DEFINITIONS

3.1 Case definitions for surveillance of invasive GAS disease

Confirmed Case

Laboratory confirmation of infection with or without clinical evidence[1] of invasive disease:

- isolation of group A streptococcus (*Streptococcus pyogenes*) from a normally sterile site[2] (blood, CSF, pleural fluid, pericardial fluid, peritoneal fluid, deep tissue specimen taken during surgery [e.g. muscle collected during debridement for necrotizing fasciitis], bone or joint fluid excluding the middle ear and superficial wound aspirates [e.g. skin and soft tissue abscesses]).

OR

- demonstration of S. *pyogenes* DNA by an appropriately validated nucleic acid test (NAT) from a normally sterile site.[2]

Probable Case

Clinical evidence[1] of invasive disease in the absence of another identified aetiology and with non-confirmatory laboratory evidence of infection:

- isolation of group A streptococcus from a non-sterile site, OR
- positive group A streptococcus antigen detection

[1] Clinical evidence of invasive disease may be manifested as one or more of several conditions:

- streptococcal toxic shock syndrome
- soft-tissue necrosis, including necrotizing fasciitis, myositis or gangrene
- meningitis
- fetal/infant death and clinical evidence of maternal illness compatible with iGAS

[2] When fetal demise or infant death occurs in association with a puerperal infection, isolation of group A streptococcus from the placenta, amniotic fluid and/or endometrium is also considered confirmatory for both the mother and the fetus/infant. ***Puerperal infection is defined as: postpartum iGAS occurring while the mother is still in hospital or within 7 days of hospital discharge or giving birth.***

3.2 Types of cases

Severe case ❶	Case of STSS❷, soft-tissue necrosis (including NF❸, myositis or gangrene), meningitis, GAS pneumonia, or death directly attributable to GAS infection.
Sporadic case	A single case occurring in a community where there is no evidence of an epidemiologic link (by person, place, or time) to another case
Index case	The first case identified in an organization- or community-based outbreak.
Subsequent case	A case with onset of illness occurring within 21 days and caused by the same strain as a previous case and with whom an epidemiologic link can be established. Most subsequent cases in the community will occur within 7 days of a previous case.

❶ Only severe cases warrant chemoprophylaxis of close contacts.

❷ Streptococcal toxic shock syndrome (STSS) is characterized by hypotension (systolic blood pressure $\leq$ 90 mmHg in adults or < 5^{th} percentile for age in children) **and at least two** of the following signs:

- **(i) renal impairment:** creatinine level $\geq$ 177 umol/L for adults
- **(ii) coagulopathy:** (platelet count $\leq$ 100,000/mm^3 or disseminated intravascular coagulation
- **(iii)liver function abnormality:** serum glutamic oxaloacetic transaminase (SGOT), aspartate aminotransferase (AST), serum glutamate pyruvate transaminase (SGPT), alanine aminotransferase (ALT) or total bilirubin $\geq$ 2x upper limit of normal
- **(iv) adult respiratory distress syndrome (ARDS)**
- **(v) generalized erythematous macular rash** that may desquamate

❸ NF (necrotizing fasciitis) may or may not be associated with STSS. NF is characterized by isolation of Group A streptococci (*Streptococcus pyogenes*) from a normally sterile body site or taken under sterile conditions from deep tissue (aspirate or deep tissue exploratory) **AND** at least one of the following:

(i) histopathologic diagnosis: necrosis of superficial fascia and polymorphonuclear infiltrate and edema of reticular dermis, subcutaneous fat and/or superficial fascia (this should be distinguished from necrosis that occurs within an abscess);

OR

(ii) clinical diagnosis: gross fascial edema and necrosis found at surgery or frank necrosis on physical examination.

4.0 MANAGEMENT OF INVASIVE GAS DISEASE

The public health response to a sporadic case of invasive GAS disease includes management of the case, contact identification and tracing, and maintenance of surveillance for further cases.

4.1 Case management

Where there is a strong clinical suspicion of invasive GAS disease, a specimen from a normally sterile site should be obtained for culture and empiric therapy started immediately.

Laboratory testing of antimicrobial sensitivity of the GAS strain may be useful for determining appropriate antibiotic therapy.

4.2 Contact management

4.2.1 Close contacts

- In order to be considered a close contact, there must have been exposure to the case during the period from 7 days prior to onset of symptoms in the case to 24 hours after the case's initiation of antimicrobial therapy.

- Children and staff of Group Day Care Centres, school classmates (kindergarten and older), work colleagues, and social or sports contacts of a case are **not** usually considered close contacts, unless they fit into one of the categories in Table 1.

Table 1: Definition of close contacts

• Household contacts of a case who have spent at least 4 hours/day on average in the previous 7 days or 20 hours/week with the case
• Non-household persons who share the same bed with the case or had sexual relations with the case
• Persons (including HCW) who have had direct mucous membrane contact with the oral or nasal secretions of a case (e.g. mouth-to-mouth resuscitation, open mouth kissing) or unprotected direct contact with an open skin lesion of the case
• Injection drug users who have shared needles with the case
• Children and staff of family or home day care centres

Discuss the management of the contacts of every case of **severe** invasive GAS with the Medical Health Officer. Chemoprophylaxis is indicated only for close contacts of cases presenting with clinical evidence of **severe** invasive GAS disease. See Subsection 3.2.

Chemoprophylaxis is not routinely recommended for contacts of cases that are not severe (such as bacteremic illness or septic arthritis cases). Such cases have milder disease than others with invasive GAS. Their contacts are also likely to have milder disease as there is consistency in the type and severity of disease caused by a particular GAS strain.

The purpose of chemoprophylaxis is to reduce the risk of subsequent episodes of severe disease in close contacts. This may also contribute to reducing transmission of GAS to others.

Administer chemoprophylaxis as soon as possible and preferably within 24 hours of case identification. However, it is still recommended for up to 7 days after the last contact with a severe invasive case. This recommendation is based on the finding that most subsequent cases occur within 7 days after the last contact with a case.

If resources permit and close contacts can be identified, alert close contacts of **all** confirmed invasive cases (i.e., regardless of whether the case is a severe one) to signs and symptoms of invasive GAS disease. Advise them to seek medical attention immediately should they develop febrile illness or any other clinical manifestations of GAS infection within 30 days of diagnosis in the index case. This may be done by the case or the attending physician.

4.3 Special settings

Table 2 outlines the criteria for special settings that warrant further investigation and consideration of chemoprophylaxis.

Table 2: Special settings

Group Child Care Centres	Children and staff of group child care centres and pre-schools when there is: • Occurrence of a confirmed or probable iGAS case, followed by a 2nd confirmed or probable iGAS case or a non-invasive case (e.g. pharyngitis, impetigo, wound or skin infections, cellulitis) within 1 month **or** • A case of varicella 2 weeks prior to a case of GAS or within 1 month of a case of GAS❶ ❷
Long-term care facility	• An incidence rate of culture-confirmed invasive GAS infections of > 1 per 100 residents per month **or** • At least 2 cases of culture-confirmed invasive GAS infection in 1 month in facilities with fewer than 200 residents **or** • An incidence rate of suspected invasive or non-invasive GAS infections of > 4 per 100 residents per month
Hospital	Patients and staff of hospitals when there is: • Occurrence of a confirmed or probable iGAS case, followed by a 2nd confirmed or probable iGAS case or a non-invasive case (e.g. pharyngitis, impetigo, wound or skin infections, cellulitis) within 1 month

❶ Assess children and staff for varicella susceptibility and offer varicella vaccine as needed.

❷ Recommend chemoprophylaxis for individuals with acute varicella.

For recommended actions in the above situations, refer to Subsections 6.3, 6.4 and Annex 3 of the Public Health Agency of Canada Guidelines for the Prevention and Control of Invasive Group A Streptococcal Disease available at: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/06vol32/32s2/index.html.

Consultation is available with Communicable Disease Epidemiology Services, BCCDC.

4.4 Recommendations for chemoprophylaxis

Chemoprophylaxis is only recommended for close contacts of **severe** invasive disease. The objective of chemoprophylaxis is to prevent infection in colonized individuals and disease in those who have recently been infected, thereby decreasing transmission of a strain known to cause severe infection.

The recommendations for chemoprophylaxis regimens have been extrapolated from treatment guidelines for acute GAS pharyngitis and evidence from clinical trials for the eradication of pharyngeal GAS colonization. Currently, there are no studies that have specifically assessed the effectiveness of chemoprophylaxis for the prevention of subsequent cases of invasive GAS disease, although antibiotic prophylaxis has been successfully used for outbreak control in LTCFs in Canada the United States. See Table 3.

A test of cure is not warranted for persons receiving chemoprophylaxis.

The cost of chemoprophylaxis is not covered by BCCDC.

Table 3: Recommended chemoprophylaxis regimens for close contacts

Drug	Dosage	Comments
FIRST LINE REGIMEN		
First-generation cephalosporins: cephalexin, cephadroxil, cephradine	**Children and adults**: 25 – 50 mg/kg daily, to a maximum of 1 g/day in 2 to 4 divided doses x 10 days	Recommended drug for pregnant and lactating women. Should be used with caution in patients with allergy to penicillin. Use of cephalosporins with nephrotoxic drugs (e.g. aminoglycosides, vancomycin) may increase the risk of cephalosporin-induced nephrotoxicity.
SECOND LINE REGIMENS		
Erythromycin	**Children:** 5 to 7.5 mg/kg every 6 hours or 10 to 15 mg/kg every 12 hours (base) x 10 days (not to exceed maximum of adult dose). **Adults:** 500 mg every 12 hours (base) x 10 days	Erythromycin estolate is contraindicated in persons with pre-existing liver disease or dysfunction and during pregnancy. Sensitivity testing is recommended in areas where macrolide resistance is unknown or known to be ≥ 10%.❶
Clarithromycin	**Children:** 15 mg/kg daily in divided doses every 12 hours, to a maximum or 250 mg po bid x 10 days **Adults:** 250 mg po bid x 10 days	Contraindicated in pregnancy. Sensitivity testing is recommended in areas where macrolide resistance is unknown or known to be ≥ 10 %.❶
Clindamycin	**Children:** 8 to 16 mg/kg daily divided into 3 or 4 equal doses x 10 days (not to exceed maximum of adult dose). **Adults:** 150 mg every 6 hours x 10 days	Alternative for persons who are unable to tolerate beta-lactam antibiotics.

❶ Since 2002, erythromycin and clarithromycin resistance for iGAS isolates has exceeded 10% in BC (data from the National Streptococcal Laboratory)

5.0 LABORATORY INVESTIGATION PROCEDURES

Identification of virulence factors and strain type in cases of invasive GAS is important for determining trends, tracking virulence changes, and further characterizing time or place of clustered cases.

Upon identification of a case of invasive GAS, arrange to have the bacterial isolates sent to PHSA Laboratories for forwarding to the National Centre for Streptococcus, the reference laboratory for *emm* gene (gene that codes for M type surface protein) typing, T-agglutination typing and detection of GAS exotoxins.

Note: Include clinical information (e.g. signs of severity) if isolated from non-sterile source as non-invasive isolates will not be typed by the reference laboratory unless part of an investigation or if the clinical information is included.

6.0 PACKAGING AND SHIPPING OF *S. PYOGENES* ISOLATES

Note: According to Transport of Dangerous Goods (TDG) Regulation 9.2a only trained staff may pack and ship these isolates.

6.1 Completion of Forms

For each isolate, complete the "Bacteriology & Mycology Requisition" from PHSA Laboratories, available at: http://www.bccdc.ca/NR/rdonlyres/008C3277-678F-4BBE-BDB0-6CB2DAD8F18B/0/BAMReq_Jan2013.pdf Submit the completed form with the sample.

6.2 Preparation of Cultures

Submit isolates on agar slants in screw-cap tubes. Tighten the cap of the tube and seal with Parafilm. Label the tube with the client name, isolate name (*S. pyogenes*), and the date slant was inoculated. Wrap cotton around the entire length of the tube and place in a water-tight sealable biohazard bag, 1 tube per bag. Place forms in the outside pocket of the biohazard bag.

6.3 Shipment of Cultures

Procedures for shipping isolates vary depending on the mode of transport. Please determine the mode of transport used by your laboratory.

Follow Transport Canada's Transport of Dangerous Goods Regulations (TDGR) for ground shipments.

Follow TDGR and IATA Dangerous Goods Regulations for air transported specimens. The cultures may be shipped as UN3373, Biological Substance Category B.

For packing instructions, refer to the BC Public Health Microbiology & Reference Laboratory Guide to Programs and Services.

7.0 REPORTING

Use the BCCDC "Invasive Group A Streptococcal Disease: Case Report Form" to record details of the clinical features of the case.

Fax a copy of the above form to BCCDC Immunization Programs and Vaccine Preventable Disease Service at (604) 707-2515.

Enter confirmed and probable (i.e. clinical) cases of invasive GAS disease into Panorama/PARIS within 1 day of health unit notification.

8.0 INVASIVE GROUP A STREPTOCOCCAL DISEASE: CASE REPORT FORM

Complete and fax the "Invasive Group A Streptococcal Disease: Case Report Form" to BCCDC, Immunization Programs and Vaccine Preventable Disease Service within 24 hours of receipt of report (fax: 604 707-2515). The form is available at http://www.bccdc.ca/health-professionals/professional-resources/surveillance-forms

9.0 AUTHORITY

Health Act 1996

10.0 REFERENCES

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