Invasive Group A Streptococcal Infections

City-Wide GIM Rounds

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Disclosures

Relevant relationships with commercial entities:

- None

Potential for conflicts within this presentation:

- None

Steps taken to review and mitigate potential bias:

- I will clearly identify any time a recommendation I make with respect to treatments is off-label and/or does not adhere to recognized national/international guidelines

Objectives

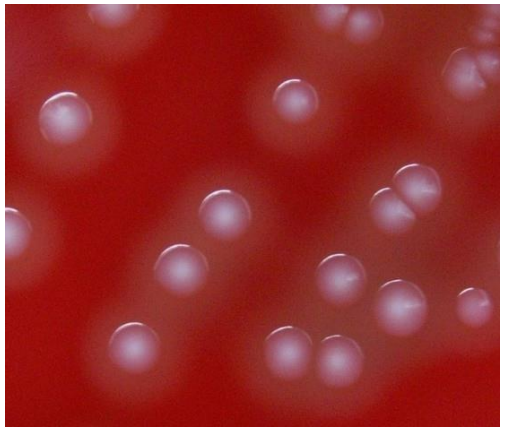
1. Review the microbiology, clinical presentation and treatment of infections caused by group A streptococcus / *S. pyogenes*

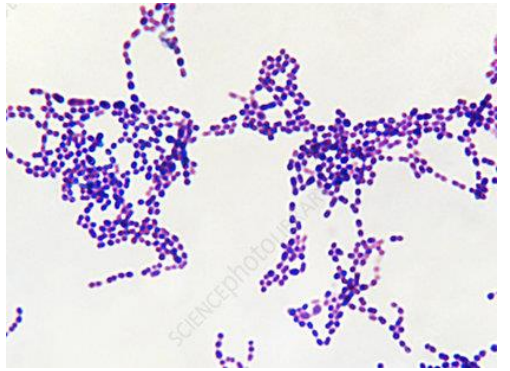
2. Share recent trends in GAS cases in Ontario

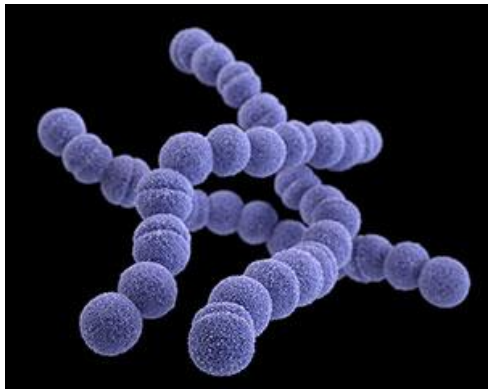
3. Briefly discuss strategies for prevention of GAS disease and its complications

Microbiology

- Group A *Streptococcus*, a.k.a. *Streptococcus pyogenes*
- gram-positive coccus, grows in chains
- Resides on human skin and mucous membranes
- Subdivided by serotypes of M and T antigens, "*emm*-typing"
- Variety of virulence factors, pyrogenic exotoxins
  - Some exotoxins are thought to act as superantigens, stimulating T cell responses and cytokine release







Clinical Spectrum of GAS Disease

- Pharyngitis
  - 2^{ary} complications:
    - Otitis media
    - Sinusitis
    - Peritonsillar cellulitis or abscess
    - Necrotizing fasciitis
- Skin, soft tissue, and musculoskeletal infections
  - Erysipelas
  - Cellulitis
  - Impetigo
  - Lymphadenitis
  - Abscess
  - Septic arthritis
  - Myositis
  - Osteomyelitis
  - Necrotizing fasciits
- Meningitis
- Pericarditis or peritonitis
- Thrombophlebitis
- Pregnancy-associated infection
- Pneumonia
- Bacteremia

Non-Suppurative Sequelae

- Rheumatic fever*
- Scarlet fever
- Post-streptococcal glomerulonephritis
- Pediatric autoimmune neuropsychiatric disorders associated with Streptococcus (PANDAS)

* greatest global disease burden associated with GAS

Invasive Group A Streptococcal Infections

- Infection with culture isolation of GAS (or PCR) from a normally sterile site (blood, or pleural, pericardial, joint, CSF fluid)

  OR

- Isolation of GAS from a non-sterile site (e.g., skin) with clinical evidence of severity

- Predisposing risk factors:
  - Varicella-zoster virus infection, influenza infection
  - Trauma, burns and surgery; post-partum state
  - Immunosuppression or immunodeficiency (glucocorticoids, DM, HIV); underlying malignancy
  - Age < 1 year (or > 65y)
  - Injection drug use; homelessness
  - Use of NSAIDS

https://www.health.gov.on.ca/en/pro/programs/publichealth/oph_standards/docs/gas_chapter.pdf

Severe iGAS

- Streptococcal toxic-shock syndrome (STSS)
  - Hypotension and at least 2 of:
    - AKI
    - Coagulopathy (thrombocytopenia or DIC)
    - Elevated liver enzymes > 2x ULN
    - ARDS
    - Generalized macular rash
- Soft tissue necrosis (necrotizing fasciitis, myositis or gangrene)
- Meningitis
- Death

https://www.health.gov.on.ca/en/pro/programs/publichealth/oph_standards/docs/gas_chapter.pdf


Sumon Chakrabarti
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LoOoOoOoOoOoOoOotta iGAS up in here. Anyone else?
@BogochIsaac @DrToddLee @zchagla @jakescottMD @LisaBarrettID
@BradSpellberg @transplantID #IDtwitter
7:49 PM · May 3, 2023 · 19.8K Views
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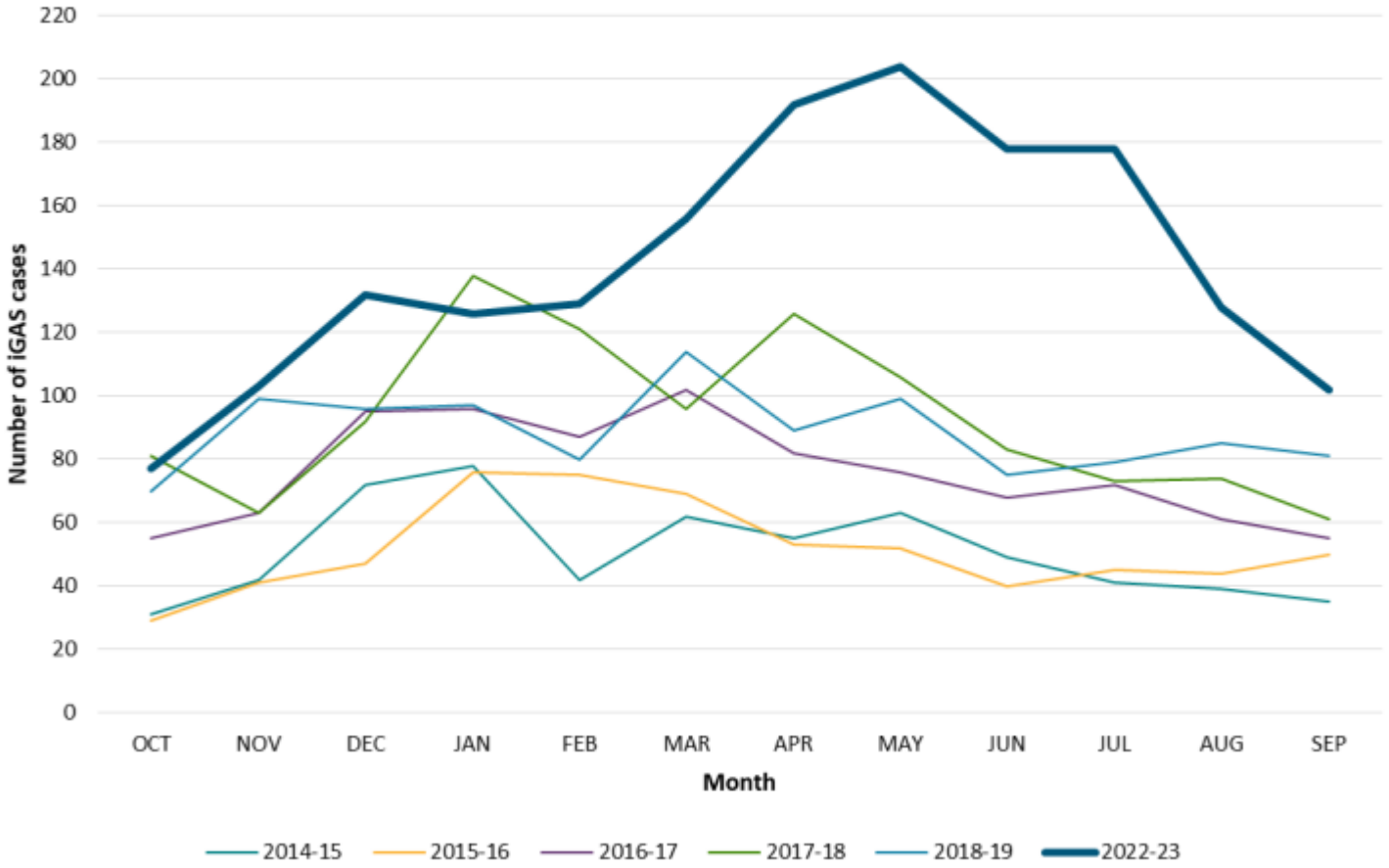
Figure 1. Confirmed iGAS case counts by month across all ages: current season (October 1, 2022 – September 30, 2023)* compared to five pre-pandemic seasons (October 1, 2014 – September 30, 2019)

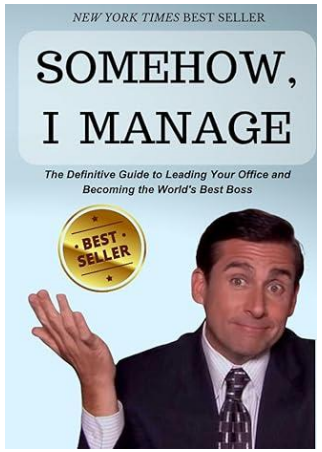


Ontario Agency for Health Protection and Promotion (Public Health Ontario). Invasive Group A Streptococcal (iGAS) Disease in Ontario: October 1, 2022 to September 30, 2023. Toronto, ON: King's Printer for Ontario; 2023.

Why are we seeing more iGAS?

- Possibly related to relative increase in other infections
  - Respiratory viruses
  - VZV
- Large pool of susceptible individuals
- Increase in pediatric cases translating to increased adult rates

FUNDAMENTALS of management



Management of Severe iGAS Infections

0. Isolate patient
1. ABC's
2. Characterize infectious syndrome
3. Antimicrobial therapy
4. Surgical intervention (if indicated)
5. Adjunctive strategies

Antimicrobial ℞ for Severe GAS Infections

Local Susceptibility for GAS

Group A streptococci**

Penicillin

** Beta-hemolytic streptococci: Susceptibilty testing to penicillin is not routinely performed since resistant strains have not been recognized. All isolates are considered susceptible to penicillin.

Clindamycin

- 79%

Vancomycin

- 100%

Source: 2021 MSH Microbiology Antibiograms, ED Blood isolates

Antimicrobial ℞ for Severe iGAS Infections

- Classically consists of β-lactam agent plus clindamycin

- Empiric combinations:
  - Piperacillin-tazobactam or meropenem

    PLUS
  - Vancomycin

    PLUS
  - Clindamycin 900 mg IV q8h

Antimicrobial ℞ for Severe iGAS Infections

- Targeted therapy:
  - Penicillin G 4MU IV q4h

    PLUS
  - Clindamycin 900 mg IV q8h (continued until hemodynamic stability attained)

- Destination treatment:
  - Total duration and timing of transition to oral antibiotics depend on a variety of clinical factors (including clinical status, adequacy of débridement, tolerability of enteral medications)
  - Usual recommendation is minimum of 14 days (some also recommend 14d from last positive culture from débridement)

Antimicrobial ℞ for Severe iGAS Infections

Clinical Infectious Diseases
VIEWPOINTS

Should Linezolid Replace Clindamycin as the Adjunctive Antimicrobial of Choice in Group A Streptococcal Necrotizing Soft Tissue Infection and Toxic Shock Syndrome? A Focused Debate

Nicolás Cortés-Penfield[a] and Jonathan H. Ryder[a]
Division of Infectious Diseases, University of Nebraska Medical Center, Omaha, Nebraska, USA

- The benefits of adjunctive clindamycin (in combination with a β-lactam) have been well-established for decades
- Concerns about increasing clindamycin resistance
- Linezolid, which also inhibits protein synthesis, has promise as an alternative adjunctive agent
  - Decreased *C. difficile* risk, and obviates the need for additional MRSA coverage

Clin Infect Dis. 2023 Jan 13;76(2):346-350.

Surgical Intervention

- Surgical exploration required for accurate diagnosis of necrotizing soft tissue infection
- Early surgical intervention associated with improved outcomes
- Repeated débridements are often required

Clues to Necrotizing Infection

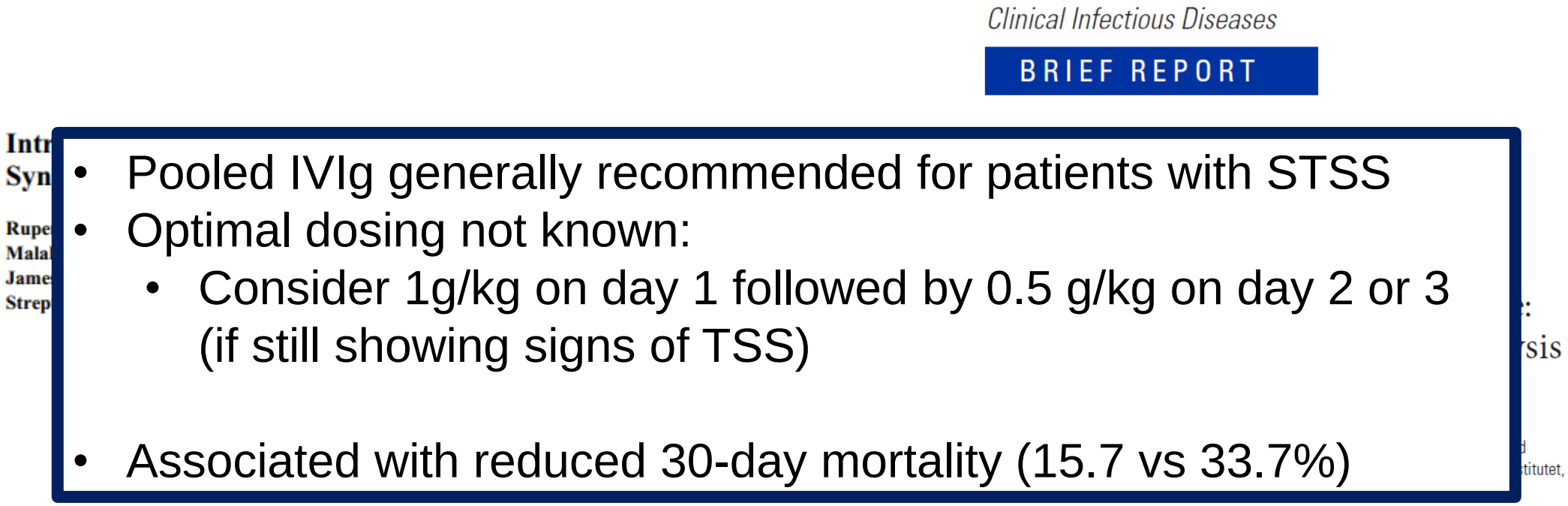
Most helpful:

- Pain out of proportion to surface appearance
- Pain beyond margins of apparently affected tissue
- Severity of illness, rapid progression of illness
- Visible areas of cutaneous necrosis, patches of anesthesia

Less helpful:

- Risk factors for iGAS
- Cutaneous bullae
- Laboratory and imaging findings

IVIg in patients with GAS TSS



- Pooled IVIg generally recommended for patients with STSS
- Optimal dosing not known:
  - Consider 1g/kg on day 1 followed by 0.5 g/kg on day 2 or 3 (if still showing signs of TSS)
- Associated with reduced 30-day mortality (15.7 vs 33.7%)

Clin Infect Dis. 1999:28(4):800-807
Clin Infect Dis. 2018:67:1434-1436

REPORTABLE DISEASES OF PUBLIC HEALTH SIGNIFICANCE

CONTACT INFORMATION:

Toronto Public Health - Communicable Disease Surveillance Unit
277 Victoria Street, 10th Floor, Toronto, ON M5B 1W2
Phone: 416-392-7411 -- Fax: 416-392-0047
After hours: 3-1-1 or 416-392-CITY (2489) for callers from outside of Toronto

Timely reporting of communicable diseases is essential for their control.

If you suspect or have laboratory confirmation of any of the following specified diseases of public health significance or their etiologic agents (as per Ontario Reg. 135/18 and amendments under the Health Protection and Promotion Act), please report them to the local Medical Officer of Health.

Diseases marked * should be reported immediately to the Medical Officer of Health by telephone (24 hours a day, 7 days a week) or fax (Mon-Fri, 8:30 am – 4:30 pm only). Other diseases can be reported the next working day by fax, phone, or mail.

Acquired Immunodeficiency Syndrome (AIDS)
Acute Flaccid Paralysis
Amebiasis
Anaplasmosis
* **Anthrax**
Babesiosis
Blastomycosis
* **Botulism**
* **Brucellosis**
Campylobacter enteritis
Food poisoning, all causes
* **Gastroenteritis, Outbreaks in institutions and public hospitals**
Giardiasis
* **Group A Streptococcal disease, invasive (iGAS)**
* ***Haemophilus influenzae* disease, all types, invasive**
Paralytic Shellfish Poisoning
Paratyphoid Fever
Pertussis (Whooping Cough)
* **Plague**
Pneumococcal disease, invasive
* **Poliomyelitis, acute**
Powassan Virus
Psittacosis/Ornithosis
* **Q Fever**
* **Rabies**

TORONTO Public Health — **Reportable Disease Notification**

Communicable Disease Surveillance Unit
277 Victoria Street, 10th Floor
Toronto, Ontario M5B 1W2

Phone: 416 392 7411
Fax: 416 392 0047
After hours : 3 1 1 or 416 392 CITY(2489) for callers from outside of Toronto

Patient Information

Last Name	First Name	Second Name	Report Date (YYYY/MM/DD) / /	Report Time (24 Hrs) M : F
Apt. No. Street Address			Telephone: Home: ( ) Cell: ( ) Work: ( )	
City		Postal Code		
Date of Birth (YYYY/MM/DD) / /	Health Card Number (Optional)		Gender M F Other	Pregnant Y N N/A

Diagnostic Information

Disease being reported (see TPH Reportable Disease List):	Hospitalized? Y N Unknown ER Visit Only? Y N Unknown Name of Hospital: (if applicable)
Laboratory Lab Name: Specimen Type: Test Type: Specimen Number: Result(s):	**Clinical** Signs and Symptoms:

https://www.toronto.ca/wp-content/uploads/2023/06/98dc-PublicHealthCDNURDNFJuly2023.pdf

Prevention of GAS Disease

Close Contacts of Patients with iGAS

- Defined as household contacts, bedmates, those with direct mucous membrane contact, those who have shared needles
- Increased risk of iGAS (200- to 2000-fold)
- Recommended antibiotic prophylaxis:
  - **Cephalexin or cefadroxil 1 g per day (in 2-4 divided doses) for 10 days**
- Prioritize contacts who are immunocompromised, pregnant, had recent surgery or have open wounds

Future Steps

- Improving strategies for early diagnosis of severe iGAS
- Clarifying optimal antimicrobial therapy for treatment of iGAS infections
- Vaccine development and other strategies to prevent complications of GAS infections

Summary

- Range of infections caused by *S. pyogenes* is vast
  - But most of us only see/recognize a few of them
- Recognition of severe iGAS infections can be challenging in early stages, and relies on some key clinical factors and progression
- Management involves:
  - optimized antimicrobial therapy
  - +/- surgical involvement
  - +/- additional strategies
  - prevention of additional infections

Thank You.

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