The Flesh-Eating Bacterium

Pierrette MELIN
Medical Microbiology, University hospital of Liege, Belgium
Streptococcus pyogenes

also named Group A Streptococci (GAS)
Introduction

Microbiological characteristics

Virulence factors

Epidemiology

Clinical types of infection

Strep TSS

Conclusion
Introduction

- Since the mid-1980s, marked increase number of highly invasive group A streptococcal infections:
  - With shock and organ failure
  - With or without necrotizing fasciitis
  "Streptococcal toxic shock syndrome (STSS)"

- 1-5 cases (up to 25 cases)/100,000 population annually
- 30% mortality despite appropriate treatment
- If survival: major tissue loss, amputation of extremities
True increase in both number and severity of cases

"Will these types of GAS infections decline, stay the same, or increase?"

- Before the advent of antibiotics
  - Many epidemics of GAS infections: waxed and waned
    - Changes in socioeconomic conditions?
    - Variations in expression of virulence factors?
    - Acquisition of herd immunity to virulence factors?

GAS epidemiology is complex
Streptococcus pyogenes
Microbiological Characteristics

- Gram positive cocci
  - In chains or pairs
- Growth on blood agar media
- Facultative anaerobe
- Growth best with 10% CO2
- β-Hemolytic
- Catalase negative
- Capsule
- Bacitracin susceptibility
Streptococcus pyogenes

- Group A antigen
- Type-specific antigen
  - M protein
    - > 80 M serotypes
    - Fimbriae
    - Major virulence factor
    - Elicits protective Ab
  - T protein
    - Useful epidemiologic marker
    - Function unknown
- Sequencing of **emm** gene encoding M protein
Streptococcal M Protein

N-terminus

C-terminus
Schematic location of intracellular, cellular and extracellular virulence factors
<table>
<thead>
<tr>
<th><strong>Virulence factor</strong></th>
<th><strong>-Biologic effect</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Capsule</strong></td>
<td>-Antiphagocytic</td>
</tr>
<tr>
<td><strong>M proteins</strong></td>
<td>-Adhesin; <strong>antiphagocytic</strong>; degrades complement component C3b</td>
</tr>
<tr>
<td><strong>M-like proteins</strong></td>
<td>-Binds IgM, IgG and α2-macroglobulin</td>
</tr>
<tr>
<td><strong>Protein F</strong></td>
<td>-Fibronectin-binding protein. Mediates adherence to epithelial cells</td>
</tr>
<tr>
<td><strong>Streptolysine S</strong></td>
<td>-Lyses leucocytes, platelets and erythrocytes; stimulates release of lysosomal enzymes; nonimmunogenic</td>
</tr>
<tr>
<td><strong>Streptolysine O</strong></td>
<td>-Lyses leucocytes, platelets and erythrocytes; stimulates release of lysosomal enzymes; immunogenic</td>
</tr>
</tbody>
</table>
Virulence factor - Biologic effect

**Hyaluronidase**
- Hydrolyzes hyaluronic acid in deeper tissue; facilitates spread of infection along fascial planes

**Streptokinase**
- Lyses blot clots, facilitates spread of infection in tissue

**C5a peptidase**
- Degrades complement component C5a

**Pyrogenic exotoxins**
- SPE type A, B and C = erythrogenic or scarlatina toxins. Cause rash seen in scarlet fever, induce lymphocytes blastogenesis, potentiate endotoxin-induced shock, induce fever, suppress antibody synthesis and act as super antigen (massive release IL, TNF)
Streptococcal Pyrogenic Exotoxins - SPE

♦ SPEA
  ♦ Carried by lysogenic phage (not all strains)
  ♦ Variation in quantity produced / decade
  ♦ Mutation, variation in potency

♦ SPEB
  ♦ Mediated by chromosome gene
  ♦ Variably expressed
  ♦ Severe cases of scarlet F and STSS

♦ SPEC
  ♦ Carried by lysogenic phage (not all strains)
Epidemiology

- **Natural reservoir**
  - Purely a human pathogen, skin and mucous mb.

- **Relationship to humans**
  - Asymptomatic colonization
    - Age: 15-20% in children; <5% in adults
  - Infections
    - Age:
      - most I.: incidence higher in younger (< 10 years)
      - Bacteremia: neonates and elderly
      - 1986-1988: prevalence bacteremia √√ 800-1000% in adolescents and adults
  - Climate:
    - Pharyngitis, scarlet fever
    - Impetigo
Epidemiology

- Pharyngeal or cutaneous acquisition, person-to-person spread via
  - Aerosolized microdroplets
  - Direct contact

- In most cases of GAS infection
  - Transmission and portal of entry ascertained

- Patients with STSS
  - Portal of entry obvious only in 50% of cases
Clinical Types of Infection

- Pharyngitis and asymptomatic carriage (1-70%)
- Scarlet fever
- Erysipelas
- Streptococcal pyoderma (Impetigo Contagiosa)
- Lymphangitis
- Cellulitis
- Necrotizing fasciitis
  - Myositis, pneumonia
- STSS
- Puerperal sepsis
- Endocarditis
- Postinfectious sequelae
  - Rheumatic fever, poststreptococcal glomerulonephritis
Strep TSS - Demographic Features

- Increasing incidence of sporadic cases!
  - North America and Europe
- In any age group
- Sometimes when underlying diseases
- Mostly in non immuno-compromised patients
- With Severe complications
  - Bacteremia with aggressive soft tissue infection
  - Shock
  - Acute respiratory distress syndrome (ARDS)
  - Renal failure
- Course of infection is rapid

Sharp contrasts with previous GAS bacteremia
## Strep TSS - Demographic Features

<table>
<thead>
<tr>
<th>Severe complications of GAS</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>soft tissue infections</td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>95</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome-ARDS</td>
<td>55</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>80</td>
</tr>
<tr>
<td>Irreversible</td>
<td>10</td>
</tr>
<tr>
<td>Reversible</td>
<td>70</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>60</td>
</tr>
<tr>
<td>Mortality</td>
<td>30 (70)</td>
</tr>
<tr>
<td>Morbidity (major surgical debridment, amputation, ...)</td>
<td>&gt; 65</td>
</tr>
</tbody>
</table>
### Strep TSS - Acquisition

<table>
<thead>
<tr>
<th>Portal of entry</th>
<th>Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
<td>35</td>
</tr>
<tr>
<td>Minor trauma</td>
<td></td>
</tr>
<tr>
<td>Surgical procedures</td>
<td></td>
</tr>
<tr>
<td>IV drug abuse</td>
<td></td>
</tr>
<tr>
<td><strong>Mucous membrane</strong></td>
<td>20</td>
</tr>
<tr>
<td>Pharynx</td>
<td></td>
</tr>
<tr>
<td>Vagina</td>
<td></td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>45</td>
</tr>
</tbody>
</table>

Risk of secondary cases = very low, despite a high prevalence of « virulent strains of GAS » in population
Strep TSS - The Clinical Picture

◆ **PAIN**
  ◆ Most common initial symptom
  ◆ Abrupt in onset
  ◆ Severe
  ◆ Usually precedes tenderness or physical findings

◆ Pain usually involves an extremity
  ◆ But may mimic peritonitis, pelvic inflammatory disease, pneumonia, acute myocardial infarction or pericarditis

◆ **Fever** : most common presenting sign
## Strep TSS

<table>
<thead>
<tr>
<th>Other symptoms and signs</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza like syndrome</td>
<td>20</td>
</tr>
<tr>
<td>Mental confusion</td>
<td>55</td>
</tr>
<tr>
<td><strong>Hypotension, systolic</strong></td>
<td></td>
</tr>
<tr>
<td>Soft tissue swelling</td>
<td>80</td>
</tr>
<tr>
<td>(necrotizing fasciitis, myositis)</td>
<td>(70)</td>
</tr>
<tr>
<td>Endophalmitis, peritonitis, perihepatitis</td>
<td>20</td>
</tr>
<tr>
<td>myocarditis, overwhelming sepsis</td>
<td></td>
</tr>
<tr>
<td>Diffuse scarlatina like erythema</td>
<td>10</td>
</tr>
<tr>
<td><strong>Positive blood culture</strong></td>
<td>69-97</td>
</tr>
<tr>
<td><strong>Positive site of infection culture</strong></td>
<td>95</td>
</tr>
</tbody>
</table>
GAS Necrotizing Fasciitis (NF)

- Deap-seated infection of subcutaneous tissue
- Progressive destruction of fascia and fat
- May spare skin and muscle
- « Streptococcal gangrene »
- Severe pain out of proportion to superficial appearance of skin
GAS Necrotizing Fasciitis

- Severe manifestation of systemic illness
- High morbidity
  - Despite antibiotics, dialysis, ventilators, IV fluids and improved surgical techniques
- Skin signs
  - Diffuse swelling and tenderness
  - Erythema, and later, bullae
  - Colour change from red to purple or black
GAS Myositis

- First, severe pain, chills and fever
- Later, swelling and erythema
  - May be apparent after development of muscle compartment syndrome
- Differentiation with gas gangrene difficult
- Case fatality rate
  - GAS NF : 20-50%
  - GAS myositis : 80-100%
GAS Bacteremia

- **In the past, in very young or elderly**
  - Among children, predisposing factors
    - Burns, varicella, immunosuppression, neoplasy, age < 2
  - In older adults + elderly
    - Source = skin infection, cellulitis or erysipelas
    - Diabetes, malignancy, corticosteroid use
  - Rare in 14-40 years of age
    - Puerperal sepsis

- **Recently**
  - IV drug addicts, highest prevalence of GAS Bacteremia
  - In the late 1980s, 600-800% increase in adolescent and young adults
  - Mortality: 24-26%
Strep TSS - The Clinical Course

- Impressive rapidity
  - Progression of shock and multi-organ failure
  - Many patients may die within 24-48 h of hospitalization
  - Shock at time of admission or within 4-8 h
  - Renal impairment often present at time of admission, progression or persistence; dialysis
  - If ARDS, intubation, ventilation in 90% cases
Strep TSS, Characteristic of Clinical Isolates

- **M types 1, 3, 6, 12 and 28**: majority of isolates
  - Sweden, 80% M-type 1 strains

- **Streptococcal exotoxin type A (SPEA) and/or type B (SPEB)**
  - SPEA in 15% of all clinical isolates / in > 80% of strains causing STSS.
  - SPEA most frequently in USA / SPEB most common in Europe

- **Streptococcal superantigen (SSA)**, a novel pyrogenic exotoxin, isolated in M-3 strains
Pathophysiology

GAS infection

- monocytes
- macrophages
- neutrophils

Important virulence mediators:
- SPEA/B
- SSA

TNF-α, IL-1β, IL-6

Septic shock

- Vasodilatation
- Myocardial depression
- Capillary leak
- Immune suppression
- Organ failure

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Strep TSS - Pathophysiology

Why worldwide increase of severe GAS infections?
Why no epidemics?

UNCLEAR!

- Host factors, immunity
  - Same strain may cause severe invasive disease / mild uncomplicated disease / carrier state
  - Level of Ab -M, and - SPEA

- Bacterial factors
  - Change in prevalence of strains with specific virulence factors
Pathogenesis of Scarlet Fever, Bacteremia and S-TSS

M-1⁺ SPEA⁺ strain

Host

+ anti M1
Abortive infection

- anti M1
Infection (local)

Anti SPEA (-)

Scarlet fever (benign)

Bacteremia

Anti SPEA +

Anti SPEA (-)

Shock (rare)
DIC
Death
- Newborns
- Elderly
- Debilitated
- Compromised

TSS
Shock (common)
Multi-organ failure
NF
Death
- Children
- Adults

Newborns
Elderly
Debilitated
Compromised
Adults
Death
Multi-organ failure
Shock (common)
TSS
Anti SPEA (-)
Anti SPEA +
Abortive infection
Infection (local)
M-1⁺ SPEA⁺ strain
Pathogenesis of Scarlet Fever, Bacteremia and S-TSS

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Strep TSS, Management

Surgical emergency is mandatory

- Diagnosis should be made by surgical exploration
- IMMEDIATE aggressive surgical debridment of all necrotic tissue
  - May include amputation
  - Repeated often daily
- Lesion often much more extensive / examination of skin surface
- Spread of infection >> rate of surgery
GAS remain Sensitive to penicillin
But reduced efficacy in severe GAS infection
High inoculum
Decrease in expression of Penicillin Binding Protein (PBP) by GAS in stationary phase
Clindamycin more effective
Not affected by inoculum or stationary phase
Inhibits synthesis of bacterial toxins
Facilitates phagocytosis of GAS by inhibiting synthesis of M protein
Suppresses PBP Synthesis & degradation
Longer post-antibiotic effect /penicillin
Strep TSS, Management

Supportive management

- Early admission to intensive care unit
- Management for septic shock
- Dialysis
- Tracheal intubation, mechanical ventilation
- Massive amounts of IV fluids
Prophylaxis

- Risk of household's contact:
  - 200 times higher/general population
  - CDC: no definitive recommendations
  - ? Cephalosporin or macrolide: 10-day?

- Nosocomial transmission and transmission to health care workers
  - Appropriate precautions
    - Gown, mask, gloves and meticulous handwashing
Where do we go from here

- A wild "flesh-eating strain" has recently emerged
- A major epidemic would be expected
- Other GAS epidemics (pharyngitis, scarlet fever, rheumatic fever) occurred in the past
- Last decade: incidence of GAS TSS has remained low
- Large outbreaks of STSS did not occur, WHY?
Where do we go from here

Large outbreaks of STSS did not occur, WHY?

- Vast majority of population
  - Probably immunity to 1 or more virulence factors

- Predisposing conditions required in a given patient
  - Varicella, use of non-steroidal anti-inflammatory drugs

- Small % of population with some other immunological predisposing factors
  - HLA class II ag type, B cell alloantigens, or ...

What should be done?

- Pathogenesis: more information needed
- Continued epidemiological and microbiological surveillance
- Improvement of therapeutic
- Prevention strategy
  - Development of M-vaccine