Invasive *Streptococcus pyogenes*: Increase in reported cases during 2008-2017 in Belgium and outbreak control

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Introduction

- Gram positive bacterial species
- Lancefield Group A, β-hemolytic streptococci
- Worldwide
- Seasonal pattern: infections occur throughout the year, with lowest incidence in autumn, steadily increasing to peak from December - April
- Colonisers of the oropharynx, genital mucosa, rectum and skin
- Carriage rates:
  - Throat:
    - Preschoolchildren (<5y): 1-7% (Shaikh et al; 2010)
    - Healthy adults: ≤ 5% (Steer et al. 2012)
  - Genital carriers:
    - ≤ 1% (Steer et al. 2012)
Introduction

- Superficial infections: URTI, skin infections, pharyngitis
- Invasive infections (iGAS): septicemia, meningitis, cellulitis, pneumonia, … 2 – 4/100,000 in developed countries (Steer et al. 2012)
- High fatality rate (163,000 deaths each year)
  - Necrotising fasciitis, STSS,
- Severe scarlet fever, puerperal sepsis, systemic disease
Introduction

• Virulence factors:
  • M-protein coded by the emm-gene
  • Virulence genes: Streptococcal pyrogenic exotoxins (Spe proteins): SpeA, SpeC, SpeG-M, streptococcal mitogenic exotoxin Z (SmeZ), streptococcal superantigen (SSA)
  • In general, isolates of the same emm-type share a similar SA profile, but variants may occur (Schmitz et al. 2003)

• Antibiotic susceptibility:
  • All strains sensitive to penicillin so far
  • Macrolide (ermA, ermB, mat/mef), tetracycline and lincosamide resistant GAS strains gradually spread among certain emm-types (Harari-Luca et al. 2008, Mihaila-Amrouche et al. 2004, Chen I et al. 2011)
• **Diagnostic tests:**
  - Bacterial culture on bloodagar, ID by MALDI-TOF
  - Rapid antigen detection tests
  - PCR:
    - In-house methods: *dnaseB*, *SpeB*, *parE*, *spy1258*, *spy1857*, *ptsl*, *MF-gene*, 16S rDNA, *rpoB*, *ntpB* (Loens and leven, 2016)
    - Commercially available methods: Xpert Xpress Strep A (Cepheid), Lyra Direct Strep Assay (Quidel), …
  - POC: Cobas Liat Strep A assay (Roche, FDA cleared) (Wang et al. 2017; Uhl et al. 2016), mariPOC (ArcDia) (Vakkila et al. 2015), …
## Diagnostic tests

<table>
<thead>
<tr>
<th>Assay</th>
<th>Nr of Specimens</th>
<th>Age</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illumigene</td>
<td>437 TS</td>
<td>1.2-18y</td>
<td>100%</td>
<td>99,2%</td>
<td>Henson et al 2013*</td>
</tr>
<tr>
<td></td>
<td>796 TS</td>
<td>&lt;1y-87y</td>
<td>99,0%</td>
<td>99,6%</td>
<td>Anderson et al 2013*</td>
</tr>
<tr>
<td>Cobas Liat</td>
<td>427 TS</td>
<td>≥ 3y</td>
<td>97,7%</td>
<td>93,3%</td>
<td>Wang et al. 2017</td>
</tr>
<tr>
<td></td>
<td>200 TS</td>
<td>UNK</td>
<td>100%</td>
<td>98,3%</td>
<td>Uhl et al 2016**</td>
</tr>
<tr>
<td>In-house PCR (ntpB-gene)</td>
<td>192 deep tissue specimens</td>
<td>0.5-92y</td>
<td>98,7%</td>
<td>100%</td>
<td>Gazzano et al. 2016***</td>
</tr>
<tr>
<td>In-house 16S rDNA PCR</td>
<td></td>
<td></td>
<td>84,0%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Immunocard StrepA Ag-test</td>
<td></td>
<td></td>
<td>94,7%</td>
<td>100%</td>
<td></td>
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<tr>
<td>NADAL StrepA Ag-test</td>
<td></td>
<td></td>
<td>90,7%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>SD Bioline StrepA Ag-test</td>
<td></td>
<td></td>
<td>88,0%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Culture</td>
<td></td>
<td></td>
<td>77,3%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

*compared to culture, ** compared to PCR, *** composite gold standard
GAS surveillance reports

- Increase in iGAS worldwide during the 80-ies
- Increase in GAS bacteremia in France between 2000-2009 (Plainvert et al. 2011)
- Increase in STSS, necrotising fasciitis and puerperal fever in The Netherlands (ProMED publication 2017)
- Increase in fatal cases among homeless people in Alaska and Canada (Hillman et al.; Finkelstein et al, 2017)
- Increase in scarlet fever in the UK and China (Guy et al. 2014; ProMED publications, 2017, 2018)
Number of iGAS infections per season in Belgium

Sentinel data

NRC data
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Sepsis (%)</td>
<td>42.2</td>
<td>43.9</td>
<td>41.6</td>
<td>40.3</td>
<td>35.6</td>
<td>48.2</td>
<td>51.7</td>
<td>56.1</td>
<td>49.3</td>
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<tr>
<td>Surg Wound (%)</td>
<td>4.2</td>
<td>3.1</td>
<td>2.0</td>
<td>1.9</td>
<td>1.4</td>
<td>4.9</td>
<td>4.5</td>
<td>2.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Cellulitis (%)</td>
<td>6.0</td>
<td>4.1</td>
<td>8.1</td>
<td>8.8</td>
<td>7.3</td>
<td>8.6</td>
<td>10.2</td>
<td>6.1</td>
<td>7.2</td>
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<tr>
<td>Fasciitis (%)</td>
<td>2.6</td>
<td>1.5</td>
<td>1.0</td>
<td>1.9</td>
<td>5.5</td>
<td>6.1</td>
<td>5.7</td>
<td>7.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Arthritis (%)</td>
<td>3.1</td>
<td>2.0</td>
<td>2.0</td>
<td>3.2</td>
<td>5.5</td>
<td>1.6</td>
<td>2.6</td>
<td>2.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Meningitis (%)</td>
<td>1.0</td>
<td>1.0</td>
<td>0</td>
<td>0.9</td>
<td>2.7</td>
<td>1.6</td>
<td>1.9</td>
<td>1.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Pneumonia (%)</td>
<td>3.1</td>
<td>3.1</td>
<td>6.1</td>
<td>5.1</td>
<td>5.0</td>
<td>6.1</td>
<td>6.8</td>
<td>2.4</td>
<td>4.0</td>
</tr>
<tr>
<td>Myositis (%)</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>0.9</td>
<td>0</td>
<td>0.4</td>
<td>0.4</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>Puerperal sepsis (%)</td>
<td>2.6</td>
<td>1.5</td>
<td>0.5</td>
<td>1.9</td>
<td>2.7</td>
<td>1.6</td>
<td>0.8</td>
<td>2.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Other (%)</td>
<td>15.9</td>
<td>15.3</td>
<td>22.5</td>
<td>16.3</td>
<td>20.1</td>
<td>19.9</td>
<td>12.8</td>
<td>11.9</td>
<td>19.1</td>
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<tr>
<td>Unknown (%)</td>
<td>18.8</td>
<td>24.5</td>
<td>16.2</td>
<td>18.8</td>
<td>14.2</td>
<td>1.0</td>
<td>0.8</td>
<td>2.1</td>
<td>5.3</td>
</tr>
<tr>
<td>STSS (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.9</td>
<td></td>
<td>4.3</td>
<td>1.6</td>
</tr>
</tbody>
</table>
Spatiotemporal distribution of number of reported iGAS episodes between 2011-2017: Sentinel data
NRC data: Spatiotemporal distribution of number of reported invasive S. pyogenes episodes between 2011-2017.
Age distribution iGAS (2011-2017)

• The highest proportion in the older age group (>15 years): >38% : Young children and preadolescents (0-14 years of age): 20.7%.

• Age distribution remained stable throughout the investigated time-period.
Emm-types iGAS received at the NRC compared to the literature

Emm-type distribution iGAS in Europe

Emm-types iGAS in Europe (1975-2015)

Emm-type distribution in invasive S pyogenes in Belgium

Number of invasive cases in 2011-2017 ('S. pyogenes')

Number of fatal cases in 2012-2017 ('S. pyogenes')
Emm-types involved in STSS and necrotising fasciitis

Number of cases of STSS (2012-2017)

Number of cases of necrotising fasciitis (2012-2017)
Emm-type distribution 2014-2018
Antibiotic susceptibility

• Penicillin: all strains S

• Macrolide R:
  • ≤5%
  • Mainly ermA and ermB
  • Mainly emm11, emm77, emm28

• Tetracycline R:
  • ≤15%
  • tetM>tetO>tetL,
  • emm77>emm5>emm11>emm22>emm50>emm83>other
Remarks and conclusions

- Increasing number of iGAS in Belgium since 2012 (based on combined NRC-data and Sentinel data)

- *Emm1, emm3, emm89, emm4, emm12, emm75, emm87 and emm28*, most detected *emm*-types, accounting for >50% of iGAS infections in Belgium

- Antibiotic susceptibility still high; resistant *emm*-types similar to those in other European countries (Luca-Harari et al. 2008, Plainvert et al. 2011, Walker et al. 2014)

- For optimal epidemiological surveillance:
  - Mandatory to report to Belgian Public Health Authorities STSS and necrotising fasciitis (puerperal fever), not only in Flanders
  - No legal obligation for laboratories to submit invasive strains ⇒ Invasive strains should be submitted to the NRC for follow-up of (re-)emerging strains.
Content

• Transmission
• Carriers
• Screening
• Prophylaxis
• Control measures
  • Surveillance
  • Outbreak control community
  • Outbreak control hospital
Transmission route

- Direct person to person transmission, skin contact (poor hand hygiene)
  - patient-close contact
  - patient-staff
  - staff-patient
  - patient-patient

Droplets inhalation: respiratory or wound

- Environmental reservoirs
  - Direct contact with contaminated objects/surfaces

- Food source
  - Inoculation through colonised food handlers, less common
Carriers

- Staff-members carriage in GAS outbreaks
  - Asymptomatic colonised = 34%
  - Symptomatic = 8.2%
  - Asymptomatic carriage less effectively cleared with treatment than symptomatic carriers
- Carriage up to 30% in household contacts of GAS-infected cases
- False negative screening results due to
  - Poor sampling quality
  - Failure in processing and testing of specimens
  - Colonisation at non-swabbed body sites
    - Reluctant to suggest swabbing rectal/vaginal sites, specially in staff-members
HCW as source of outbreak

- Report of 8 clusters
  - 6/8 same strain of GAS in case patients and asymptomatic HCW
  - 6/6 outbreaks subsided after effective treatment of the HCW carrier
  - 1/6 sustained outbreak: household contact of HCW asymptomatic carrier of outbreak strain, served as reservoir for the GAS outbreak
    - Household carriers play role in recolonising treated HCW
- HCW carriers positive in throat, anus, vagina and skin lesions
Screening HCW

Who

- HCW direct contact with the patient within 7 days of the onset of the infection in the patient
- Identify HCW which suffered signs of GAS infection up to 7 days before the onset of the infection in the patient (sore throat, skin infection, vaginitis, pruritis ani,..)

Where

- Sites for screening: throat, skin lesions, vagina, rectal
- If negative and clonal spreading proved, broader screening is necessary
Screening environment

- Persistence of environmental contamination of GAS for up to 6 ½ months
- Shedding in large numbers of microbes in the immediate environment of infected untreated individuals
  - Cultivated from clothing, bedding, curtains, bathrooms, toilets, and other high-risk areas.
- Food contamination due to inoculation by carriers
- Poor quality screening results
  - Dry swabs use, swab after cleaning
  - Negative result not necessarily indicative of a non-contaminated environment
- In 9.8% (6/61) of outbreaks source identified, mostly on maternity wards
Chemoprophylaxis

- Only household contacts if iGAS infections (STSS or NF)
- Definition household contact
  - > 24 h in same household for 7 days before disease until 24 h after start antibiotics for iGAS case
  - Start chemoprophylaxis within 7 days after contact
- Close contacts no prophylaxis but awareness
  - Close contact definition is
    - > 4 h/day or > 20 h/week contact
    - Or room mates
    - Or direct mucosal contact
  - Awareness of symptoms up to 30 days after last contact
## Scheme prophylaxis (AZG)

<table>
<thead>
<tr>
<th>Adult</th>
<th>Pregnant</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycine</td>
<td></td>
<td>Azithromycine</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Clindamycin</td>
<td>Clindamycin</td>
</tr>
</tbody>
</table>

**Clindamycin**
- Adult: 600 mg 3x/day for 10 days
- Children: 25 mg/kg in 4 doses for 10 days

**Azithromycine**
- Adult: 500 mg/d first day, 250 mg/day further for 5 days
- Children: 10 mg/kg/day for 5 days

**Effectiveness of different regimens in eradicating asymptomatic pharyngeal carriage**
- Clindamycin = 100%
- Azithromycine = 95%
- peniG IM = 30%-70%
Household prophylaxis

• UK: Only entire household if 2 or more cases of iGAS infections within 30 days period
• CDC: prophylaxis only for those at highest risk of
  • Subsequent iGAS infection
  • Death from invasive infections (elderly, immunocompromised,…)

• Reasons?
  • Low attack rate
    • 2000 needs treated for prevention of one case
  • Negative effect antimicrobial use (selection of resistance, drug reaction)
Chemoprophylaxis healthcare setting

- No chemoprophylaxis in hospital
  - With exception if positive screening of staff-member in case of outbreak
  - Positive HCW exclusion from work until 24 hours appropriate treatment and resolution of symptoms
  - Control culture 7-10 days after completion of therapy
    - Still positive than household contacts of HCW screening and if positive chemoprophylaxis provided
Control measures outbreak

- Surveillance
- Outbreak management
  - Community
  - Hospital
Surveillance and Case definition

- **Hospital acquired iGAS infection**
  - No symptoms at admission
  - During first 7 days of the hospital stay or 7 days after discharge
  - > 7 days is community acquired as incubation period of GAS infection is short

- **iGAS infection**
  - Isolation of GAS from sterile site or Non sterile site in presence of STSS or NF symptoms
  - AND clinical symptoms of severe infection (hypotense, necrosis tissue, ARDS,…)

- Positive investigation for additional cases retrospective and prospective through surveillance of microbiology records
- Identify possible linked cases of GAS infections
Outbreak in the community

- Secondary case mostly simultaneous presentation with index case, no opportunities for intervention
- Number of clusters small
  - Risk of disease substantial in household contacts
- Risk management strategies
  - Antibiotic prophylaxis to household contacts (individuals at great risks)
  - Communication close contacts of signs and symptoms of disease and need to seek medical attention
- > 3 patients in a community in 1 month
  - Screening of group
  - Treatment of cases
Hospital outbreaks

- Uncommon 5-12%, mostly
  - Post-surgical
  - Childbirth associated, maternity wards
- Rapid investigation essential
  - Identify possible sources
  - Investigate effective control measures
- Screening of staff, patients and environment
  - Seek transmission routes
  - Identify targets for prevention measures such as decontamination and antibiotic prophylaxis
- Droplet isolation
  - Until 24 hours after initiation of effective therapy
  - Contact Precautions for draining wound as above; follow rec. for antimicrobial prophylaxis in selected conditions
Respons to cases postpartum and postsurgical cases (CDC)

- 1 or more cases of postpartum/post-surgical Group D Streptococcus (GAS) infection
- Save isolates from all cases for at least 6 months
- Enhanced surveillance:
  - Review microbiology records from previous 6 months
  - Consult with obstetricians/surgeons and review records to identify additional possible cases
  - Encourage active culturing for all suspected new cases
- Continue enhanced surveillance for additional cases
- Report cases in states where GAS infection is reportable
- Number of cases identified in the facility
- 1 Case: Consider HCW screening
- 2 or more cases: Screen HCWs
- HCWs NOT screened

- Who to screen:
  - Postpartum: HCWs present at vaginal or abdominal delivery or performed vagin al exams prior to delivery
  - Postsurgical: HCWs present in operating room during procedure or who changed dressings on open wounds
  - Either: Contact with case patients during the postpartum/postsurgical period, if disease develops ≥72 h postpartum/post-surgery
- Sites to screen:
  - anus, skin lesions, throat, and vagina
- Reassess epidemiologic data. If ≥2 cases AND PFGE or amn typing implicate a single clone, consider broader search for carrier.
- Continue enhanced surveillance for additional cases

- HCW carrying GAS identified
- Begin therapy
- HCW isolates match case isolates
- HCW management: see Figure 2
- Stop therapy. No further follow up.
Management of health care worker colonised with GAS (CDC)

Figure 2. Recommended management for health care workers (HCWs) colonized with group A Streptococcus
Outbreak management and prevention measures

- Surveillance
- Bacteriological screening of environment
  - Environment decontamination
- Bacteriological screening of potentially exposed individuals
  - Close contacts in households
  - Close contacts in schools
  - Close contacts in health care settings
- Carriers
  - Exclusion from workplace or school for positive carriers or cases
  - Antibiotic prophylaxis and treatment of carriers or cases
- Improve hand hygiene and standard precautions
- Communication of elevated risk