Epidemiology of Invasive Meningococcal Disease

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Vaccination Working Group

Severe bacterial infections

Pneumococcus
Haemophilus influenzae b
Meningococcus
Group B Streptococcus

Infectious Disease Mortality in the United States, 1900 to 1996
Invasive Meningococcal Disease

"Case Report"

Insidious onset → rapid progression

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Symptoms</td>
<td>4 - 8 hours</td>
</tr>
<tr>
<td>Rapid Growth of Meningoccci</td>
<td>12 - 15 hours</td>
</tr>
<tr>
<td>Hospital Admission</td>
<td>15 - 24 hours</td>
</tr>
</tbody>
</table>

Intervention frequently late in the course of disease

Variants:
- Transient Bacteremia
- Organ infections (Pneumonia)
- Meningitis purulenta
- Sepsis + Meningitis
- Fulminant Sepsis

Mortality: 1 - 10% after Ebola, Avian Influenza & Smallpox
- Meningitis 1%
- Meningitis + Sepsis 5-10%
- Fulminant Sepsis (WFS) > 25%

Permanent Sequelae: 10-20%
- Amputation, Deafness, Paralysis, Organ damage

Prehospital Antibiotic Therapy

Post-Exposition Chemoprophylaxis

Vaccination!?
Persistence of Men C Ab-Titers following conjugate vaccination (infants / adolescents)

Kinetics of Booster Response vs Polysaccharide-Antigens in children after conjugate vaccination in infancy

Day 3

Day 7

Day 4-5

Day 10-14

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Nasopharyngeal Bacterial Colonisation (Meningococci)

NP-Colonisation ("Carriage") is a Prerequisite for Invasive Meningococcal Disease

Nasopharyngeal Bacterial Colonisation (Meningococci)

NP-Colonisation ("Carriage") is a Prerequisite for Invasive Meningococcal Disease
Indirect Vaccine Effects – Herd Immunity

Susceptibility for Meningococcal Infection

- Nearly everyone colonized during lifetime
- Antibodies are protective
- Incidence in infants: 1:10000
  (what about the other 9999?)
- Other mechanisms???
**Complement Factor H**

- Most significant human gene related to susceptibility
- Inhibits human complement (C3)
- Increased production of factor H → increased complement inhibition → higher susceptibility for invasive meningococcal disease

**Bacteria produce factor H binding protein (fHBP)**

- Get covered with fH ("protective coat")
- Human complement is inactivated on bacterial surface

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**Risik Factor „Age“**

In incidence of invasive meningococcal disease according to age groups, Austria (2010-2012)
Poor Immune Response of Infants versus bacterial capsular Polysaccharide Antigens (Meningococci, Pneumococci, Haemophilus influenzae B, GBS)

Physiological Immune Deficiency

Antibody Test

Maternal passive immunity

Mature Immunity

3-36 months

5 years

Neisseria meningitidis
Age dependant Carriage

Percentage carriage rate

Outbreak in Stonehouse, Gloucestershire, UK, 1986


Promoters of Carriage

Military barracks

Hospital

Crowded house

Travel

Smoking

Coughing

Kissing

Overall Rate = 10.9%
Carriage Rates of Neisseria meningitidis
Among First-Year University Students

Percentage carriage rate

<table>
<thead>
<tr>
<th>Days of first week of first term</th>
<th>First 3 months in catered halls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Day 2</td>
</tr>
<tr>
<td>6.9</td>
<td>11.2</td>
</tr>
<tr>
<td>19.0</td>
<td>23.1</td>
</tr>
<tr>
<td>34.2</td>
<td>31.8</td>
</tr>
</tbody>
</table>

Number of students swabbed: Day 1 = 825; Day 2 = 669; Day 3 = 691; Day 4 = 268; Oct = 1872; Nov = 542; Dec = 653.


Carriage rate

6.9 11.2 16.0 19.0 23.1
2.0 3.99
1.00–1.99
0.50–0.99
<0.50

Incidence of Meningococcal Disease Europe 2011

Incidence* /100,000 persons

- 2.00–3.99
- 1.00–1.99
- 0.50–0.99
- <0.50

*Confirmed cases of meningococcal disease.
Levels of surveillance vary across countries, which may limit direct comparisons of disease incidence.

Invasive Meningococcal Disease
Austria 2012

Incidence (overall): 0.71/100,000

Typing of Meningococci

- Low variability of polysaccharide capsule
  - 5 serogroups

- High variability of cell membrane proteins
  - Por A 135 x 375 x variable
  - Fet A 186
  - 45 clonal complexes

- High genetic variability
  - 8976 multi locus sequence types (MLST)

Maiden; Caugant D. in Handbook of Meningococcal disease Wiley VCH, 2006

Neisseria meningitidis
Serogrouping and typing

- Polysaccharide capsule: 13 different serogroups

- Outer Membrane Proteins (OMP): porA, fetA
  - porA: 3 variable gene regions (v1, v2, v3) represent serosubtype
    - e.g.: P1.7,16,35 (4cMenB vaccine contains P1.4)
  - fetA: 1 variable region (vr1) 6 families (F1,...,F6)
    - e.g.: F1-2

- 7 house-keeping genes
  - Multi locus sequence typing (MLST) of these genes results in sequence type
    - e.g.: ST-11

Example for complete antigen formula:
Different MenB strains (variable PorA proteins) in UK 2003/4

- PorA
  - Immunodominant in the outer
    membrane vesicles
  - Highly variable across different
    strains of meningococcus
  - Immune response in infants/
    younger children relatively sera-
    subtype (porA) specific
  - Makes 'coverage' of OMV vaccines
    limited, only useful if epidemic
    due to single strain

Gray et al, Journal of Medical Microbiology 2006

Incidence of Invasive Meningococcal C Disease
in Austria and in the province of Styria
1995 - 2013

Invasive Meningococcal Disease
France 2003-2007

Group B: 1,997 cases / 180 deaths = 9% mortality
Group C: 907 cases / 145 deaths = 16% mortality

Isabelle Parent du Châtelet, Paris, 7 Nov 2008
Invasive Meningococcal Disease cases reported by main Clonal Complexes (MLST) and Serogroups
France 2011

Neisseria meningitidis
13 Serogroups / capsular antigens

5 Serogroups most important!

Invasive Meningococcal Disease - Global Serogroup - Distribution
Meningococcal serogroup dynamics
USA 1989–2007

1989-1991
Serogroup B 46%
Serogroup C 8%
Serogroup Y 17%
Serogroup W-135 7%
Serogroup non-groupable 6%

1998
Serogroup B 29%
Serogroup C 22%
Serogroup Y 17%
Serogroup W-135 9%
Serogroup non-groupable 3%

2007
Serogroup B 37%
Serogroup C 6%
Serogroup Y 8%
Serogroup W-135 9%
Serogroup non-groupable 3%


Meningococcal Y Disease in Europe 2010-2012

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of meningococcal cases, 2012</th>
<th>Relative proportion 2012</th>
<th>Relative proportion 2013</th>
<th>Relative proportion 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>England</td>
<td>14,176</td>
<td>7.1%</td>
<td>4.6%</td>
<td>4.6%</td>
</tr>
<tr>
<td>France</td>
<td>7,969</td>
<td>3.9%</td>
<td>3.4%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Germany</td>
<td>3,900</td>
<td>1.9%</td>
<td>1.9%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Portugal</td>
<td>176</td>
<td>0.9%</td>
<td>1.6%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Scotland</td>
<td>177</td>
<td>0.8%</td>
<td>2.3%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Greece</td>
<td>15,326</td>
<td>7.7%</td>
<td>7.7%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Finland</td>
<td>4,702</td>
<td>2.3%</td>
<td>2.3%</td>
<td>2.3%</td>
</tr>
<tr>
<td>France</td>
<td>3,964</td>
<td>2.0%</td>
<td>2.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Spain</td>
<td>72,795</td>
<td>37.0%</td>
<td>37.0%</td>
<td>37.0%</td>
</tr>
<tr>
<td>Sweden</td>
<td>6,287</td>
<td>3.2%</td>
<td>3.2%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Switzerland</td>
<td>44,000</td>
<td>22.5%</td>
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<td>22.5%</td>
</tr>
</tbody>
</table>

Ceyhan M, et al. Poster presented at: 31st Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); May 28-June 1, 2013; Milan, Italy.

*May include serogroups X, 29E, 29F, 29G or non-groupable. †Serogroup not identified.

Meningococcal Serogroups causing Invasive Disease
Turkey 2005-2011

*May include serogroups X, 29E, 29F, 29G or non-groupable. †Serogroup not identified.

Collier M, et al. Paper presented at: The Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); May 28-June 1, 2013; Milan, Italy.
England and Wales is experiencing a year-on-year increase in Meningococcal Serogroup W disease since 2009/10, following rapid expansion of a single endemic hyper-virulent ST-11 clone.

Meningococcal infections were associated with severe disease, atypical clinical presentations (septic arthritis, severe RTIs) and fatal outcomes.

SN Ladhani et al. Clinical Infections Diseases, 10 Nov 2014
Invasive Meningococcal Disease and Death Rates in Austria 1995-2013

~ 50% of fatal cases due to serotype B

Serogroup Distribution in Austria 1995-2012

Austrian National Reference Center for Meningococci

Invasive Meningococcal Disease in Austria
Serogroup Distribution in Austria according to Age Groups (1995 - 2012)

Source: National Reference Center for Meningococci (AGES)
Daily surveillance, additional cases with Serogroups C, W, Y entered disease charts
“Moving Targets”
for Meningococcal Vaccines ...