Educational Workshop

EW08: Epidemiology of Clostridium difficile infection
arranged with ESGCD
(ESCMID Study Group for Clostridium difficile)

Convenor: Petra Gastmeier (Berlin, DE)

Faculty: Petra Gastmeier (Berlin, DE)
Anni Virolainen-Julkunen (Helsinki, FI)
Jean O'Driscoll (Aylesbury, UK)
Abraham Goorhuis (Leiden, NL)
Epidemiology of Clostridium difficile infection

Optimal surveillance methods to study the epidemiology of CDI

Petra Gastmeier
Charité - University Hospital Berlin, Germany

PubMed search: "CDI surveillance method
April 2009
n= 250

Optimal CDI surveillance method?

Definition for CDI + Method for surveillance = Surveillance data
Gastmeier – Epidemiology of CDI

CDAD CASE
This is a patient to whom one or more of the following criteria applies:
1. diarrhoeal stools or toxic megacolon, and a positive laboratory assay for C. difficile ToxA and/or ToxB in stools or a toxin-producing C. difficile organism detected in stool via culture or other means;
2. pseudomembranous colitis revealed by lower gastrointestinal endoscopy;
3. colonic histopathology characteristic of C. difficile infection (with or without diarrhoea) on a specimen obtained during endoscopy, colectomy or autopsy.

This definition may be focused on criterion no. 1 in laboratory-based surveillance systems performing tests for C. difficile only on unformed stools (i.e., stools that take the shape of their container). All three criteria can be used in patient-based surveillance systems targeting diarrhoeal symptoms (i.e., at least three liquid or unformed stools for at least 24 h).

This definition excludes diarrhoea with other known aetiology (as diagnosed by the attending physician), and asymptomatic patients with a stool culture positive for toxin-producing C. difficile or an assay positive for C. difficile ToxA and/or ToxB.
Strategies to Prevent Clostridium difficile Infections in Acute Care Hospitals

Dubberke et al. ICHE 2008; 29: Suppl.1

A CDI case is defined as a case of diarrhea or toxic megacolon without other known etiology that meets 1 or more of the following criteria: (1) the stool sample yields a positive result of a laboratory assay for *C. difficile* toxin A and/or B, or a toxin-producing *C. difficile* organism is detected in the stool sample by culture or other means; (2) pseudomembranous colitis is seen on endoscopic examination or surgery; and (3) pseudomembranous colitis is seen on histopathological examination.
RECURRENT CDAD CASE
This is a patient with an episode of CDAD that occurs within 8 weeks following the onset of a previous episode. A recurrence can correspond to a relapse involving the same strain or to a re-infection with a different strain [79-82]. The simultaneous occurrence of multiple PCR ribotypes in faecal samples may also result in isolation of a different strain in a recurrent episode [83]. In clinical practice, it is not possible to differentiate between relapse and re-infection; the term recurrence is therefore used as a designation for both. The risk of complications in the case of a recurrence due to the new emerging strain may be higher than previously thought [43].

Optimal CDI surveillance method?

Definition for CDI + Method = Surveillance data
Surveillance

... is information for action

- in the own hospital

- on a national/global level

Surveillance

... is information for action

- in the own hospital:
  • to observe the situation and to stimulate further infection control measures
  • To stop outbreaks and perform risk factor analyses
Gastmeier – Epidemiology of CDI

Surveillance of *Clostridium difficile*-associated disease with the German nosocomial infection surveillance system KISS (CDAD-KISS)

<table>
<thead>
<tr>
<th>Table 1. Incidence and classification of <em>Clostridium difficile</em>-associated disease (CDAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category</strong></td>
</tr>
<tr>
<td>Hospitals</td>
</tr>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>Patient days</td>
</tr>
<tr>
<td>CDAD patients</td>
</tr>
<tr>
<td>CDAD cases</td>
</tr>
<tr>
<td>CDAD present on admission</td>
</tr>
<tr>
<td>Ambulant cases</td>
</tr>
<tr>
<td>Cases from another healthcare facility</td>
</tr>
<tr>
<td>Nosocomial CDAD cases</td>
</tr>
<tr>
<td>Severe cases</td>
</tr>
</tbody>
</table>

Distribution of CDAD incidence density rates 2007

<table>
<thead>
<tr>
<th>Rate</th>
<th>Mean</th>
<th>25th percentile</th>
<th>Median</th>
<th>75th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall incidence density</td>
<td>6.6</td>
<td>1.2</td>
<td>3.1</td>
<td>9.2</td>
</tr>
<tr>
<td>Incidence density of nosocomial cases</td>
<td>4.9</td>
<td>1.9</td>
<td>3.6</td>
<td>6.7</td>
</tr>
<tr>
<td>Incidence density of severe CDAD cases</td>
<td>0.4</td>
<td>0.0</td>
<td>0.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

(per 10,000 patient days)
Gastmeier – Epidemiology of CDI

Distribution according to speciality 2007

<table>
<thead>
<tr>
<th>Departments</th>
<th>Cases</th>
<th>CDAD cases per 10,000 patient days</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICUs</td>
<td>193</td>
<td>9.1</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>1,687</td>
<td>12.1</td>
</tr>
<tr>
<td>Surgery</td>
<td>394</td>
<td>4.1</td>
</tr>
<tr>
<td>Other conservative</td>
<td>572</td>
<td>5.8</td>
</tr>
<tr>
<td>Other surgical</td>
<td>187</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3,033</strong></td>
<td><strong>6.4</strong></td>
</tr>
</tbody>
</table>

KISS Krankenhaus-Infektions-Surveillance-System

Modul CDAD-KISS Referenzdaten 2008

Development 2006-2008

<table>
<thead>
<tr>
<th></th>
<th>2006 (Pilot study)</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of hospitals</td>
<td>14</td>
<td>34 (1.7 %)</td>
<td>54 (2.7 %)</td>
</tr>
<tr>
<td>CDI cases</td>
<td>1,128</td>
<td>3,033</td>
<td>4,338</td>
</tr>
<tr>
<td>Incidence (per 10,000 patients)</td>
<td>46.5</td>
<td>30.6</td>
<td></td>
</tr>
<tr>
<td>Incidence density (median, per 10,000 patient days)</td>
<td>7.3</td>
<td>5.1</td>
<td>6.0</td>
</tr>
<tr>
<td>Overall incidence</td>
<td>4.7</td>
<td>3.6</td>
<td>3.7 (66 %)</td>
</tr>
<tr>
<td>Nosocomial cases</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1 (5 %)</td>
</tr>
<tr>
<td>Severe cases</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Gastmeier – Epidemiology of CDI

Distribution of the nosocomial CDAD incidence density

Questionnaire to the hospitals 2007

**Data from 40 hospitals**
*(for data interpretation)*

When do you perform CDAD diagnostics?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the case of diarrhea, immediately</td>
<td>57.5 %</td>
</tr>
<tr>
<td>In the case of diarrhea, when the patient has been in the hospital for &gt; 72 hours</td>
<td>42.5 %</td>
</tr>
<tr>
<td>In the case of diarrhea, when the patient has received prior antibiotic therapy</td>
<td>60.0 %</td>
</tr>
<tr>
<td>In the case of diarrhea, when the patient is above 65 years old</td>
<td>17.5 %</td>
</tr>
<tr>
<td>If the patient was already positive in the past</td>
<td>65.0 %</td>
</tr>
<tr>
<td>If the patient admitted from an at risk area</td>
<td>20.0 %</td>
</tr>
</tbody>
</table>
Who is responsible for initiating CDAD diagnostics?

- It has to be ordered specifically by the treating physician 80 %
- In the case of diarrhea CDAD diagnostics it is automatically included by the laboratory 20 %

Acquisition of CDAD (2007 data)

- Nosocomial 2213 (73 %)
- Patients from other healthcare facilities 201 (6.6 %)
- Ambulatory cases 619 (20.4 %)

Can you distinguish between ambulatory acquired and acquired in another healthcare facility?

- no 15.0
- yes 35.0
- yes, but only with high efforts 45.0
Comparison of surveillance data

<table>
<thead>
<tr>
<th></th>
<th>Hospitals</th>
<th>Incidence (per 10,000 patients)</th>
<th>Incidence density (per 10,000 patient days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDAD-KISS 2007</td>
<td>34</td>
<td>46.5</td>
<td>6.6</td>
</tr>
<tr>
<td>CDAD-KISS 2008</td>
<td>54</td>
<td>30.6</td>
<td>6.0</td>
</tr>
<tr>
<td>Canada (CNISP) (2007)</td>
<td>49</td>
<td>48</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Voluntary versus mandatory surveillance

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Voluntary participation, confidential data</th>
<th>Mandatory participation and public reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Workload</td>
<td>Should be limited</td>
<td>Can be determined</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Overrepresentation of facilities with CDI problems ?</td>
<td>All facilities</td>
</tr>
<tr>
<td>Diagnostics</td>
<td>No bias expected</td>
<td>Underreporting due to public reporting?</td>
</tr>
</tbody>
</table>


Figure 10: Trend in C. difficile reports for patients aged 65 years and over reported via the mandatory and voluntary reporting systems, 2000 to 2007

- Voluntary
- Mandatory
Summary points and commentary on quarterly (January 2006 to September 2008), calendar year (2004-2007) and financial year (2007/08) *Clostridium difficile* data derived from Mandatory Surveillance, January 2009

- Quarterly reports of *C. difficile* infections are summarised in the table below:

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Number of <em>C. difficile</em> reports in patients aged 2-44 years</th>
<th>Number of <em>C. difficile</em> reports in patients aged 65+ years</th>
<th>Number of <em>C. difficile</em> reports in patients aged ≥2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>January-March 2006</td>
<td>-</td>
<td>13,340</td>
<td>-</td>
</tr>
<tr>
<td>April-June 2006</td>
<td>-</td>
<td>14,689</td>
<td>-</td>
</tr>
<tr>
<td>July-September 2006</td>
<td>-</td>
<td>13,821</td>
<td>-</td>
</tr>
<tr>
<td>October-December 2006</td>
<td>-</td>
<td>12,776</td>
<td>-</td>
</tr>
<tr>
<td>January-March 2007</td>
<td>-</td>
<td>15,644</td>
<td>-</td>
</tr>
<tr>
<td>April-June 2007</td>
<td>2,044</td>
<td>13,924</td>
<td>18,868</td>
</tr>
<tr>
<td>July-September 2007</td>
<td>2,536</td>
<td>10,884</td>
<td>13,422</td>
</tr>
<tr>
<td>October-December 2007</td>
<td>2,230</td>
<td>10,000</td>
<td>12,230</td>
</tr>
<tr>
<td>January-March 2008</td>
<td>2,156</td>
<td>10,669</td>
<td>12,825</td>
</tr>
<tr>
<td>April-June 2008</td>
<td>2,102</td>
<td>6,096</td>
<td>10,088</td>
</tr>
<tr>
<td>July-September 2008</td>
<td>3,116</td>
<td>7,063</td>
<td>8,947</td>
</tr>
</tbody>
</table>

Figure 22: Changes in distribution of *C. difficile* PCR ribotypes between the two sampling periods (2005-6 and 2007-8)

Patient Safety Component

Protocol: Multidrug-resistant Organism (MDRO) and Clostridium difficile-Associated Disease (CDAD) Module

CDI Incidence Rate = Number of non-duplicate and Incident CDI LabID Events per patient per month identified > 3 days after admission to the location or facility / Number of patient days for the location or facility x 10,000

Facility CDI Healthcare Facility-Onset Incidence Rate = Number of all Incident HO CDI LabID Events per patient per month / Number of patient days for the facility x 10,000

Facility CDI Combined Incidence Rate = Number of all Incident HO and CO-HCFA CDI LabID Events per patient per month / Number of patient days for the facility x 10,000

**MDRO or CDAD Infection Event**

- Event Type
- Date of Event
- Event Type Specific
- Event Type Code
- Event Type Code Definition
- Event Type Code Description
- Event Type Code Notes

- Organism Name
- Organism Code
- Organism Code Definition
- Organism Code Description
- Organism Code Notes

- Species
- Species Code
- Species Code Definition
- Species Code Description
- Species Code Notes

- Genus
- Genus Code
- Genus Code Definition
- Genus Code Description
- Genus Code Notes

- Family
- Family Code
- Family Code Definition
- Family Code Description
- Family Code Notes

- Laboratory or Clinical Test
- Test Name
- Test Code
- Test Code Definition
- Test Code Description
- Test Code Notes

- Test Result
- Test Result Code
- Test Result Code Definition
- Test Result Code Description
- Test Result Code Notes

- Test Result Value
- Test Result Value Code
- Test Result Value Code Definition
- Test Result Value Code Description
- Test Result Value Code Notes

- Test Result Unit
- Test Result Unit Code
- Test Result Unit Code Definition
- Test Result Unit Code Description
- Test Result Unit Code Notes

- Test Result Interpretation
- Test Result Interpretation Code
- Test Result Interpretation Code Definition
- Test Result Interpretation Code Description
- Test Result Interpretation Code Notes

- Test Result Range
- Test Result Range Code
- Test Result Range Code Definition
- Test Result Range Code Description
- Test Result Range Code Notes

Gastmeier – Epidemiology of CDI

Public reporting in Ohio, 2006

- Approximately 14,100 cases
- Hospital onset:
  - ca. 5,000 initial cases = 7-8 per 10,000 patient days
  - ca. 1,200 recurrent cases = 1-2 per 10,000 patient days
- Long term care facility onset:
  - ca. 4,800 initial cases = 2-3 per 10,000 patient days
  - ca. 3,100 recurrent cases = 1-2 per 10,000 patient days

Comparison of surveillance data

<table>
<thead>
<tr>
<th></th>
<th>Hospitals</th>
<th>Incidence (per 10,000 patients)</th>
<th>Incidence density (per 10,000 patient days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany CDAD-KISS 2007</td>
<td>34</td>
<td>46.5</td>
<td>6.6</td>
</tr>
<tr>
<td>CDAD-KISS 2008</td>
<td>54</td>
<td>30.6</td>
<td>6.0</td>
</tr>
<tr>
<td>Canada (CNISP) (2007)</td>
<td>49</td>
<td>48</td>
<td>7.2</td>
</tr>
<tr>
<td>Ohio 2006 Mandatory reporting</td>
<td>?</td>
<td></td>
<td>7-8</td>
</tr>
</tbody>
</table>

Surveillance

... is information for action
- in the own hospital:
  - to observe the situation and to stimulate further infection control measures
  - To stop outbreaks and perform risk factor analyses
Case control study:

- Retrospective analysis
- To record as much as possible risk factors (depending on the quality of documentation)

A case control study

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No. of patients</th>
<th>No. of CDI patients (%)</th>
<th>Odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 50</td>
<td>26</td>
<td>14 (53.8%)</td>
<td>1.00</td>
<td>0.47</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11</td>
<td>4 (36.4%)</td>
<td>0.68</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking</td>
<td>9</td>
<td>4 (44.4%)</td>
<td>1.00</td>
<td>0.78</td>
</tr>
<tr>
<td>Previous PD</td>
<td>16</td>
<td>4 (25.0%)</td>
<td>0.68</td>
<td>0.06</td>
</tr>
<tr>
<td>Cerebro</td>
<td>3</td>
<td>0 (0%)</td>
<td>-</td>
<td>0.96</td>
</tr>
<tr>
<td>All other causes</td>
<td>1</td>
<td>1 (100%)</td>
<td>-</td>
<td>0.86</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>27 (50.0%)</td>
<td>2.06</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

An outbreak of Clostridium difficile-associated disease (CDMA) in a German university hospital

Cohort study (when ongoing)

- Prospective analysis
- To record as much as possible risk factors (depending on the possibilities)
Gastmeier – Epidemiology of CDI

Table 3. Multivariate analysis of the characteristics of the adult patients with healthcare-associated Clostridium difficile infection (CDI) independently associated with severe outcomes (stepwise logistic regression model) (n = 1128).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>SE</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased past year of age, starting at age 18 years</td>
<td>0.0215</td>
<td>0.0079</td>
<td>1.02 (1.01-1.04)</td>
<td>.006</td>
</tr>
<tr>
<td>Admitted from another hospital or nursing home</td>
<td>0.7347</td>
<td>0.2922</td>
<td>2.09 (1.35-3.20)</td>
<td>.001</td>
</tr>
<tr>
<td>Liver disease</td>
<td>0.9637</td>
<td>0.4388</td>
<td>2.62 (1.39-4.06)</td>
<td>.027</td>
</tr>
<tr>
<td>Receiving vancomycin as radical treatment</td>
<td>0.9463</td>
<td>0.2497</td>
<td>2.61 (1.49-4.80)</td>
<td>.001</td>
</tr>
<tr>
<td>Treatment for CDI was changed</td>
<td>0.7405</td>
<td>0.2485</td>
<td>2.16 (1.33-3.46)</td>
<td>.002</td>
</tr>
</tbody>
</table>

**NOTE:** Adjusted for location of the patient or crew of intensive care unit, department, surgery department, or intensive care unit.

Identify undetected carriers/contact patients

Identify transmissions

CID 2009; 48:568

Health Care–Associated Clostridium difficile Infection in Adults Admitted to Acute Care Hospitals in Canada: A Canadian Nosocomial Infection Surveillance Program Study
Surveillance

... is information for action
- on a national/global level:
  • to survey the development in the whole country (including risk factor analysis)
  • to analyze consequences of infections

Figure: Incidence of Clostridium difficile-associated disease per 100,000 inpatients upon discharge from hospitals in Germany

Vonberg et al. EID 2007

CDAD development in Germany according to discharge diagnoses

Vonberg RP, Epi Bull 2006
Discharge data 2006:
9.75 per 10,000 admitted patients

CDAD-KISS data 2008:
30.6 per 10,000 admitted patients

**National point prevalence of *Clostridium difficile* in US health care facility inpatients, 2008**

Gastmeier – Epidemiology of CDI

13.1 per 1000 in patients
79% had received antimicrobials within 30 days

Hospitals Incidence (per 10,000 patients)

<table>
<thead>
<tr>
<th></th>
<th>Incidence density (per 10,000 patient days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>CDAD-KISS 2007</td>
</tr>
<tr>
<td></td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>46.5</td>
</tr>
<tr>
<td></td>
<td>6.6</td>
</tr>
<tr>
<td>Canada</td>
<td>CDAD-KISS 2008</td>
</tr>
<tr>
<td></td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>30.6</td>
</tr>
<tr>
<td></td>
<td>6.0</td>
</tr>
<tr>
<td>Ohio</td>
<td>Mandatory reporting</td>
</tr>
<tr>
<td></td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>7-8</td>
</tr>
<tr>
<td>Canada</td>
<td>CNISP (2007)</td>
</tr>
<tr>
<td></td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>7.2</td>
</tr>
<tr>
<td>US</td>
<td>National point prevalence study 2008</td>
</tr>
<tr>
<td></td>
<td>648</td>
</tr>
<tr>
<td></td>
<td>131</td>
</tr>
<tr>
<td></td>
<td>Prevalence !</td>
</tr>
</tbody>
</table>

Comparison of surveillance data

Cohort studies versus cross sectional studies

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Cohort study</th>
<th>Cross section study</th>
</tr>
</thead>
<tbody>
<tr>
<td>results</td>
<td>Incidence data</td>
<td>Prevalence data</td>
</tr>
<tr>
<td>workload</td>
<td>high</td>
<td>low</td>
</tr>
</tbody>
</table>
| limitations  | -Risk factor analysis not possible (what was first?)
|              | -Higher chance to include patients with prolongation of stay |
Surveillance

... is information for action on a national/global level:
- to survey the development in the whole country (including risk factor analysis)
- to analyse consequences of infections

Costs of nosocomial Clostridium difficile-associated diarrhoea


*Institute for Medical Microbiology and Hospital Epidemiology, Medical School Hannover, Hannover, Germany
**Institute for Hygiene and Environmental Medicine, Charité - University Medicine Berlin, Germany
†Financial Controlling, Medical School Hannover, Hannover, Germany

Received 27 December 2007; accepted 7 May 2008

Other CDAD costs studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases</th>
<th>Extra costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilcox et al. 1996</td>
<td></td>
<td>£ 4 107</td>
</tr>
<tr>
<td>Kyne et al. 2002</td>
<td>439</td>
<td>$ 3 669</td>
</tr>
<tr>
<td>Dubberke et al. 2008</td>
<td>439</td>
<td>$ 2 454</td>
</tr>
<tr>
<td>Vonberg et al. 2008</td>
<td>45</td>
<td>€ 7 147</td>
</tr>
</tbody>
</table>
Total annual cost estimation for Germany

2006: 16,800,000 patients hospitalized
Incidences 46.2 per 10,000 patients
\[ \rightarrow 78,000 \text{ cases per year} \]
\[ \times 3,000 \text{ €} \]
\[ = 234 \text{ Mio €} \]

Summary

The CDI surveillance method depends
• on the objective of the surveillance
• the available resources
• the background (size of the problem)
The most appropriate method should be selected
according to the situation.
The data should be collected in a way, that comparison
with reference data is possible.
Severity of *Clostridium difficile* infection - implications for action

Anni Virolainen-Julkunen, MD, PhD

May 16th, 2009 ECCMID2009 / CDI workshop / Anni Virolainen-Julkunen

Disclosures

- No financial or other conflict of interest to disclose

- The findings and conclusions in this presentation have not been formally disseminated by the National Institute for Health and Welfare and should not be construed to represent any agency determination or policy

*Clostridium difficile, CD*

- Anaerobe bacterium
- Gram-positive rod
- Forms spores
- Produces toxins
- Found in soil, water and environmental surfaces
- Asymptomatic colonization in gastrointestinal tract of animals and humans

Spores remain on surfaces and in environment and are not destroyed by alcohol-based agents
**Clostridium difficile infection, CDI**

- Toxin-producing CD - the most common cause of healthcare-associated diarrhoea
- From mild diarrhoea to life-threatening enterocolitis
- Both in healthcare facilities and in community
- Incidence and severity reported increasing
- Antimicrobial exposure, hospitalization, advanced age

Bartlett JG and Gerding DN. Clin Infect Dis 2008; 46 (Suppl 1)

**Clinical presentation of CDI**

- Diarrhoea with prior antibiotic use
  - Loose stools (Bristol Chart), increased frequency
  - Abdominal pain, fever, nausea, vomiting, dehydration
  - Pseudomembranous colitis, toxic megacolon, sepsis or shock, multiorgan failure
  - Paralytic ileus – no diarrhoea!
- Leukocytosis, elevated serum creatinine, hypoalbuminemia

Courtesy of Mark W. Hull

**Assessing severity of CDI**

- Public health burden
  - Morbidity and mortality
  - Case fatality (%)
- Clinical presentation
  - Case definitions for surveillance
  - Case definitions for treatment trials and research
- Molecular characteristics of the CD isolate
  - Toxins A/B, binary toxins, mutations and/or truncations of the tcdC gene
  - Genotyping of isolates in relation to morbidity and mortality
  - Sporulation
Assessing severity of CDI

- Public health burden
  - Morbidity and mortality
  - Case fatality (%)

- Clinical presentation

- Molecular characteristics of the CD isolate

News from Canada...

Hospitals battling outbreaks of *C. difficile*

A retrospective chart review of all cases of *C. difficile*-associated disease in one Quebec hospital between 1991-2003:
- Incidence from 36/100 000 in 1991 to 156/100 000 in 2003
- Proportion of cases with complications from 7% to 18%
- Death within 30 days of diagnosis: from 5% to 14%
Virolainen-Julkunen – Severity of CDI

...leading to studying of the CD isolates

Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe

- Isolates from 124 consecutive patients with C. difficile–associated disease in Quebec, June 2004 – April 2005
- A new epidemic strain NAP1/027 implicated in outbreaks associated with severe disease

...also in the U.S.

An Epidemic, Toxin Geno–Type strain of Clostridium difficile

- 187 C. difficile isolates from 8 healthcare facilities in 6 states in which outbreaks of C. difficile–associated disease had occurred between 2000 and 2003
- A strain B1/NAP1, toxigenotype III, positive for binary toxin and containing of an 18bp tcdC gene deletion
- Resistance to gatifloxacin and moxifloxacin

...with further epidemiology from Canada

A Predominantly Clonal Multi-Institutional Outbreak of Clostridium difficile–Associated Diarrhea with High Morbidity and Mortality

- Marked increase in the incidence reported in 2003
- A prospective study in 12 Quebec hospitals to determine incidence in 2004
  - Incidence and mortality increased
- A case-control study to identify risk factors
  - Exposure to fluoroquinolones and cephalosporins
CDI incidence in the U.S.
discharge diagnosis coding data

![Graph showing CDI incidence in the U.S.](image)

**Increase in Clostridium difficile-related Mortality Rates, United States, 1999-2004**

Matthew D. Redelings, Frank Burdick, and Laurenza Mascetti

Reported mortality rates from *Clostridium difficile* in the United States increased from 0.1 per million population in 1999 to 2.7 per million in 2004. Increased rates may be due to emergence of a highly virulent strain of *Clostridium difficile* that is more difficult to treat than previous strains.

Redelings et al. Emerg Infect Dis 2007; 13

**Increase in Adult Clostridium difficile-related Hospitalizations and Case-Fatality Rate, United States, 2000-2005**

Ways D. Zilberberg, Andrew S. Horan, and Morris K. Kubly

Reported hospitalizations and case-fatality rates from *Clostridium difficile* infection in the United States increased from 0.2 per 100,000 population in 2000 to 1.04 per 100,000 in 2005, and the associated case-fatality rate rose from 1.1 to 2.9% in 2004.

Zilberberg et al. Emerg Infect Dis 2006; 14
C. difficile-associated disease in 10 peripartum and 23 previously healthy people in the community.

Similar observations reported from Connecticut, 2006 (MMWR 2008;57:340-3)

CD incidence in the United Kingdom

CD-related deaths in the U.K.
Hospital discharges with CD in Denmark and consumption of antibiotics

[Graph showing hospital discharges and antibiotic consumption]

Sorensen et al. Eurosurveillance 2009; 14

Hospital discharges with CD in Finland

[Graph showing hospital discharges by diagnosis]

Lyytikäinen et al. Emerg Inf Dis 2009; 15

Hospital discharges with CD in Finland by age

[Graph showing hospital discharges by age]

Lyytikäinen et al. Emerg Inf Dis 2009; 15
Virolainen-Julkunen – Severity of CDI

Mortality rates with CD in Finland by age

Which of the following statements is true?

a. Incidence of CDI has increased during the past years reported from many countries
b. Severity of CDI has increased during the past years reported from many countries
c. Surveillance activity and/or methodology is influencing C. difficile epidemiology figures
d. Diagnostic activity and/or methodology is influencing C. difficile epidemiology figures
e. None of the above
f. All of the above

Assessing severity of CDI

• Public health burden
• Clinical presentation
  – Case definitions for surveillance
  – Case definitions for treatment trials and research
• Molecular characteristics of the bacterium
Virolainen-Julkunen – Severity of CDI

Healthcare vs. community

<table>
<thead>
<tr>
<th>Healthcare</th>
<th>Community</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Onset</td>
</tr>
<tr>
<td>Associated</td>
<td>Non-associated</td>
</tr>
</tbody>
</table>

Definitions for CDI

- Healthcare onset, community associated
- Community onset, healthcare associated
- Onset – initiation of symptoms or sampling date?
- Associated – origin of infection
- Different definitions for different objectives
  - Case definitions for CDI, recurrent and severe CDI

Case definition for CDI

- A case of diarrhoea or toxic megacolon without any other cause and one of the following
  - Stool positive for C. difficile toxin or toxin-producing C. difficile
  - Pseudomembranous colitis by endoscopy or surgery
  - Pseudomembranous colitis by histology
- Applicable to laboratory-based surveillance by the first criterion
Virolainen-Julkunen – Severity of CDI

**Case definition for recurrent CDI**
- An episode of CDI within 8 weeks after the onset of the previous episode – provided the symptoms have resolved meanwhile
- Definition implemented for laboratory-based reporting
  - Positive lab result within 2 weeks: same case
  - Positive lab result within 2-8 weeks: recurrent case
  - Positive lab result more than 8 weeks: new case
- Relapse vs reinfection? Role of genotyping?
- Applicable to treatment trials and research purposes

McDonald et alii. Infect Cont Hosp Epidemiol 2007; 28

**Case definition for severe CDI**
- A CDI case within 30 days from onset of symptoms or the index laboratory test and any of the following
  - Admission to ICU for complications of CDI
  - Colectomy for toxic megacolon, perforation or refractory colitis
  - Death caused by CDI (primary or contributive)
- Applicable to case-based surveillance

McDonald et alii. Infect Cont Hosp Epidemiol 2007; 28

**Assessing severity of CDI by case definitions**
- ... in relation to individual suffering
- ... in relation to need of (re)hospitalization
- ... in relation to outcome
  - of an individual episode of CDI
  - of repeated episodes of CDI
- ... in relation to outbreak potential
- ... in relation to costs
Assessing severity of CDI

- Public health burden
- Clinical presentation
- Molecular characteristics of the CD isolate
  - Toxins A/B, binary toxins, mutations and/or truncations of the tcdC gene
  - Genotyping of isolates in relation to morbidity and mortality
  - Sporulation

Which diagnostic test do you use?

a. Cytotoxin assay
b. Toxin detection of clinical samples
  a. Toxin A only
  b. Toxin A and B
c. Isolation of *C. difficile* by culture
d. Toxinogenic *C. difficile* culture
e. Glutamate dehydrogenase (GDH) antigen test
f. PCR methods for detecting toxin genes
g. PCR methods for detecting toxin genes (A/B and binary) and tcdC deletions or other molecular markers

Primary laboratory diagnosis of CDI

- Toxin detected from fecal samples/cultivated isolates
  - Cell cytotoxicity assay
  - Enzyme-linked assays (EIA), membrane-bound assays
- Toxin genes detected by PCR-assays (real-time, multiplex)
- Antigen test: glutamase dehydrogenase (GDH)
- Stool culture
- Toxigenic stool culture – optimal
  - Toxin detection: clinical dg, transmission control
  - Culture: molecular epidemiology, antibiotic susceptibility
Evaluation of CD toxin detection assays

Virolainen-Julkunen – Severity of CDI

Table 1. Summary of results for toxigenicity of commercial C. difficile toxin detection kits with cytotoxic assay

<table>
<thead>
<tr>
<th>Assay</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preporagen Test</td>
<td>97.7 (93-100)</td>
<td>99.1 (98-100)</td>
</tr>
<tr>
<td>Vitek C. difficile Test A/60</td>
<td>98.6 (96-100)</td>
<td>99.8 (99-100)</td>
</tr>
<tr>
<td>CLO</td>
<td>99.7 (98-100)</td>
<td>97.3 (96-98)</td>
</tr>
<tr>
<td>Modified test A/60</td>
<td>98.6 (96-100)</td>
<td>97.3 (96-98)</td>
</tr>
<tr>
<td>Toxinogen Test</td>
<td>98.6 (96-100)</td>
<td>97.3 (96-98)</td>
</tr>
<tr>
<td>Toxinogen A/60</td>
<td>98.6 (96-100)</td>
<td>97.3 (96-98)</td>
</tr>
<tr>
<td>Manual Multiplex</td>
<td>99.7 (98-100)</td>
<td>97.3 (96-98)</td>
</tr>
<tr>
<td>Manual Rapid</td>
<td>99.7 (98-100)</td>
<td>97.3 (96-98)</td>
</tr>
<tr>
<td>Total C. difficile A/60</td>
<td>99.7 (98-100)</td>
<td>97.3 (96-98)</td>
</tr>
<tr>
<td>EI toxin A/B</td>
<td>99.7 (98-100)</td>
<td>97.3 (96-98)</td>
</tr>
<tr>
<td>EI toxin A</td>
<td>99.7 (98-100)</td>
<td>97.3 (96-98)</td>
</tr>
<tr>
<td>EI toxin A/B</td>
<td>99.7 (98-100)</td>
<td>97.3 (96-98)</td>
</tr>
</tbody>
</table>

Molecular characteristics of the CD isolates

- Detection of toxin genes by PCR-assays (real-time, multiplex) and/or sequencing:
  - Pathogenicity locus, PaLoc (tcdA, tcdB, tcdC)
  - Binary toxin genes (cdtA, cdtB)

- Emergence of new, hypervirulent epidemic clone of toxin-producing C. difficile NAP1/027/toxinotype III

- ... in relation to molecular typing techniques
  - PFGE – North American standard
  - PCR ribotyping – European standard
  - Toxinotyping (tcdA and tcdB by RFLP)
  - MLVA, AFLP, REA, spAST and others

References:
- Peterson et alii. Clin Microbiol Infect 2007;45
- Sloan et alii. J Clin Microbiol 2008;46
- Persson et alii. Clin Microbiol Infect 2008;14
- Antikainen et alii. APMIS, in press

NATIONAL INSTITUTE FOR HEALTH AND WELLBEING
**C. difficile PCR ribotype 027 in the U.S.**

States with \( \text{DHHS} = 1027 \) strain of \( \text{C. difficile} \) (\( n=40 \)), October 2008

- Outbreaks due to CD PCR ribotype 027
- Sporadic cases due to CD PCR ribotype 027

Kuijper et alii. Euro Surveill 2008; 13(31) updated in April 2009

---

**C. difficile PCR ribotype 027 in Europe**

- Outbreaks due to CD PCR ribotype 027
- Sporadic cases due to CD PCR ribotype 027

---

**C. difficile PCR ribotypes in Finland**

Kotila et alii, unpublished
Control strains: Cardiff-ECDC collection

---
Virolainen-Julkunen – Severity of CDI

\[ \text{C. difficile PFGE types in Finland} \]

\[ \text{PFGE} \]

\[ \text{Ibrahem et al., unpublished; Control strains: Cardiff-ECDC collection} \]

Which of the following might be true?

a. Toxin B is essential for virulence of CD
b. Binary toxins are necessary for virulence of CD
c. Deletion at position 117 of the \text{tcdC} \text{ gene is more important for virulence of CD than the larger 18 bp deletions in the same gene}
d. PCR ribotype 027 is the only CD genotype producing toxins in excess amounts
e. Some toxigenic C. difficile may have increased spore-forming capability

Implications for action

- Information from different levels...
  - International
  - National
  - Local
  - Individual
  - Microbial
- ...to be implemented by
  - Early diagnosis
  - Surveillance
  - Education and communication
  - Isolation precautions
  - Hand hygiene
  - Protective clothing
  - Environmental cleaning
  - Use of medical equipment
  - Good antibiotic stewardship
  - Specific measures during outbreaks

Dubberke et al. Infect Control Hosp Epidemiol 2008; 29 (Suppl 1)
Vonberg et al. Clin Microbiol Infect 2008; 14 (Suppl 5)
**Action: Awareness**

- Early diagnosis
  - Prompt testing for CD toxins on unformed stools
  - No testing after treatment
  - Faecal samples stored for further typing
- Routine surveillance
  - Unit-specific baseline and threshold incidence
  - Alert for changes in rate, complications, severity
- Education and communication
  - Health-care workers
  - Visitors (next of kin)

**Action: Treatment**

- Role of antimicrobial agents
  - Stop any non-CD antimicrobial treatment
  - Oral vancomycin – the only FDA approved agent
  - Metronidazole, rifaximin
- Role of non-antimicrobial agents
  - Probiotics
  - Toxin-binding resins and polymers
  - Passive immunotherapy
- Role of restoring normal flora
  - Non-toxigenic strains of *C. difficile*
  - Faecal transplantation

**Action: Control and prevention**

- Isolation precautions
- Hand hygiene
- Protective clothing
- Environmental cleaning
- Use of medical equipment
- Good antibiotic stewardship
- Specific measures during outbreaks
Virolainen-Julkunen – Severity of CDI

Action: Control and prevention in short

- Prevention of acquisition and transmission
  - Single patient rooms and/or cohorting
  - Duration of isolation precautions
  - Hand hygiene: soap, water and gloves
  - Environmental cleaning: clean first, then bleach
  - Dedicated/disposable medical devices
- Antimicrobial stewardship
  - Need, choice, dose, duration
  - Outpatient – hospital setting
- Vaccine

What to do next – or not?

a. New diagnostic tools are needed to detect CDI
b. Surveillance is needed to estimate the disease burden by CDI
c. On-line genotyping of CD isolates is needed to control outbreaks of CDI
d. More effective hand hygiene and cleaning agents are needed to control spread of CD
e. New antimicrobial agents are needed to treat CDI
f. Antibiotic stewardship is needed to control CDI
g. I would consider faecal transplant if I contracted CDI myself

Summary of basis for action

- Burden of disease
  - Incidence, mortality/case fatality
  - Severity of clinical presentation
- Epidemiological dynamic
  - Outbreak potential, trend, emerging potential
- Information need
  - Evidence for risk factors, validity of epidemiologic information, international and public attention, evidence for pathogenesis
- Health gain opportunity
  - Treatability, preventability
Acknowledgements

- Outi Lyytikäinen, Marja Snellman, Teemu Mänttäri, Irma Meri-Hietanen
- Jari Jalava, Tuula Randell
- Eija Könönen, Saara Kollia, Sáhá Ibrahim, Anne Bryk, Arja Kanervo-Nordström, Anne Rinta-Oapas

- Clinical Microbiology Laboratories in Finland
- Infectious Diseases Teams in the Finnish Hospitals
Combating C difficile 027 in the UK

Dr Jean O'Driscoll
Stoke Mandeville Hospital

19th ECCMID, Helsinki,
16th May 2009
O’Driscoll – Ribotype 027 in the UK

Outbreak Curve

SMH Acquired C.difficile Dec 03 - Feb 06
O’Driscoll – Ribotype 027 in the UK

**Clostridium difficile at Stoke Mandeville Hospital - First Outbreak Peak**

Predisposing factors:
- Antibiotic use
- Inability to isolate
- Alcohol gel use
- A&E targets
- High bed occupancy
- Excessive movement of patients
- Cleaning methods
- Organism strain

**Critical action plan points**
- Isolation of symptomatic patients
- Prompt treatment of patients with suspected CDAD
- Prudent antibiotic prescribing
- removal of high-risk antibiotics
- Standardised assessment of patients with diarrhoea
  - use of Bristol stool chart
- Hand hygiene – patients and staff
- Environmental decontamination
- Mortality analysis and lessons learnt

**Typing Results (2004)**

133 strains
O’Driscoll – Ribotype 027 in the UK

**Clostridium difficile at Stoke Mandeville Hospital - Second Outbreak Peak**

Predisposing factors:
- Increased use of quinolones
- Still problems with patient isolation
- Still A&E targets
- Still excessive movements of patients
- Still type 027

Outbreak control:
- Removal of quinolones
- Formation of C diff ward
- Reduce number of patient movements

**Risk factors for C difficile infection and how they were addressed**

- Environmental contamination by spores:
  - Change in cleaning agent
  - Increase in cleaning frequency
  - Attention to detail!
- Poor hand-washing practices:
  - Emphasising soap-and-water
  - Spot checks on all grades of staff
- Control of antibiotic use:
  - 1st peak: removal of broad-spectrum antibiotics from wards
  - 2nd peak: Ciprofloxacin removed in addition
  - 3rd peak: restriction extended to orthopaedics/gynaecology

**Control Measures**

[Graph showing SMH Acquired C.difficile Dec 03 - Feb 06 with dates and actions listed]

March 04:
- Removal of co-amoxiclav, amoxicillin, clindamycin, cephalosporins
- Use of hypochlorite disinfectant
- Creation of cohort area

March 05:
- Removal of ciprofloxacin
- Use of hydrogen peroxide vapour on a few wards
- Creation of a C.diff ward.
O'Driscoll – Ribotype 027 in the UK

Cefuroxime Use

Comparison of Cefuroxime use and the Number of Cases of Hospital Acquired C. Difficile

Co-amoxiclav Use

Comparison of Co-amoxiclav use with Number of Hospital Acquired C. diff Cases

Ciprofloxacin Use

Comparison of Ciprofloxacin use and the Number of Hospital Acquired cases of C Difficile.
O’Driscoll – Ribotype 027 in the UK

Media and Department of Health interest

- **April 2005**: Type 027 same as Canadian/US strains; interest from Department of Health
- **May 2005**: Local press article about death of patient at local hospital
- **June 2005**: Independent articles
  - BBC News Headline
  - Healthcare Commission Enquiry called

**Type 027 (UK)**

- Identical to: Pulsovar A (PFGE) (Montreal)
  - NAP1 (PFGE) (US)
  - BI (REA) (US)
- Lacks a regulatory tcdC gene
- Has an additional toxin (binary toxin)
O'Driscoll – Ribotype 027 in the UK

1998 – Popoff
1999 – Preston
2002 – Birmingham
2004 – Stoke Mandeville

C. difficile PCR ribotypes in hospital patients
England and Wales 1995-2003

PCR ribotypes of C. difficile in England
(mandatory surveillance) 2005–06 (n=881)
O’Driscoll – Ribotype 027 in the UK

PCR ribotypes of *C. difficile* in England (mandatory surveillance) 2007–08 (n=677)

Subtyping of Ribotype 027 by MLVA
- multilocus variable-number tandem-repeat analysis

(Fawley et al: Journal of Clinical Microbiology March 2008)

91 UK isolates of 027
23 MLVA types found
O’Driscoll – Ribotype 027 in the UK

Use of MLVA to distinguish clindamycin-resistant strains of 027 from clindamycin-sensitive strains

(Drudy et al: Emerging Infectious Diseases, September 2008)

![C difficile toxin positive stools](image)

C difficile toxin positive stools

(year)

(number of reports)
O’Driscoll – Ribotype 027 in the UK

C difficile rates for BHT vs UK Average
Cases/1000 bed days (>65 years)

<table>
<thead>
<tr>
<th>Year</th>
<th>BHT Rate</th>
<th>UK Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BHT: Hospital Acquired C. diff per 1000 Admissions

---

---

---
UK Targets

Baseline year: 2007/2008
Target: 30% reduction in cases by 2010/11
(all ages >2 years)
Includes Community cases

National Guidelines

- Clostridium difficile infection: How to deal with the problem. DH and HPA January 2009.
- A good practice guide to control Clostridium difficile. HPA January 2007.
- Saving Lives: reducing infection, delivering clean and safe care. High Impact Intervention No 7: Care Bundle to reduce the risk from Clostridium difficile. DH 2007.
New emerging types of Clostridium difficile

National Reference Laboratory for Clostridium difficile
Leiden University Medical Centre/ RIVM, Bilthoven
The Netherlands

Introduction

- Characterization of Clostridium difficile
- Clostridium difficile infection (CDI) caused by the hyper virulent strain PCR-ribotype 027
- Predominant types in The Netherlands and Europe
- Predominant types among animals
- Emergence other virulent types causing human CDI (PCR-ribotypes 078 and 017)

Characterisation of C. difficile

- Pathogenicity locus: TcdA, TcdB, TcdC
- Toxinotyping: 24 types
- Pulse field gel electrophoresis
- Restriction enzyme analysis: at least 100 groups and numerous subtypes
- PCR-ribotyping: more than 200 types
- Amplified fragment length polymorphism
Goorhuis – New emerging *C. difficile* types

### Pathogenicity locus (PaLoc)

![Pathogenicity locus (PaLoc)](image)

---

### Distribution type 027 across Europe


---

### Dynamics in CDI by type 027

*Emerg Infect Dis. 2008 Sep;14(9):1485-7.*

---

*Clin Microbiol Infect. 2008 May;14(5):514-5.*
**Clostridium difficile** in animals

- **C. difficile** is a ubiquitous bacterium in the environment
- **CDI in Animals**
  - Poultry: 62% of 61 chicken-faces samples positive, age dependent (M. Rupnik, Anaerobe 2006; 14:325-7).
- The role of **C. difficile** in porcine neonatal diarrhoea has increased
  - The pathogenesis such as the role of toxins still needs to be established

**Is CDI an unrecognized and underestimated disease entity in animals?**

**Is there an association of antibiotics with C. difficile colonization or diarrhoea in animals?**

**Animals as source for humans by direct, indirect contact, the environment and the food.**

### Predominant types per host

<table>
<thead>
<tr>
<th>Host</th>
<th>Number of ribotypes found</th>
<th>Most Prevalent toxinotypes/ribotypes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humans</td>
<td>App. 200</td>
<td>0/001, 0/014, 0/027, 0/020, 0/017</td>
<td>Barbout et al. 2007</td>
</tr>
<tr>
<td>Horses</td>
<td>10 to 12</td>
<td>V078 (up to 35%)</td>
<td>Keel et al. 2007; Arroyo et al. 2005; Marks and Rupnik, unpublished</td>
</tr>
<tr>
<td>Calves</td>
<td>3 to 8</td>
<td>V078 (up to 94%)</td>
<td>Rodriguez-Palacios et al. 2006; Hammett et al. 2006; Keel et al. 2007</td>
</tr>
<tr>
<td>Piglets</td>
<td>2 to 4</td>
<td>V078 (up to 83%)</td>
<td>Keel et al. 2007; Pirs et al. 2008</td>
</tr>
</tbody>
</table>
Goorhuis – New emerging *C. difficile* types

Incidence human CDI in The Netherlands

- 14 study centres with continuous monitoring of all patients with CDI
- Study period: July 2006-December 2008
- Average incidence 17 per 10,000 admissions
- No seasonal variation

Incidence per 10,000 admissions

Distribution of PCR-ribotypes

- 130 typed isolates
- Other types
- Type 014
- Type 078
- Type 001
- Type 027
- Type 002
- Type 004
- Type 017
- Type 015
- 18%
Other types causing severe CDI?

2 fatal cases caused by PCR-ribotype 078

- PCR ribotype 078 was the predominant type among calves (94%) and pigs (83%).
- Type 078 has the binary toxin and a 38 bp deletion in TcdC.

Type 078 also predominant type among cattle in Europe

Prevalence of C. difficile PCR ribotype 078 toxigenic type V found in diarrheic and non-diarrheic piglets

Environmental Microbiology, 2009

Veterinary Microbiology, 2009
Goorhuis – New emerging *C. difficile* types

**Emergence of human CDI caused by type 078 in The Netherlands**

---

**Emergence of *Clostridium difficile* Infection Due to a New Hypervirulent Strain, Polymerase Chain Reaction Ribotype 078**

*Clin Infect Dis.* 2008 Nov 1;47(9):1162-70

<table>
<thead>
<tr>
<th>icdA and icdB</th>
<th>Type 027</th>
<th>Type 078</th>
</tr>
</thead>
<tbody>
<tr>
<td>icdC</td>
<td>positive</td>
<td>positive</td>
</tr>
<tr>
<td>icdC</td>
<td>18 bp deletion</td>
<td>39 bp deletion</td>
</tr>
<tr>
<td>binary toxin</td>
<td>positive</td>
<td>positive</td>
</tr>
<tr>
<td>tcdA</td>
<td>positive</td>
<td>positive</td>
</tr>
<tr>
<td>tcdB</td>
<td>positive</td>
<td>positive</td>
</tr>
<tr>
<td>tcdC</td>
<td>deletion at 117, frameshift</td>
<td>C184T mutation at 184, stop codon</td>
</tr>
</tbody>
</table>

**Clinical aspects of type 078**
- Attributable mortality within 30 days: 3.6%
- Complications: 9.6%
- Relapse rate: 15.8%
- Severe diarrhoea as 027, but affects younger patients

**Distribution types 027 and 078**

---
Animal farms in the Netherlands

Relatedness of human and porcine type 078

Clustering of human and porcine strains in Clonal Complexes

CDI caused by PCR-ribotype 017

- TcdA negative
- Toxinotype VIII
- TcdB similar to C. Sordellii lethal toxin
- Described causing multiple outbreaks
  - Followed by outbreaks in
    - Japan (Sato et al, Kansenshogaku Zasshi, 2004)
    - Ireland (Drudy et al, Infect Control Hosp Epidemiol, 2007)
    - Argentina (Goorhuis, Clin Microbiol. Infect, 2009, in press)
Goorhuis – New emerging *C. difficile* types

**Simultaneous outbreaks with types 017 and 027**

- Large outbreak with 2 PCR-ribotypes simultaneously in a large teaching hospital in The Netherlands
  - 168 patients
    - 57 (34%) with type 017, 46 (27%) with type 027 and 65 (39%) with other types (non-027/non-017)
  - Period: May 2005-February 2007
  - Clinical comparison between types 027, 017 and other (non-027/non-017) types
  - See poster presentation (P628, poster session 15.30-16.30, 16-05-2009)

**Types 017 and 027: type specific risk factors**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Type 017</th>
<th>Other types</th>
<th>Type 027</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>0.99 (0.41-2.38)</td>
<td>0.91 (0.34-2.46)</td>
<td>0.43 (0.16-1.13)</td>
</tr>
<tr>
<td>Age</td>
<td>1.65 (0.75-3.64)</td>
<td>1.90 (0.75-4.86)</td>
<td>0.99 (0.46-2.14)</td>
</tr>
<tr>
<td>Charlson co-morbidity score</td>
<td>1.90 (0.88-4.09)</td>
<td>1.04 (0.37-2.89)</td>
<td>1.51 (0.74-3.11)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.61 (0.05-6.97)</td>
<td>0.62 (0.04-8.71)</td>
<td>0.61 (0.17-2.17)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.64 (0.11-3.66)</td>
<td>0.62 (0.10-3.96)</td>
<td>3.29 (1.20-9.04)</td>
</tr>
<tr>
<td>Other</td>
<td>3.29 (1.20-9.04)</td>
<td>3.47 (1.10-10.9)</td>
<td>2.37 (0.86-6.49)</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>0.99 (0.41-2.38)</td>
<td>0.91 (0.34-2.46)</td>
<td>0.43 (0.16-1.13)</td>
</tr>
<tr>
<td>Cytostatic agents</td>
<td>1.91 (0.48-7.53)</td>
<td>1.88 (0.40-8.93)</td>
<td>3.24 (0.96-11.0)</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>1.90 (0.88-4.09)</td>
<td>1.04 (0.37-2.89)</td>
<td>1.51 (0.74-3.11)</td>
</tr>
<tr>
<td>Immunosuppressive agents</td>
<td>1.73 (0.66-4.53)</td>
<td>1.87 (0.65-5.42)</td>
<td>5.35 (2.33-12.3)</td>
</tr>
</tbody>
</table>

**Application of multivariate random-effect analysis**

To determine clinical spread of toxic & negative *C. difficile* in a general hospital in Buenos Aires, Argentina

- 62 (22%) were sampled, of which 61 were included in the analysis. 6 (10%) were excluded due to missing data.
Goorhuis – New emerging *C. difficile* types

**Types 017 and 027: type specific outcome**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Type 027</th>
<th>Type 017</th>
<th>Other type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude mortality (%): Overall in hospital</td>
<td>26/39 (66.7)</td>
<td>22/51 (43.1)</td>
<td>18/48 (37.5)</td>
</tr>
<tr>
<td>OR (95% C.I.)</td>
<td>3.33 (1.38-8.08)</td>
<td>4.01 (1.41-11.4)</td>
<td>1.26 (0.57-2.83)</td>
</tr>
<tr>
<td>Adjusted mortality (%): Overall in hospital</td>
<td>9/46 (19.6)</td>
<td>10/57 (17.5)</td>
<td>11/65 (16.9)</td>
</tr>
<tr>
<td>OR (95% C.I.)</td>
<td>1.19 (0.45-3.17)</td>
<td>0.84 (0.28-2.48)</td>
<td>1.04 (0.41-2.68)</td>
</tr>
<tr>
<td>Attributable mortality (%): Overall in hospital</td>
<td>3/46 (6.5)</td>
<td>4/57 (7.0)</td>
<td>1/64 (1.6)</td>
</tr>
<tr>
<td>OR (95% C.I.)</td>
<td>4.40 (0.44-43.7)</td>
<td>5.46 (0.42-70.7)</td>
<td>4.75 (0.52-43.8)</td>
</tr>
<tr>
<td>Contributable mortality (%): Overall in hospital</td>
<td>6/46 (13.0)</td>
<td>5/57 (8.8)</td>
<td>3/64 (4.7)</td>
</tr>
<tr>
<td>OR (95% C.I.)</td>
<td>3.05 (0.72-12.9)</td>
<td>2.91 (0.62-13.7)</td>
<td>1.96 (0.45-8.57)</td>
</tr>
<tr>
<td>Overall 30-day mortality (%)</td>
<td>7/27 (25.9)</td>
<td>8/35 (22.9)</td>
<td>1/31 (3.2)</td>
</tr>
<tr>
<td>OR (95% C.I.)</td>
<td>10.5 (1.20-92.0)</td>
<td>8.27 (0.72-94.3)</td>
<td>8.89 (1.04-75.8)</td>
</tr>
<tr>
<td>Overall 1 year mortality (%)</td>
<td>18/27 (66.7)</td>
<td>22/35 (62.9)</td>
<td>7/31 (22.6)</td>
</tr>
<tr>
<td>OR (95% C.I.)</td>
<td>6.86 (2.15-21.9)</td>
<td>7.21 (1.71-30.3)</td>
<td>5.80 (1.96-17.2)</td>
</tr>
</tbody>
</table>

**Virulence type 017?**

- More potent TcdB
  - TcdB more important in pathogenesis of CDI
  - Possible role accessory gene regulation in promoting toxin production

**Conclusions**

- Type 027 remains a problem
  - In the Netherlands: decrease in the share of 027-CDI
  - Emergence clindamycin resistant clones
- Other types emerging with similar attributable mortality as type 027
  - Type 078: link cattle breeding industry? Plausible, not proven
  - Type 017: TcdA negative
- Circulating types in The Netherlands also predominant in Europe
- Risk factors, clinical course and outcome for CDI are type specific
  - Typing pivotal in case of an increased incidence
- High disease burden / all-cause mortality among virulent types
- Clones persist on wards for prolonged periods of time
  - Continuous clinical awareness is needed
**Goorhuis – New emerging *C. difficile* types**

## Acknowledgments

<table>
<thead>
<tr>
<th>Acknowledgments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ed Kuijper, LUMC</td>
</tr>
<tr>
<td>Jeroen Gorver, LUMC</td>
</tr>
<tr>
<td>Dennis Bakker, LUMC</td>
</tr>
<tr>
<td>Celine Harmanus, LUMC</td>
</tr>
<tr>
<td>Daan Noterman, RIVM</td>
</tr>
<tr>
<td>Birgit van Benthen, RIVM</td>
</tr>
<tr>
<td>Tjallie van der Kooi, RIVM</td>
</tr>
<tr>
<td>Caroline van Kinschot, LUMC</td>
</tr>
</tbody>
</table>