Clostridium difficile infection – underestimated public health problem

Franz Allerberger  AT
13.15 – 13.35
**Clostridium difficile**

*C. difficile* is a Gram-positive, spore-forming, anaerobic bacillus that was first identified in 1935\(^1\)

*C. difficile* is the leading cause of nosocomial diarrhoea in industrialised countries\(^2\)

*C. difficile* passes through a life cycle where it exists in two forms, as vegetative cells and as spores\(^3\)

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Vegetative form

Spores surrounding a vegetative cell

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The disease cycle of *Clostridium difficile* infection (CDI)

1. Ingestion of spores transmitted from other patients, via hands of healthcare personnel and the environment

2. Germination into growing (vegetative) cells

3. Disruption of normal colonic microflora allows colonisation and overgrowth of *C. difficile* in the colon

4. Toxin production leads to inflammation and damage to intestinal cells

5. Transmission of spores via the faecal–oral route

Overcoming barriers to effective recognition and diagnosis of CDI

“Many clinicians still believe that a majority of CDI cases occur endogenously, with patients already harbouring *C. difficile* on admission to hospital and CDI developing following subsequent antibiotic therapy. This is a common misconception, as asymptomatic carriers of toxigenic *C. difficile* are significantly less likely than non-carriers to develop CDI”\(^1,^2\)

Prevalence of *C. difficile* colonisation at hospital admission

707/6,855 patients admitted to 1 of 5 participating departments at a 2000-bed University Hospital in Vienna between July 2013–July 2014 were included.

Prevalence of colonisation at admission was 3.5% (25/707; 95% CI: 2.4–5.2).

Out of the 707 study patients, 202 were available for follow-up examination at discharge.

Of the 177 patients negative for *C. difficile* at admission, two developed CDI and one became colonised.

None of the 25 patients already colonised at admission developed CDI during stay.

CDI imaging

ENDOSCOPY:
**Pseudomembranous colitis** with yellowish pseudomembranes on inflamed mucosa

COMPUTED TOMOGRAPHY: **Pancolitis (75 yrs, male)**
Bowel wall thickening (most common), accordion sign (oral contrast material is trapped between thickened edematous folds and pseudomembranes in the colonic mucosa), shaggy mucosal outline

Acknowledgement:
C. Högenauer


Acknowledgement:
R. Forstner
CDI in the ICU in European acute care hospitals

<table>
<thead>
<tr>
<th>Speciality</th>
<th>Proportion of all patients with CDI, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical</td>
<td>17.7 (53/299)</td>
</tr>
<tr>
<td>Medical</td>
<td>64.9 (194/299)</td>
</tr>
<tr>
<td>ICU</td>
<td>9.7 (29/299)</td>
</tr>
<tr>
<td>Gynaecology</td>
<td>2.0 (6/299)</td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>0.3 (1/299)</td>
</tr>
<tr>
<td>Geriatrics</td>
<td>3.0 (9/299)</td>
</tr>
<tr>
<td>Paediatrics</td>
<td>2.3 (7/299)</td>
</tr>
</tbody>
</table>

van Dorp SM, et al. for the European *Clostridium difficile* infection surveillance network (ECDIS-Net) 2015. Standardised *Clostridium difficile* infection surveillance in European acute care hospitals: a feasibility study; submitted.
CDI more likely to kill than other types of infective diarrhoea

- Recent study in Austria
- Patients with CDI twice as likely to die while in hospital than patients with other types of infective diarrhoea
- All-cause mortality in CDI patients pre-discharge 20.0% versus 7.2% in non-CDI diarrhoea patients


Case fatality rate higher with CDI

CFR, case fatality rate (pathogen-specific deaths divided by the number of cases)
Incidence of CDI in European acute care hospitals

Median of 3.7 cases/10,000 patient-days in ECDIS-Net (37 hospitals)

ECDIS-Net, European *Clostridium difficile* infection surveillance network (ECDIS-Net); HA, healthcare-associated; Results do not represent national estimates

van Dorp SM, et al. for the European *Clostridium difficile* infection surveillance network (ECDIS-Net) 2015. Standardised *Clostridium difficile* infection surveillance in European acute care hospitals: a feasibility study; submitted.
The incidence of CDI in Austria

Which of the following do you think are risk factors for severe CDI?

1. Age (≥65 years)
2. Marked leucocytosis
3. Decreased blood albumin
4. Elevated serum creatinine
5. Comorbidity (severe underlying disease and/or immunodeficiency)
6. All of the above
## Risk factors for severe CDI

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≥65 years)</td>
<td>A</td>
<td>II</td>
</tr>
<tr>
<td>Marked leucocytosis (leucocyte count &gt;15×10⁹/L)</td>
<td>A</td>
<td>II</td>
</tr>
<tr>
<td>Decreased blood albumin (&lt;30 g/L)</td>
<td>A</td>
<td>II</td>
</tr>
<tr>
<td>Elevated serum creatinine (≥133 µM or ≥1.5× premorbid level)</td>
<td>A</td>
<td>II</td>
</tr>
<tr>
<td>Comorbidity (severe underlying disease and/or immunodeficiency)</td>
<td>B</td>
<td>II</td>
</tr>
</tbody>
</table>

Antibiotic dose-dependent elevation in CDI risk

Number of antibiotics received (median)

- 2 antibiotics: Hazard ratio compared with only 1 antibiotic = 2.5
- 3 or 4 antibiotics: Hazard ratio = 3.3
- 5 or more antibiotics: Hazard ratio = 9.6

Days on antibiotic

- 4-7 days: Hazard ratio compared with <4 days = 1.4
- 8-18 days: Hazard ratio = 3
- >18 days: Hazard ratio = 7.8

Number of CDI events, N=241; 240 patients

Intermediate Summary

CDI is an infection of the large intestine by *C. difficile* that typically causes diarrhoea\(^1\)

Leading gastrointestinal infection in European hospitals\(^2\)

Can be severe and life-threatening

- Associated with severe bowel inflammation and shock\(^1\)
- Approximately 1 in 10 CDI cases causes (or contributes to) ICU admission or death, or leads to bowel surgery\(^3\)

CDC considers *C. difficile* an **urgent threat**\(^4\)

- Assessed according to seven factors associated with resistant infections:
  - Health impact, economic impact, how common the infection is, a 10-year projection of how common it could become, how easily it spreads, availability of effective antibiotics, and barriers to prevention\(^4\)

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Microorganisms with a Threat Level of Urgent.

*Clostridium difficile.*
Carbapenem-resistant Enterobacteriaceae.
Drug-resistant *Neisseria gonorrhoeae.*

Microorganisms with a Threat Level of Serious.

Multidrug-resistant *Acinetobacter.*
Drug-resistant *Campylobacter.*
Fluconazole-resistant *Candida.*
Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs).
Vancomycin-resistant *Enterococcus* (VRE).
Multidrug-resistant *Pseudomonas aeruginosa.*
Drug-resistant non-typhoidal *Salmonella.*
Drug-resistant *Salmonella Typhi.*
Drug-resistant *Shigella.*
Methicillin-resistant *Staphylococcus aureus* (MRSA).
Drug-resistant *Streptococcus pneumoniae.*
Drug-resistant tuberculosis.

Microorganisms with a Threat Level of Concerning.

Vancomycin-resistant *Staphylococcus aureus* (VRSA).
Erythromycin-resistant Group A *Streptococcus.*
Clindamycin-resistant Group B *Streptococcus.*
Centers for Medicare & Medicaid Services (CMS)

Coverage of MDRO/CDI LabID Event Reporting in NHSN

- Nationwide Coverage Due to CMS Reporting Requirements:
  - Acute care hospitals
    - MRSA bacteremia and CDI inpatients facility-wide in 2015
  - Long-term acute care hospitals
    - MRSA bacteremia and CDI inpatients facility-wide in 2015
  - Inpatient rehabilitation facilities
    - MRSA bacteremia and CDI inpatients facility-wide in 2015

- State mandates add other MDROs and facility types

- Numerous Collaboratives and Initiatives:
  - CMS Quality Improvement Organization Scopes of Work (current 11th)
    - CDI and MRSA in long-term care and critical access
    - CRE in acute care and long-term care
HAI s are a major public health problem in the Member States (according to figures compiled by the European Centre for Disease Prevention and Control (ECDC), 1 in 20 hospital in-patients on average suffer from an HAI in the EU, that is to say, 4.1 million patients annually, and every year 37,000 people in the EU die as a result of an HAI, although 20 to 30% of those infections are considered to be preventable by intensive hygiene and control programmes), and this places a heavy burden on limited health service budgets.
Continued support for and monitoring of appropriate use of accurate diagnostic testing for HAI's and antimicrobial resistance in EU/EEA Member States

Implementation of EU-standardised surveillance of alcohol hand rub consumption, complemented if possible by hand hygiene compliance monitoring.

Implementation of standardised surveillance of *C. difficile* infections at local, national and EU level.

Development of guidance for the prevention and control of HAI's with carbapenem-resistant Gram-negative bacteria.

Burden of *C. difficile* infections (CDIs), EU/EEA

- Rise of CDIs since appearance of NAP I/Ribotype 027 in 2000-2005
- Point prevalence survey (PPS) 2011-2012: 124,000 healthcare-associated CDI cases/year in EU/EEA, underdiagnosed, 3% attributable mortality (3,700 deaths/year)
- EU/EEA: 8th most frequent microorganism in HAIs (1st in US CDC PPS)
### Tabelle Nr. I.

<table>
<thead>
<tr>
<th>Jahr</th>
<th>Anzahl der Entbindungen</th>
<th>Anzahl der Verstorbenen</th>
<th>Die Anzahl der Entbindungen verhältnis zur Anzahl der Verstorbenen wie 100 zu</th>
<th>Anzahl der Verstorbenen</th>
<th>Die Anzahl der Entbindungen verhältnis zur Anzahl der Verstorbenen wie 100 zu</th>
</tr>
</thead>
<tbody>
<tr>
<td>1841</td>
<td>3036</td>
<td>237</td>
<td>7.7</td>
<td>2442</td>
<td>86</td>
</tr>
<tr>
<td>1842</td>
<td>3287</td>
<td>518</td>
<td>15.8</td>
<td>2659</td>
<td>202</td>
</tr>
<tr>
<td>1843</td>
<td>3060</td>
<td>274</td>
<td>8.9</td>
<td>2739</td>
<td>164</td>
</tr>
<tr>
<td>1844</td>
<td>3157</td>
<td>260</td>
<td>8.2</td>
<td>2956</td>
<td>68</td>
</tr>
<tr>
<td>1845</td>
<td>3492</td>
<td>241</td>
<td>6.8</td>
<td>3241</td>
<td>66</td>
</tr>
<tr>
<td>1846</td>
<td>4010</td>
<td>459</td>
<td>11.4</td>
<td>3754</td>
<td>105</td>
</tr>
<tr>
<td>Summa</td>
<td>20042</td>
<td>1989</td>
<td>9.92</td>
<td>17791</td>
<td>691</td>
</tr>
</tbody>
</table>

**Ignaz Semmelweis †1865**

born 1818 in Ofen (= Buda/Budapest)
While the [CDI] numbers were stable at 200 patients per year from 2009 to 2011 (0.56, 0.51, and 0.50 per 1,000 patient days, respectively), an increase to 313 patients was observed in 2012 (0.88/1,000 patient days). In the first quarter of 2013, a further increase in CDI patients was detected. 1.98/1000; 294 cases in 5 months before intervention -> 1.06/1000; 7 months after intervention.

We report a 25% 30-day case fatality rate for patients with CDI. Reducing moxifloxacin use in combination with providing structured information on CDI was associated with an immediate decrease in CDI rates in this large community teaching hospital.
In our hospital, the numbers of CDI patients are continuously recorded and reported. While the numbers were stable at 200 patients per year from 2009 to 2011 (0.56, 0.51, and 0.50 per 1,000 patient days, respectively), an increase to 313 patients was observed in 2012 (0.88/1,000 patient days). In the first quarter of 2013, a further increase in CDI patients was detected, ......

The mean (SEM) numbers of CDI cases in period 1 were 593 per month and in period 2 were 323 per month (46% reduction; P0.0044). Reducing moxifloxacin use in combination with providing structured information on CDI was associated with an immediate decrease in CDI rates in this large community teaching hospital.
### Characteristics

<table>
<thead>
<tr>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N=171</td>
<td></td>
</tr>
</tbody>
</table>

**Female:** male 118:53

**Median age (range):** 76 (9-97)

**Age >= 65 years:** 117/158 (74.1%)

#### Clinical Signs

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>162/171 (94.7)</td>
</tr>
<tr>
<td>Ileus</td>
<td>3/171 (1.8)</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>6/171 (3.5)</td>
</tr>
<tr>
<td>Toxic megacolon</td>
<td>1/171 (0.6)</td>
</tr>
<tr>
<td>Other clinical signs</td>
<td>3/171 (1.8)</td>
</tr>
</tbody>
</table>

#### Asymptomatic

<table>
<thead>
<tr>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/171 (2.9)</td>
</tr>
</tbody>
</table>

#### Primary Episode

<table>
<thead>
<tr>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>152/171 (88.9)</td>
</tr>
</tbody>
</table>

#### Recurrent Episode

<table>
<thead>
<tr>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>19/171 (11.1)</td>
</tr>
</tbody>
</table>

#### Severe CDI by

<table>
<thead>
<tr>
<th>Type</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive care</td>
<td>8/171 (4.7)</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>2/171 (1.2)</td>
</tr>
</tbody>
</table>

#### Case classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare acquired</td>
<td>125/171 (73.1)</td>
</tr>
<tr>
<td>Community acquired</td>
<td>34/171 (19.9)</td>
</tr>
<tr>
<td>Indeterminable</td>
<td>12/171 (7.0)</td>
</tr>
</tbody>
</table>

1 based on ECDC case classification; 2 clinical signs other than given in the ECDC case definition including vomiting and abdominal cramps


<table>
<thead>
<tr>
<th>Ribotypes</th>
<th>Vienna n=92 (%)</th>
<th>Burgenland n=8 (%)</th>
<th>Lower Austria n=9 (%)</th>
<th>Carinthia n=11 (%)</th>
<th>Salzburg n=10 (%)</th>
<th>Styria n=10 (%)</th>
<th>Tyrol n=12 (%)</th>
<th>Upper Austria n=13 (%)</th>
<th>Vorarlberg n=6 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>027</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N1=34)</td>
<td>27 (29.3)</td>
<td>4 (50.0)</td>
<td>3 (33.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>078</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N2=9)</td>
<td>4 (4.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (9.1)</td>
<td>0 (0)</td>
<td>1 (10.0)</td>
<td>1 (8.3)</td>
<td>1 (7.7)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N3=128)</td>
<td>61 (66.3)</td>
<td>4 (50.0)</td>
<td>6 (66.7)</td>
<td>10 (90.9)</td>
<td>10 (100)</td>
<td>9 (90.0)</td>
<td>11 (91.7)</td>
<td>12 (92.3)</td>
<td>5 (83.3)</td>
</tr>
</tbody>
</table>

PCR ribotypes of *C. difficile* isolates from 171 hospital patients by province of participating hospitals (n)
## Treatment of a severe first episode

<table>
<thead>
<tr>
<th>ESCMID recommended treatment</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin 125 mg qid for 10 days</td>
<td>A-I</td>
</tr>
<tr>
<td>Fidaxomicin 200 mg bid for 10 days</td>
<td>B-I</td>
</tr>
<tr>
<td>Vancomycin 500 mg qid for 10 days</td>
<td>B-III</td>
</tr>
<tr>
<td>Metronidazole 500 mg tid for 10–14 days</td>
<td>D-I</td>
</tr>
</tbody>
</table>

ESCMID, European Society of Clinical Microbiology and Infectious Diseases; bid, twice daily; qid, four-times daily; tid, three-times daily

When oral therapy is not feasible

Parenteral metronidazole is recommended, preferably combined with intracolonic or nasogastric administration of vancomycin.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ESCMID recommended treatment</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-severe</td>
<td>Metronidazole 500 mg tid iv for 10–14 days</td>
<td>A-II</td>
</tr>
<tr>
<td>Severe</td>
<td>Metronidazole 500 mg tid iv for 10–14 days plus vancomycin retention enema 500 mg in 100 mL normal saline qid intracolonic and/or vancomycin 500 mg qid by oral/nasogastric tube</td>
<td>B-II</td>
</tr>
</tbody>
</table>

Rates of clinical success for metronidazole and vancomycin

Rates of clinical success in two identical multicentre, randomised, double-blind, parallel-group trials

Clinical success was defined as diarrhoea resolution and absence of severe abdominal discomfort due to CDI on Day 10; NS, not significant

Fidaxomicin phase 3 trial results

1. European Public Assessment Report, 22 September 2011 (EMA/857570/2011);  

<table>
<thead>
<tr>
<th></th>
<th>Study 003</th>
<th>Study 004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects achieving endpoint (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical cure</td>
<td>88.2/253</td>
<td>85.8/253</td>
</tr>
<tr>
<td>Recurrence</td>
<td>265/287</td>
<td>15.4/39</td>
</tr>
<tr>
<td>Sustained</td>
<td>265/287</td>
<td>67/265</td>
</tr>
<tr>
<td>Clinical cure</td>
<td>214/287</td>
<td>198/309</td>
</tr>
<tr>
<td>Recurrence</td>
<td>221/252</td>
<td>223/257</td>
</tr>
<tr>
<td>Sustained</td>
<td>28/221</td>
<td>60/223</td>
</tr>
</tbody>
</table>

85.8
15.4
25.3
74.6
74.6
64.1
87.7
86.8
76.6
63.4

Data from modified intent-to-treat population

NS, not significant; Study 003: USA, Canada; Study 004: Belgium, Canada, France, Germany, Italy, Spain, Sweden, UK, USA
Summary

Treatment involves:
- Supportive therapy (fluid and electrolyte replacement)
- Antibiotic therapy directed against *C. difficile* (vancomycin, metronidazole, fidaxomicin, telcoplanin)

If treated early, CDI is not always independently associated with increased mortality

Fighting the spread of resistance

Healthcare providers can:
- Order a *C. difficile* test (preferably a nucleic acid amplification test) if the patient has had 3 or more unformed stools within 24 hours
- Be aware of infection rates in your facility or practice, and follow infection control recommendations with every patient

CDI case costs

- Ananthakrishnan (IBD patients)\(^1\)
- Dubberke (primary admission)\(^1\)
- Dubberke (inpatient over 180 days)\(^1\)
- Kyne (inpatients only)\(^1\)
- Lawrence (ICU stay only)\(^1\)
- Lawrence (hospital-wide)\(^1\)
- O’Brien (secondary diagnosis)\(^1\)
- Vonberg (hospital-wide)\(^2\)
- Zerey (surgical inpatients)\(^1\)


IBD, irritable bowel disease
BACKGROUND: Multifaceted national prevention efforts in the United Kingdom, including antimicrobial stewardship, patient isolation, hand hygiene, environmental cleaning and disinfection, and audit, resulted in a 59% reduction in CDI cases reported from 2008 to 2012.

CONCLUSION: The potential benefits of a multifaceted national CDI prevention program are sizeable from the federal perspective.

* Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention