From obscurity to “superbug”: the rise of *Clostridium difficile*

**Background**

- *Clostridium difficile* - an anaerobic Gram +ve bacillus
- *C. difficile* disease gained prominence because of renewed interest in anaerobic bacteria in the 1960s and 70s
- Specific anti-anaerobe drugs had been developed, e.g. clindamycin
- Clindamycin-associated diarrhoea became a real problem in some hospitals in the USA
- Outbreaks of pseudomembranous colitis cause elucidated in 1978

**C. difficile-associated disease**

- *C. difficile* the most common cause of diarrhoea in hospital patients
- Produces at least 2 major toxins:
  - Toxin A (an enterotoxin)
  - Toxin B (a cytotoxin)
- 3rd “binary” toxin

**What are the major risk factors for *C. difficile***?

- Exposure to the organism
- Exposure to antibiotics - particularly clindamycin and extended spectrum cephalosporins (until now)
- Old age
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CDAD at SCGH 1983-92, rates, by age and gender, and cephalosporin use
Riley et al. Epidemiol Infect 1994; 113: 13-20

Canadian outbreak in Quebec (CHUS)
(Pepin et al. CMAJ 2004;171:466-72)
- In late 2002, increase in fulminant C. difficile colitis → emergency colectomy.
- Rates ↑ from 35.6/100,000 pop. in 1991 to 156.3 in 2003.
- In ≥65 years age group ↑ from 102 in 1991 to 866.5 in 2003.
- Complications ↑ from 7.1% in 1991 to 18.2% in 2003 (p<0.001)
- Death within 30 days of diagnosis ↑ from 4.7% (8/169) in 1991 to 13.8% (59/390) in 2003 (p<0.001)

C. difficile Quebec 2000-2003

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>Deaths</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>3262</td>
<td>395</td>
<td>12</td>
</tr>
<tr>
<td>2001</td>
<td>3675</td>
<td>562</td>
<td>15</td>
</tr>
<tr>
<td>2002</td>
<td>4097</td>
<td>661</td>
<td>16</td>
</tr>
<tr>
<td>2003</td>
<td>7004</td>
<td>1270</td>
<td>18</td>
</tr>
</tbody>
</table>

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Resistance of current BI/NAP1 isolates to clindamycin and FQs compared with current non-BI/NAP1 isolates and historic BI/NAP1 isolates

<table>
<thead>
<tr>
<th></th>
<th>Current BI/NAP1 Isolates n=24 (%)</th>
<th>Current non-BI/NAP1 Isolates n=24 (%)</th>
<th>P-Value for BI/NAP1 vs. Non-BI/NAP1 Isolates</th>
<th>Historic BI/NAP1 Isolates n=14 (%)</th>
<th>P-Value for Current vs. Historic BI/NAP1 Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>19 (79)</td>
<td>19 (79)</td>
<td>1.0</td>
<td>10 (71)</td>
<td>0.7</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>24 (100)</td>
<td>23 (96)</td>
<td>1.0</td>
<td>14 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>24 (100)</td>
<td>10 (42)</td>
<td>&lt;0.001</td>
<td>14 (100)</td>
<td>0.001</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>24 (100)</td>
<td>10 (42)</td>
<td>&lt;0.001</td>
<td>10 (71)</td>
<td>0.001</td>
</tr>
</tbody>
</table>


England distribution of PCR ribotypes 2005/6 to 2007/8 as percentages

2005-6 (n=1881)

Clindamycin resistance rates from laboratory reports in people 45-64 years of age in England (excludes North West, South East and London regions) (Health Protection Agency, 2006).

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Superbug kills one person an hour

Research suggests the compounding effect is too powerful to ignore, and that large-scale measures are needed to mitigate the spread of 10 to 20 times more cases than the current trend. The research shows the impact of 10 to 20 cases of Clostridium difficile may be even more significant than previously thought. The research also suggests that the number of cases could be underestimated.

Quarterly counts of C. difficile: comparison of mandatory and voluntary quarterly reporting

![Graph showing quarterly counts of C. difficile comparing mandatory and voluntary reporting]

In Australia

- We have CDT+ strains
- We have hyper-toxin A & B producers
- No evidence of widespread quinolone resistance (~2%)
- Currently no widespread evidence of all 3 features in one strain — no PCR ribotype 027
- First case reported last year (Riley et al. Med J Aust 2009) — current outbreak in Melbourne
- Continued surveillance required — but how?

What is driving this apparent epidemic?

- Aging population
- New fluoroquinolone use
- Gastric acid suppressant use
- ?Animal reservoir, pigs/cattle for example

Is C. difficile infection part of a zoonoses?

Potential animal reservoirs of C. difficile

- Camels
- Seals
- Cattle
- Snakes
- Donkeys
- Deer
- Horses
- Hares
- Guinea pigs
- Native cats
- Kodiak bear
- Domestic cats
- Dogs
- Quokkas
- Numbats
- Antelopes
- Pigs
- Hamsters

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Keel et al. 2006

C. difficile in companion animals
- 21 cats and 60 dogs at 2 veterinary clinics
- 32 (39.5%) yielded C. difficile
- cats (38% positive) vs dogs (40% positive)
- clinic 1, 61% positive vs 17.5%, clinic 2
- positive animals receiving antibiotics
- 62% of environmental sites positive


C. difficile in pigs
- First described over 20 years ago in gnotobiotic pigs
- PMC then described in conventional pigs
- Early this century outbreaks of CDAD in 5d old piglets in USA - high mortality (16%)
- Since 2000, C. difficile the major & most common cause of enteritis in neonatal piglets in USA
- Most producers didn’t realise they had a problem – now over 90% herds affected
- Apart from mortality, affected piglets are 10% under weight when ready for market leading to significant losses in income
- Piglet isolates mainly PCR ribotype 078 (~80%) – this is/ was an uncommon human ribotype
- PCR ribotype 078 increasing in USA & The Netherlands
- No data from other big pig growing countries such as Denmark and China
- Preliminary work in WA indicates some affected herds but mainly being ignored by the industry!

O’Neill et al. Epidemiol Infect 1993; 111: 257-264

Relationship between human and animal strains of C. difficile
- Total of 116 isolates of C. difficile
- Pets (26) and humans (37)
- Veterinary clinics (33) and hospitals (20)
- REA and ribotyping
- Good correlation between vet clinics & pets
- Good correlation between humans & hospital
- No relationship between pets and humans

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C. difficile in cattle
- Neonatal calf diarrhoea a common illness (10%) in calves
- Many cases idiopathic
- C. difficile has been suggested as a cause
- 278 calves, 144 with diarrhoea (7.6% pos by culture, 39.6% pos by toxin) and 134 controls (14.9%/20.9%), in 58 of 102 diary farms (Rodriguez et al. EID 2006)
- Sampling time/age related to outcome, not Abs

C. difficile in cattle
- Both PCR ribotypes 017 & 027 detected
- 83% of calf isolates ribotype 078
- Convenience sample of beef (53) and veal (7) samples purchased from butchers
- Meat cultured in enrichment broth first, then alcohol shocked
- C. difficile isolated from 20% of samples
- One strain appeared to be 027 related (Rodriguez et al. EID 2007)

C. difficile in horses
- 1st described in mid 1980s
- Still relatively little known about this problem
- Expensive race horses in USA have died from fulminant colitis
- Most commonly associated with Ab exposure (ery, tmp/sul, β-lactams, gent)

C. difficile in horses
- Carriage of C. difficile by adult horses is rare
- Stress may play a role in disease (possibly for all animals)
- Withholding roughage a risk (VFAs)
- Both foals with & without out diarrhoea get infected (colonised)
- Dams of foals treated with erythromycin for Rhodococcus equi get severe disease
- Wide range of ribotypes found in horses

What does this all mean?
- Approx. 20 years ago no overlap between dog/cat and human strains
- Now most animal isolates produce binary toxin (horses 43%, piglets 83%, cattle 100%)
- Binary toxin producing strains occurring more in the community, and causing more severe disease

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Culture/toxin +ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>273</td>
<td>0</td>
</tr>
<tr>
<td>Acute colitis+Ab</td>
<td>43</td>
<td>18 (42%)</td>
</tr>
<tr>
<td>Colitis, no Ab</td>
<td>72</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>No disease+Ab</td>
<td>47</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Colic, no Ab</td>
<td>65</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>23</td>
</tr>
</tbody>
</table>

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Emergence of Clostridium difficile Infection Due to a New Hypervirulent Strain, PCR Ribotype 078

- Compared 027 infections with 078
- 078 increased from 3% to 13% (2005-8)
- In parts of The Netherlands where 90% of pig farms 22.4%
- 078 patients were younger (67 vs 74 yrs)
- More community acquired 17.5% vs 6.7%
- Severity and attributable mortality similar
- Pig & human 078 strains genetically indistinguishable

Goorhuis et al Clinical Infectious Diseases 2008; 47:1162–70
Ribotype 078 now the 3rd most common isolate in Europe (Bauer et al ECCMID 2009)

Why is this happening?
+ antibiotics = disaster

Approx. 50% increase in numbers

Approx. 400% increase in penicillins, β-lactamase sens.
Other penicillins, cephalosporins 1000% increase

Table 1. Production of food animals (including export of live animals) and the production of meat and milk.

<table>
<thead>
<tr>
<th>Animal</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep</td>
<td>51</td>
<td>52</td>
<td>53</td>
<td>54</td>
</tr>
<tr>
<td>Cattle</td>
<td>156</td>
<td>160</td>
<td>165</td>
<td>170</td>
</tr>
<tr>
<td>Pigs</td>
<td>120</td>
<td>125</td>
<td>130</td>
<td>135</td>
</tr>
</tbody>
</table>

Table 2. Source and characteristics of C. difficile isolates obtained from retail meats sold in Tucson, Arizona, USA, 2002

<table>
<thead>
<tr>
<th>Source of meat</th>
<th>C. difficile isolates</th>
<th>% (n)</th>
<th>C. difficile isolates</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ground beef</td>
<td>26 (10)</td>
<td>5.9%</td>
<td>26 (10)</td>
<td>5.9%</td>
</tr>
<tr>
<td>Ground sausage</td>
<td>7 (5)</td>
<td>3.8%</td>
<td>7 (5)</td>
<td>3.8%</td>
</tr>
<tr>
<td>Ground pork</td>
<td>9 (4)</td>
<td>4.8%</td>
<td>9 (4)</td>
<td>4.8%</td>
</tr>
<tr>
<td>Ground liver</td>
<td>3 (2)</td>
<td>1.6%</td>
<td>3 (2)</td>
<td>1.6%</td>
</tr>
<tr>
<td>Ground turkey</td>
<td>5 (3)</td>
<td>2.6%</td>
<td>5 (3)</td>
<td>2.6%</td>
</tr>
<tr>
<td>Ground organ</td>
<td>1 (0.5)</td>
<td>0.5%</td>
<td>1 (0.5)</td>
<td>0.5%</td>
</tr>
<tr>
<td>Ground edible</td>
<td>10 (5)</td>
<td>5.3%</td>
<td>10 (5)</td>
<td>5.3%</td>
</tr>
<tr>
<td>Ground bone</td>
<td>2 (1)</td>
<td>1.1%</td>
<td>2 (1)</td>
<td>1.1%</td>
</tr>
<tr>
<td>Ground liver</td>
<td>3 (1.5)</td>
<td>1.5%</td>
<td>3 (1.5)</td>
<td>1.5%</td>
</tr>
<tr>
<td>Ground turkey</td>
<td>6 (3)</td>
<td>3.2%</td>
<td>6 (3)</td>
<td>3.2%</td>
</tr>
<tr>
<td>Ground organ</td>
<td>1 (0.5)</td>
<td>0.5%</td>
<td>1 (0.5)</td>
<td>0.5%</td>
</tr>
<tr>
<td>Ground edible</td>
<td>1 (0.5)</td>
<td>0.5%</td>
<td>1 (0.5)</td>
<td>0.5%</td>
</tr>
<tr>
<td>Ground bone</td>
<td>2 (1)</td>
<td>1.1%</td>
<td>2 (1)</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

Table 3. Emergence of C. difficile infection due to a new hypervirulent strain, PCR Ribotype 078.

<table>
<thead>
<tr>
<th>Strain</th>
<th>% in 1998</th>
<th>% in 2000</th>
<th>% in 2001</th>
<th>% in 2002</th>
<th>% in 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>078</td>
<td>3%</td>
<td>13%</td>
<td>16%</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>027</td>
<td>97%</td>
<td>87%</td>
<td>84%</td>
<td>80%</td>
<td>92%</td>
</tr>
</tbody>
</table>

Table 4. Trends in the estimated total consumption (kg active compound) of prescribed antimicrobials for production animals. (kg)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>1000</td>
<td>1200</td>
<td>1500</td>
<td>2000</td>
<td>2500</td>
</tr>
<tr>
<td>β-Lactams</td>
<td>500</td>
<td>600</td>
<td>800</td>
<td>1000</td>
<td>1200</td>
</tr>
<tr>
<td>Other penicillins, cephalosporins</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td>400</td>
<td>500</td>
</tr>
</tbody>
</table>
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Population per km²
- 20 South Korea 498
- 24 The Netherlands 395
- 73 People’s Republic of China 138
- 81 Denmark 126
- 177 United States of America 31
- 232 Australia 2.84

What are the risks from animal exposure?
- Direct exposure to pigs, horses, cattle colonised/infected with C. difficile and associated dust contaminated with C. difficile spores in piggeries, stables.
- Direct exposure to waste/compost made from pig litter and contaminated with C. difficile spores.
- Exposure through the handling or consumption of contaminated meat and meat products.

How can this be fixed?
- Stop giving animals broad-spectrum cephalosporins
- Stop giving humans broad-spectrum fluoroquinolones
- Improved cleaning practices in healthcare institutions
- Improved cleaning practices in production animal industries

Infection control (Baverud Vet Clin Equine 2004)
- Restrict use of antimicrobials – lincosamides, macrolides & cephalosporins
- Minimise stress factors
- Reduce environmental contamination (How?)
- Isolate animals with diarrhoea
- Avoid accidental ingestion of erythromycin by dams
- Hand hygiene & gloves
- Test suspect animals

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