Educational Workshop

EW06: *Clostridium difficile* – future directions?

arranged with ESGCD (ESCMID Study Group for *Clostridium difficile*)

Convenors: Emilio Bouza, Madrid, ES
Mark Wilcox, Leeds, UK

Faculty: Maja Rupnik, Maribor, SI
Mark Wilcox, Leeds, UK
Ed Kuijper, Leiden, NL
Ian Poxton, Edinburgh, UK
Emerging CDAD among animals and possible transmission to humans?

Maja Rupnik
Institute of Public Health Maribor and Medical Faculty, University of Maribor, Maribor, Slovenia

Clostridium difficile
- human (nosocomial) pathogen
- increasingly important as animal pathogen

→
new potential reservoir for human infections
possible transmission routes

Question for the audience
Which statement describes your interest in the best way?

a) I'm associated with veterinary setting and/or am working mainly on animal associated C. difficile
b) I do occasionally work with animal associated C. difficile strains
c) Animal associated C. difficile is potentially important, but I do not have the contact with such strains in my everyday work
d) I'm planning to work with animal-associated C. difficile in the future
e) Animal associated C. difficile is of minor importance at the time
CDAD in animals

- *C. difficile* is described in several animal species (symptomatic, asymptomatic)
  - camels, seals, deer, elephant, tiger
  - laboratory rodents (hamster, guinea pigs, rabbit, mice)
  - cats, dogs, horses, pigs, calves

- disturbed normal gut flora (?)
  - antibiotics
  - young age
  - diet (inhibiting growth of intestinal microorganisms; broccoli connected with cases of fatal CDAD in captive elephant, Bojesen et al., Vet. Microbiol., 2006)

- sporadic cases, outbreaks

Question for the audience

In my experience *C. difficile* is important pathogen in:

1) pigs
2) calves
3) horses
4) rabbits
5) turkeys
6) dogs
7) cats

CDAD in domestic animals

<table>
<thead>
<tr>
<th>Type of population</th>
<th>Horses</th>
<th>Dogs</th>
<th>Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>asymptomatic adults</td>
<td>42 %</td>
<td>21 %</td>
<td>2 – 38,1 %</td>
</tr>
<tr>
<td>(hospital/without ARB)</td>
<td>6 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>healthy adults</td>
<td>0 - 2 %</td>
<td>0-40%</td>
<td>0 %</td>
</tr>
<tr>
<td>asymptomatic neonates</td>
<td>11 – 35%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>asymptomatic neonates</td>
<td>29 % (&lt; 14 days)</td>
<td>3,1 – 67,1% (&lt; 10 weeks)</td>
<td>ND</td>
</tr>
</tbody>
</table>
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Emerging CDAD among animals and possible transmission to humans?

CDAD in pigs – economic importance

Neonates
1 to 7 days of age
morbidity from 10 to 90%, mortality up to 16%
precolonization with nontoxigenic strain decreases CDAD rates (Songer et al., 2007)

Isolation rates – symptomatic piglets (Songer, 2000)
52.8% of pig neonatal enteritis samples
in 36% of samples C. difficile only known pathogen

Adult animals
postparturient sow after antibiotic therapy
(Kiss and Bilkei, 2005)

CDAD in calves – often present in healthy animals

<table>
<thead>
<tr>
<th></th>
<th>diarrheic</th>
<th>nondiarrheic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodriguez-Palacios et al., 2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4 weeks</td>
<td>culture +</td>
<td>7.6 %</td>
</tr>
<tr>
<td></td>
<td>toxin +</td>
<td>39.6 %</td>
</tr>
<tr>
<td></td>
<td>culture +</td>
<td>25.3 %</td>
</tr>
<tr>
<td></td>
<td>toxin +</td>
<td>22.9 %</td>
</tr>
<tr>
<td>Hammitt et al., 2007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6 weeks</td>
<td>culture +</td>
<td>14.9 %</td>
</tr>
<tr>
<td></td>
<td>toxin +</td>
<td>20.9 %</td>
</tr>
<tr>
<td></td>
<td>culture +</td>
<td>13.2 %</td>
</tr>
<tr>
<td></td>
<td>toxin +</td>
<td>30.2 %</td>
</tr>
</tbody>
</table>

Question for the audience
We perform culture and toxin testing on animal samples and
1) results of culture and toxin test correlate well
2) results of culture and toxin test rarely correlate
3) results of culture and toxin test correlate only in some animal species
Emerging CDAD among animals and possible transmission to humans?

**C. difficile** diagnostic in animals

- Culture enrichment used in most reports
- Commercial toxin tests - low concordance between toxin testing and culture testing of toxin positive samples
  - 44.8% were culture +
  - 55.1% were culture -
- toxin positive and culture positive
  - 4.2% in diarrheic animals
  - 5.2% in control animals

**C. difficile** as potential reservoir for human disease

- changes in human epidemiology in part a consequence of introduction of new animal types in the community?
- how similar are the animal and human **C. difficile** types
- what are the potential routes of transmission

Changes of CDAD in humans

- General increase in the prevalence of CDAD and increase in disease severity
- Increase in population previously at low risk
- Spread of a specific types
  - toxinotype VIII (serogroup F; 017, A-B+CDT+)
  - toxinotype III (type BI/NAP1/027; 027, A+B+CDT+)
- Increased number of binary toxin positive strains
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Emerging CDAD among animals and possible transmission to humans?

**Mostly used typing methods for *C. difficile***

<table>
<thead>
<tr>
<th>Method</th>
<th>Europe</th>
<th>North America</th>
</tr>
</thead>
<tbody>
<tr>
<td>ribotyping</td>
<td>L 81 82 83 84 85 L 86 87 88 89 90 L</td>
<td>A2 1 2 3 4 5 6 7 8 9 10 11 12 13 A2</td>
</tr>
<tr>
<td>PFGE</td>
<td>Others: MLVA, AFLP, MLST, slpA-typing</td>
<td>Others: MLVA, AFLP, MLST, slpA-typing</td>
</tr>
</tbody>
</table>

**Other characteristics for differentiation of *C. difficile* strains**

- **Toxinotyping**
  - differentiation according to variability in genes for toxins TcdA and TcdB
  - types 0, I to XXVII
  - good correlation with other molecular typing methods

- **Presence of binary toxin CDT**
  - unrelated to toxins TcdA and TcdB
  - produced only by some *C. difficile* strains
  - good correlation with other molecular typing methods

**Prevalence of CDT+ *C. difficile* strains**

<table>
<thead>
<tr>
<th>Species</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>human</td>
<td>1.6 – 5.5%</td>
</tr>
<tr>
<td></td>
<td>(14 – 20%)</td>
</tr>
<tr>
<td></td>
<td>17.2%</td>
</tr>
<tr>
<td>equine</td>
<td>23.5 – 57.8%</td>
</tr>
<tr>
<td></td>
<td>65.5%</td>
</tr>
<tr>
<td>calves</td>
<td>45 – 97%</td>
</tr>
</tbody>
</table>
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**C. difficile** types in humans and animals

- cats and dogs, humans (Australia) (O’Neill et al., Epidemiol. Infect. 1995)
  - no overlap between animal and human strains
  - good correlation between animal and veterinary clinic environment strains
- calves (Canada) (Rodriguez-Palacios et al., Emerg Infect Dis., 2006)
  - 7 ribotypes
    - 078 (V), 017 (VIII), 027 (III), 033 (XI), 077 (0), 014 (0)
- calves and pigs (USA) (Keel et al., 2007)
  - 4 ribotypes
    - all of them known in human isolates
    - 078 (V), 017 (VIII), 033 (XI), 002 (0), 126 (ND)

**C. difficile** transmission between animal and human host

- contact
  - veterinarians, farmers
  - pets
- environment
- food

Environment – Veterinary clinics

  - 4.5% of environmental sites positive in Large Animal Clinic
  - 8.1% of environmental sites positive in Small Animal Clinic
- correlation with *C. difficile* carriage rates (Riley et al., 1991)
  - higher percentage of *C. difficile* positive environmental samples correlates with higher percentage of *C. difficile* positive cats and dogs
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Environment – Farm environments

<table>
<thead>
<tr>
<th>soil samples</th>
<th>% culture positive</th>
<th>num of toxin positive isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>stud farms</td>
<td>11</td>
<td>10 out of 14</td>
</tr>
<tr>
<td>stables with mature horses</td>
<td>1</td>
<td>2 out of 2</td>
</tr>
<tr>
<td>non-animal associated public places</td>
<td>4</td>
<td>6 out of 9</td>
</tr>
</tbody>
</table>

Question for the audience

Are animals (e.g. dogs) allowed in hospitals/elderly care facilities in your local environment

1) yes
2) no
3) only in special programs

Contact - *C. difficile* in dogs

<table>
<thead>
<tr>
<th>animal</th>
<th><em>C. difficile</em> carriage rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>visitation dogs (healthcare facilities)</td>
<td>28 %</td>
</tr>
<tr>
<td>visitation dogs (non-healthcare facilities)</td>
<td>15 %</td>
</tr>
<tr>
<td>dogs in households</td>
<td>2.3 %</td>
</tr>
</tbody>
</table>

Risk factors for *C. difficile* acquisition:
healthcare contact, contact with children, antimicrobial treatment, antimicrobial treatment of household member

Type BI/NAP1/027 isolated from healthy visitation dog

(Lefebvre et al., 2006)

S. Weese, unpublished data
Emerging CDAD among animals and possible transmission to humans?

**C. difficile** in food (meat and meat products)

- Canada (Rodriguez-Palacios et al., Emerg. Infect. Dis., 2007)
  *C. difficile* isolated from 20% of ground meat samples
  Ribotypes 077, 014, M31, M28 – similar to type BI/NAP1/027

- USA (Songer et al., 2nd ICDS meeting 2007)
  *C. difficile* isolated from 44.7% of samples
  43.8% of beef products, 46.7% of pork products, 37.5% turkey products
  Ribotypes 012, 078 (68.4%), BI/NAP1/027 (31.4%)

- EU
  Unpublished data from some countries suggest levels below 5%

**Toxinotype V in animals and humans**

- **animals**
  Prevalent type isolated from several animal species worldwide
  078 (USA, Canada, Netherlands) and 066 (Slovenia)

- **food**
  078 (USA)

- **humans**
  078 more prevalent (EU prevalence study 2005)
  10% of community-associated strains in USA
  (Limbago et al., 2nd ICDS meeting, 2007)

**Summary**

- **C. difficile** is a primary pathogen in animals

- Animals can be a multiplying host for the microorganism and source for human infection

- Transmission from/to animal reservoir can be via contact, environment or food
Mark Wilcox
Effective and non-effective infection control measures during outbreaks of CDAD

**CDI transmission pressure**

- 'CDAD pressure' = a modified form of colonization pressure based on symptomatic CDAD cases
- Retrospective cohort and nested case-control studies of patients admitted to US hospital during 2003
- 36,275 patients were included in the cohort, of which 382 had CDAD


**CDI transmission pressure**

- Median CDAD pressure was higher for case patients than non-case patients (1.4 vs 0.3; P<0.001)
- Only 1 patient with CDAD had a CDAD pressure of 0
- Nested case-control study, CDAD pressure remained an independent risk factor for CDAD after adjustment for other risk factors (incl. antibiotics)


**CD ribotype prevalence in England**

- PFGE identified 5 groups
- MLVA markedly more discriminatory: 23 groups (1-15 isolates)

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Effective and non-effective infection control measures during outbreaks of CDAD

Dendrogram for 91 C. difficile 027 isolates to indicate relatedness according to 7 MLVA markers

Distribution in time and space of CD 027 cases (n=46)

Linked cases:
- gut surgery
- renal medicine
- elderly medicine
- haematology
Mark Wilcox
Effective and non-effective infection control measures during outbreaks of CDAD

Prevalence of *C. difficile* ribotypes in Leeds, UK Jan 2006 - Jul 2007 n=1603 isolates

C. difficile 027/other virulent strains

- cannot reliably detect CD 027 cases clinically i.e. many cases are indistinguishable from 'normals'
- high index of suspicion
- when to review control measures
- when to escalate therapy

When to consider CDRNE

Increase in frequency or severity of cases of CDI
- or
Increase in mortality
- or
Increase in the recurrence rate
- or
High baseline rate of infection

Must routinely store faecal samples/aliquots (-20°C) to enable enhanced surveillance
Severe CDI

- 3 ‘predictive’ factors for complicated course
  - Age
  - Peak leukocytosis
  - Peak creatinine


- Caecotectomy (total/subtotal)
  - Lactate >5
  - Caecal dilatation >10cm


Note: Of 53 patients classified as severe CDI, only 1 had colitis confirmed. This individual was negative for the other 3 markers of severe infection; thus, only the 52 remaining severe CDI cases are included here.

Diarrhoea frequency
as measured between day -4 & +2

- Group 0
  No evidence of diarrhoea before or after stool sample sent

- Group 1
  1 or 2 episodes of diarrhoea in a 24 h period

- Group 2
  ≥3 episodes of diarrhoea in a 24 h period

- Group 3
  ≥3 episodes of diarrhoea per day, for 24-48 h

- Group 4
  ≥3 episodes of diarrhoea per day for >2 days
Mark Wilcox
Effective and non-effective infection control measures during outbreaks of CDAD

Proportions of patients with 'severe' CDI according to frequency of diarrhoea

New issues pertinent to transmission control

- Asymptomatic carriage as risk factor for environmental contamination or transmission
- Cohorting (CDI wards) vs side rooms
- Incontinence devices
- Airborne dispersal
- Effectiveness of cleaning for spore removal
  - Chlorine, hydrogen peroxide, steam

Evidence for role of chlorine-based cleaning to control CDi (iii)
Mark Wilcox
Effective and non-effective infection control measures during outbreaks of CDAD

Use of Hypochlorite Solution to Decrease Rates of Clostridium difficile-Associated Diarrhea

Kathleen M. McQuillan, MPH; Jennifer Zuck, RN, CIC; Craig M. Cooper, RN; Min M. Koffel, MD; Erik Debbink, MD; David R. Warren, MD, MPH

An increased rate of Clostridium difficile-associated diarrhea (CDAD) was noted in 2 intensive care units of a university-affiliated tertiary care facility. One unit instituted enhanced environmental cleaning with a hypochlorite solution in addition to routine cleaning, whereas the other unit used hypochlorite solution only in rooms of patients with CDAD. The CDAD rates decreased in both units.


Evidence for role of chlorine-based cleaning to control CDI (iv)


Frequency of C. difficile culture-positive environmental sites

Effective and non-effective infection control measures during outbreaks of CDAD

**CDI carriage & contamination**

- Previous CDI ($P < 0.001$) and previous antibiotic use ($P=0.017$) were associated with asymptomatic carriage
- Combination of these 2 variables was predictive of asymptomatic carriage (sensitivity, 77%; specificity, 58%; positive predictive value, 66%; negative predictive value, 70%)

**CDI key control measures**

- Early warning system to identify changes in local epidemiology
- Reduce risk of transmission
- Isolation/cohorting of cases
- Environmental cleaning, chlorine
- Hand hygiene soap & water
- Examine/optimise/reduce overall antibiotic use
- Limit high risk agents in high risk patients
- Feedback CDI and antibiotic data on a regular basis
Recognition of community-acquired CDAD

Ed J. Kuijper, M. Bauer and J. van Dissel
National Reference Laboratory, Centre for Infectious Diseases, Leiden University Medical Centre, The Netherlands

Clostridium difficile
Spore-forming, obligate, anaerobic gram-positive rod
Ubiquitous, also in animals
Toxins:
- 308 kDa enterotoxin (A)
- 269 kDa cytotoxin (B)
- binary toxin

Clostridium difficile-associated infection (CDI)
Asymptomatic carriage in intestinal tract
Hospital-acquired diarrhoea
- mild self-limiting diarrhoea
- cholera-like
- pseudomembranous colitis
Community-acquired diarrhoea
Ed Kuijper
Recognition of community-acquired CDAD

### Emergence of Clostridium difficile-associated disease in North America and Europe

- **Admission**
- **Discharge**
- **48h**
- **4 weeks**
- **8 weeks**

- Community-acquired
- Healthcare-associated
- Unknown

(*) - May be community- or healthcare-associated, depending on case’s history.
- If healthcare-associated, may have been acquired in the same facility or imported from another.

### Assessment of Clostridium difficile-Associated Disease Surveillance Definitions, North Carolina, 2005

- Of 1046 CDAD cases, 442 (42%) were HO-HCFA cases and 604 (58%) were community-onset cases.
- Of the 604 community-onset cases, 94 (15%) were CO-HCFA, 40 (7%) were of indeterminate exposure, and 208 (34%) were community-associated.
Ed Kuijper  
Recognition of community-acquired CDAD

Pathogenesis of CDI

CDI?

2-years old boy attending an emergency department with acute severe diarrhoea after treatment of otitis media 2 month earlier
70-years old male patient with bloody diarrhoea after an antibiotic course with ciprofloxacin
34-years old pregnant patient with severe bloody diarrhoea after a period of mild diarrhoea of 3 weeks
25-years old male patient with watery diarrhoeae after a travel to India and a course of metronidazole
45-years old female patient with diarrhoea who has been hospitalized abroad (Mallorca) 2 months earlier
70-years old male patient with bloody diarrhoea, who regularly visits his wife in a nursing home

Incidence of Clostridium difficile-associated disease and distribution of various strains before the recognition of the emerging PCR ribotype 027 in The Netherlands.

* Mean incidence: 17 per 10 000 admissions
* 87 patients, 61% nosocomial and 36% community onset
* 2 patients (2%) died due to CDAD.
Ed Kuijper
Recognition of community-acquired CDAD

**CA-CDI**

<table>
<thead>
<tr>
<th>83-years old male, diarrhoea for more than 4 weeks without any predisposing factor for CDI. Died (attributable) 5 days after hospital admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>86-years old female, admitted with diarrhoea since 7 days without any predisposing condition. Died 1 week later (contributable), due to heart failure.</td>
</tr>
</tbody>
</table>

**General risk factor for C difficile infection**

- Antibiotic administration; overestimated?
- Elderly age
- Duration of hospital (ICU) stay
- Renal failure
- Chemotherapy
- Cancer (solid tumours, leukemia or lymphoma)
- Gastrointestinal disease or intestinal surgery
- Antacids, proton pump inhibitors
- Diabetes mellitus
- COPD
- Liver cirrhosis

**Characteristics that may help to discriminate between patients with CD-diarrhoea due to *C. difficile* infection or due to another cause**

- Age > 65 years
- Hospitalisation > 3 days in the previous 3 months
- Use of antibiotics within the previous 3 months
- Family members in hospital or nursing home
- Use of immunosuppressive medication
- Pregnancy?
- Use of proton pump inhibitors?
Recognition of community-acquired CDAD

6.7% of CDI is high and raises the possibility that CDI is associated with antibiotic use in children.

*6.7% of CDI is high and raises the possibility that CDI is associated with antibiotic use in children*
Ed Kuijper  
Recognition of community-acquired CDAD

<table>
<thead>
<tr>
<th>General conclusions</th>
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</thead>
<tbody>
<tr>
<td>Underestimation of CA-CDI and CO-CDI</td>
</tr>
<tr>
<td>Children?</td>
</tr>
<tr>
<td>Role of PPI and pregnancy unclear</td>
</tr>
<tr>
<td>Recent studies from Germany, UK and The Netherlands do not have uniform conclusions</td>
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</tbody>
</table>
Changing host susceptibility to C. difficile infections

Plan of this session
- Introduction
  - Some facts and perceptions
- Questions
  - to gain awareness and experience of participants
- Discussion
  - On relative importance of changes in bacterial virulence versus changes in host susceptibility
- Conclusions
  - Some answers, agreements and more questions.....

Some facts
- Cases have increased over past 25 years or so
- A hypervirulent strain has emerged (027/NAP1/BI)
- Resistance to antibiotics is generally increasing
Changing host susceptibility to C. difficile infections

Some recent perceptions in C. difficile infections

- The severity of disease has increased
- CDI is contributing to more deaths
- Treatment is more difficult by traditional methods
- The rate of relapse/recurrence has increased
- There is more severe disease in "unusual host groups"
  - seemingly healthy, non-institutionalised individuals in the community
  - younger patients/paediatric patients
  - peripartum women
  - those without apparent exposure to antimicrobial agents
- CDI seen in associations with other GI pathogens e.g. norovirus

A changing picture....

Recognition of 027/NAP1/BI

- Major outbreaks in North America and Western Europe
- More severe disease
- More deaths
- Increased level of toxin production
- Resistance to fluoroquinolones
- Binary toxin positive

A new hypervirulent strain has emerged

Questions

1. Is the virulence of the bacterium the main driving force?

   or

2. Is the susceptibility of the patient crucial and is this changing?
Changing host susceptibility to *C. difficile* infections

**Awareness of participants?**

1. Are you aware of changes in number of cases?
2. Are you aware of changes in severity of disease?
3. Are you aware of different groups of patients being affected?

**Why are perceptions changing?**

- Is there increased awareness?
- Is there increased reporting?
- Because of awareness is *CDI* being included more on death certificates?

**CDI mortality rates in USA**

- Increased from 5.7 per million population in 1999 to 23.7 per million in 2004.
- Increase rates may be due to emergence of a highly virulent strain of *C. difficile*.
- Rates were higher for whites than for other racial/ethnic groups.

Changing host susceptibility to *C. difficile* infections

**Proton pump inhibitors and \(H_2\) receptor antagonists**

A meta-analysis to evaluate any association between acid suppression and enteric infection

- 12 papers (2,948 patients) with *C. difficile* included.
- Increased risk of taking acid suppression therapy in those infected with *C. difficile* (OR 1.94, 95% CI 1.37-2.75).
- Marginally greater for PPI use compared with H\(_2\)RA use
- Similar for other enteric infections due to *Salmonella*, *Campylobacter* etc. (OR 2.55, 95% CI 1.53-4.26)

Conclusions
- Association between acid suppression and an increased risk of enteric infection.
- Further prospective studies are needed to establish whether this association is causal.


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**Paediatrics – a problem?**

- *C. difficile* is a common commensal in neonates – but usually only considered an indicator of cross infection in a neonatal ICU
- Increasing awareness in paediatric populations

Changes seen in numbers of positive samples from patients in Hospital for Sick Children in Edinburgh 2000-2006

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**CDI in paediatric patients**

Study in Cleveland OH, USA in a Children’s Hospital July 2001 to June 2006

- A steady increase in the number of paediatric patients seen in the emergency department with community-acquired CDI.
- Suggested that the characteristics of CDI are changing in children.
- Further investigations required to explore changes in the disease and patient risk factors.

Changing host susceptibility to C. difficile infections

**CDI in peripartum women**

- From the baby to the mother?
  - Recent report of hypervirulent/“epidemic” strain being transferred between asymptomatic baby and peripartum mother resulting in recurrent disease in mother
  - Direction of transfer unclear
  
  (Hecker et al CID 2008; 46:956-7)

**If host susceptibility is changing, what are the causes?**

- More severe underlying disease
- Reduced immunity – immunosuppression

**Immunity and host defences**

- **Innate**
  - normal bowel flora (colonisation resistance)
  - gut motility
  - gastric acid

- **Acquired**
  - systemic IgG and secretory (IgA) antibodies to toxins A and B
  - mucosal IgA to cell surface components?
  - Cell-mediated involvement?

Suggestions that patients are susceptible because they are unable to mount a protective response
Ian Poxton
Changing host susceptibility to C. difficile infections

**Immune Response: current views**
- Asymptomatic carriers have higher IgA and IgM against *C. difficile* than CDI patients?
- Anti-toxin A IgG provides protection against recurrence?
- Other highly immunogenic antigens: e.g. SLPs have they a role?
- Immunotherapy & vaccines may be useful

**Is a failure to mount an immune response important?**
- Site of immune response?
- Innate recognition
- To toxins only - or other antigens?
- Antibody v cell mediated
- Is it of equal importance in primary infection or relapse?

**Antibody responses**
- Everyone has pre-existing antibodies to toxins and cell surface antigens
- Symptomatic patients have highest levels - typical "boosting" response
- No indication of patients being deficient in antibody response - but may have importance in recurrent disease
  
  (Sanchez-Hurtado et al JMM in press)
Ian Poxton
Changing host susceptibility to C. difficile infections

**Immunosenescence and immunosuppression?**

- Immunosenscence - a link proposed:
- Possible associations with CMV - cause or effect?
  - CMV causes PMC
    Olliffe Made O, Chang C. J Clin Gastroenterol. 2000; 32: 82-84
  - No significant association
- A lethal complication of anti-rejection therapy?
  - Cytomegalovirus and Clostridium difficile ischemic colitis in a renal transplant recipient
    Veroux et al. Urol Int. 2007; 79: 177-179

**And finally…..**

- Is there a link with immunosuppression and/or immunosenescence?
- And are these changing?
- Or is it simply because there are more severely ill patients around with more antibiotics being prescribed and exposure to infection increasing?
- And are asymptomatic carriers, the non-hospital environment, or animals considered risks

**Conclusions reached?**

- Virulence of bacterium has changed
  - Just 027 or are there other hypervirulent strains?
- Spectrum of severity is increasing
- More (hospital) patients are being exposed to C. difficile
- But is there any evidence for susceptibility of patients changing?
Ian Poxton
Changing host susceptibility to C. difficile infections

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