Clostridium difficile infection in children

Dr Andreas Karas
HPA Addenbrookes Hospital
Cambridge, UK
The team:
David Enoch
Sani Aliyu
Sumita Pai
Matthew Butler
• Colonisation
• Disease
• Our experience
• Paediatric criteria
• Questions that need answers?
Contact with infants aged 2 years was significantly associated with community acquired CDI (14% vs. 2%; p=0.02).
Colonisation

- Wide variation
  - 2.5 to 90% colonisation among neonates
  - High rates are from hospitalised babies

- Believed mostly asymptomatic in under 2yr’s
  - Lack of colonisation resistance
  - Absence of receptors for toxin A
• Searched Pubmed January 1997 to January 2011
  – 244 articles
• Other articles sourced from these articles
  – total article list of 407 titles.
• Data represented graphically were taken directly from the cited articles
• Large variation in studies:
  – Differences in laboratory testing
• The middle of the age range used when median or mean age not stated.
• Graphs: size of groups represented as size of data bubble plots
C. difficile colonisation by age in first 20 days of life (11 studies)

Percentage of Clostridium difficile culture positives in neonates (Pooled data)

Enoch DA et al J. Infection 2011 63: 105-113
First 20 days of life

• Low rates in healthy term babies
• Most studies done on hospitalised infants
  • Rates among neonates varied 2-52% depending on ward
  • Most only acquired after 20 days of life
• Donta ST, Myers MG. J Pediatr 1982;100(3)
  • 10.5% of healthy infants
  • 55% of intensive care infants

• Acquisition:
  • Some proof of maternal
  • Most show environmental acquisition
C. difficile colonisation by age up to 13 years of age (30 studies)

Enoch et al. J. Infection 2011 (63) 105-113
Pooled data for 5887 patients for *C. difficile* colonisation separated into different ages (30 studies)

Enoch et al *J. Infection* 2011 63: 105-113
Risk factors in children

• Active disease
  – Largely associated with significant co-morbidities
    • Haematological malignancies
      – Chemotherapy
      – Broad spectrum antibiotics
    • Immunosuppression
    • Bowel disorders / IBD

  – Inconclusive:
    • Mode of delivery
    • Prior antibiotics
      – Associated mostly in older age groups
    • Breast versus formula feeding
Mortality in adults

Pooled mortality attributable to C. difficile by age group

Attributable mortality

Age group

<\= 60 61-70 71-80 >80

Our experience

• There is increasing evidence of the pathogenic role of *C. difficile* in the paediatric population.
• Ascertain the clinical presentation and severity of CDI in children at our institution
• Develop criteria to aid management.
• Descriptive retrospective study over a 5-year period, 2005 to 2009, tertiary hospital in Cambridge UK

• Case defined as a patient aged 0-16 years with a positive cell culture cytotoxin result
  – Recurrence if C. difficile isolated 28 days after the initial positive test

• UK National guidelines for adults were used to assess the severity and management of CDI
• Hospital onset infection was a positive test after 2 days of hospital admission

• Community onset was if positive test within 2 days of admission

• Healthcare-associated if patients came from nursing homes or palliative care
Severity of disease using the UK national classification:

- Four categories are defined as mild, moderate, severe and life-threatening.
- These guidelines also recommend treating according to severity, daily monitoring using the Bristol Stool Chart and multidisciplinary clinical review of cases.
Our experience

• 75 patients with a mean age of 2.97 years.
• 49 were hospital onset, 22 community onset and 4 healthcare-associated.
• Thirty-one (58.5%) of the HA cases had prior in-patient days of >1 month in the preceding year
• Sixty-eight patients (90.7%) had significant co-morbidities
  – Most common in HA was malignancy.
  – Gastrointestinal conditions in CO infections.
## Blood parameters and symptoms of infection (n=75)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood parameters at CDT date</td>
<td></td>
</tr>
<tr>
<td>WCC (&gt;15x10⁹)</td>
<td>28 (37)</td>
</tr>
<tr>
<td>Rising Creatinine</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Falling Albumin (&lt;25g/L)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>CRP (&gt;25mg/L)</td>
<td>40 (53)</td>
</tr>
<tr>
<td>Hb (&lt;10g/L)</td>
<td>28 (37)</td>
</tr>
<tr>
<td>Fever ≥ 38.5° C</td>
<td>34 (45)</td>
</tr>
<tr>
<td>Abdominal pain, tenderness, distension</td>
<td>17 (23)</td>
</tr>
<tr>
<td>Diarrhoea &gt; 5 times a day</td>
<td>50 (67)</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>2 probable 1 definite</td>
</tr>
<tr>
<td>Surgery required</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>
• Fifty-five cases (73.3%) had received antibiotics in the preceding month.
• According to national adult guidelines 57 (76%) cases were categorised as severe.
• Thirty cases received oral metronidazole.
• No *C. difficile* related mortality observed.
Our experience

• Confirmed association of paediatric CDI with co-morbidities such as haematological and solid organ malignancies, recent antibiotic use and hospitalisation

• Observed an association between cows milk protein intolerance and C. difficile

• Based on adult criteria most cases were categorised as severe but experienced a mild course of illness with low morbidity and no mortality

• Adult scoring criteria are not useful in guiding management
Recent studies

- Sandora et al Epidemiology and Risk Factors for Clostridium difficile Infection in Children PIDJ 30 (7) July 2011

- Of 1891 toxin A/B tests in children <18 yrs 14% positive
- 95 patients > 1 yr compared with 238 controls
- Risk factors
  - Recent antibiotic exposure
  - Lack of recent hospitalisation
  - Co-morbidities: solid organ transplant, gastro-jejunostomy
- No severe outcomes
Recent studies

- Nested case-control study to identify the risk factors
- + Prospective cohort study to determine the outcomes associated with severe CDI
- Severe CDI defined as at least 1 complication or ≥2 laboratory or clinical indicators consistent with severe disease.
- Outcomes included relapse, treatment failure, and CDI-related complications.
82 patients with CDI
- 48 had severe disease.
- Median age in years was 5.93 (1.78–12.16) for severe, 1.83 (0.67–8.1) in non severe
- All patients with malignancy had severe disease and 1 death
- Risk factors for severe disease
  - age (adjusted odds ratio [95% confidence interval]: 1.12 [1.02, 1.24])
  - receipt of 3 antibiotic classes in the 30 days before infection (3.95 [1.19, 13.11])
• Nylund et al Arch Ped & Adol Med Jan 3 2011
  – Upward trend from 3565 cases in 1997 to 7779 cases in 2006 (p<0.001) in the USA
• Stoesser et al J Clin Micro 2011 49:11(3994)
  – Molecular analysis of 28 isolates from infants < 30/12, 27% of these isolated had same MLST type as from concurrent adult infections
  – Children may participate in some adult disease causing genotypes
• Rousseau et al J Med Micro 2011, 60: 1112-8
  – Molecular typing on 98 isolates from infants < 2yrs
  – Majority non-toxigenic, but toxigenic adult strains circulate in asymptomatic infants even in the community
Proposed criteria for CDI in children
Proposed criteria for CDI in children

Fulfils likely diagnosis of *C. difficile* infection if –

• *C. difficile* toxin positive

• Diarrhoea (Bristol stool chart 5-7) and at least one of the following:
  – Significant co-morbidities – Haematology/Oncology, Gastrointestinal disease
  – Stay in hospital for >2 days
  – Antibiotic use in the last 1 month
    » (especially ciprofloxacin and cephalosporins)
### Proposed criteria for CDI in children

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea &gt; 5 times a day</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain and discomfort</td>
<td>1</td>
</tr>
<tr>
<td>Rising white cell count</td>
<td>1</td>
</tr>
<tr>
<td>Raised C-reactive protein (CRP)</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia &gt;38.5°C</td>
<td>1</td>
</tr>
<tr>
<td>Evidence of pseudomembranous colitis</td>
<td>2</td>
</tr>
<tr>
<td>Intensive care unit requirement</td>
<td>2</td>
</tr>
</tbody>
</table>

**Score**

1-2 = mild disease  
3-4 = moderate disease  
≥5 = severe disease
Proposed criteria for CDI in children

Back to our study:

- Only 54/75 (72%) of children fulfilled criteria for disease.
- Only 9% classified as severe.
  - (76% using adult criteria)
Proposed criteria for CDI in children

Proposed medical management

• **Mild disease** – No need to treat if symptoms settle within 24 hours but consider oral metronidazole for 10-14 days if symptoms persist beyond 24 hours.

• **Moderate disease** – Oral metronidazole for 10-14 days and consider escalation by changing to oral vancomycin if non-resolution of symptoms or decline in severity score.

• **Severe disease** – Oral vancomycin and IV metronidazole. Colectomy should be considered if there if evidence of caecal dilatation.
Questions

• Is the high rate of colonisation of neonates only a feature of hospitalisation?
  – What happens to neonates that are well and leave hospital soon after birth?
• Do children under 1 year have true disease with CDI?
• Is there a link between cows milk protein intolerance and CDI?
• Is there a link between inflammatory bowel disorders and CDI?
• How significant is the presence of co-infection with other pathogens in CDI in children?
• Are the proposed criteria for CDI in children valid?