Observational Study of Risk factors for Clostridium difficile Infection in Hospitalised Patients with Infective Diarrhoea (ORCHID): Consistency of Risk

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Introduction

Clostridium difficile infection (CDI), already the most common cause for nosocomial diarrhoea in developed countries, remains a prevalent threat. Literature has shown patients with certain risk factors are at an increased risk for CDI. Identifying such a population would facilitate efforts in reducing CDI incidence and improving patient outcomes.

The aim of the study was to determine various risk factors for developing CDI in hospitalised patients and explore the consistency across different patient cohorts.

Methods

During a prior prevalence point study of CDI in Europe (EUCILD), cohorts of CDI cases/controls were identified by standardised testing (CDDVirus) at two time points, one day each in winter 2012/2013 and summer 2013. Parallel cohorts of CDI cases/controls were identified at University Hospital Cologne, Germany (parallel study site (PSS)) using the same standardised testing method, for the period July-October 2015. A retrospective CDI case-control study (ORCHID) was performed to determine the risk factors for infection in hospitalised patients at the PSS site and in those 7 European countries with higher rates of CDI incidence, as identified by the EUCILD study. These countries included Czech Republic, Germany, Hungary, Poland, Romania, Slovakia, and UK. For each confirmed case of CDI, 4 controls were randomly selected from the same hospital (matched by location) as the initial target population. Where available, data on risk factors were extracted from the available medical notes via a standardised clinical report form (CRF), which were sent then to the European coordinator for upload into the study database.

For the analysis, a subset of patients were removed from the control cohort if they had had evidence of previous CDI within the previous 8 weeks or within the subsequent 8 weeks of the index sample to provide 'clean' controls. In addition, for the multivariate analysis, all cases that had a previous toxin positive were removed. Statistics were analysed using univariate analysis and a multivariate analysis and a chi-squared (fisher's exact where numbers were below 5).

Results – Study population

For the analysis population, there were 253 and 358 cases and 921 and 584 controls in the PSS and EUCILD cohorts, respectively.

The PSS cohort came from one hospital site, whilst the EUCLID cohort comprised subjects in 59 hospitals across 7 countries.

Both cohorts had slightly more males than females. Whilst the median age of all patients in the PSS cohort was significantly older than those in the EUCLID cohort (67 vs. 60, p < 0.001) the median ages of cases were similar (median age PSS cases 71 years vs. 72 years in cases EUCLID cohort, p = 0.885).

Results – Consistent risk variables

Table 1. Summary of variables significant across both cohorts following univariate analysis

<table>
<thead>
<tr>
<th>Baseline covariation</th>
<th>EUCILD</th>
<th>PSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n)</td>
<td>460</td>
<td>104</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>104</td>
<td>26</td>
</tr>
<tr>
<td>Fold odds ratio</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.1, 1.5</td>
<td>1.1, 1.5</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 2. Variables consistently significant across all cohorts following multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>1.8 (1.4-2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥2 antibiotics</td>
<td>1.8 (1.5-2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>1.3 (1.1-1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>1.3 (1.1-1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1.3 (1.1-1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior hospital admission</td>
<td>2.0 (1.5-2.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Significant risk factors from univariate analysis in both cohorts were age >65 years, number of antibiotics, cefepime use, high Charlson comorbidity score, surgery and prior hospital admission. When compared for antibiotic prescription (all p<0.001). The OR for each antibiotic prescribed was 1.3 (p<0.001). In both cohorts, antibiotics received by cases were more likely to have been prescribed to patients with acute bacterial disease, while antibiotics in controls were significantly associated with prophylactic use. This aligns with data, where cases were more likely to be admitted with acute bacterial illness.

Multivariate analysis (38% of observations PSS = 1664, EUCLID = 721; Combined = 1885) consistently identified age >65, number of antibiotics and prior hospital admission as significant in each independent model and in a combined dataset. Patients admitted with other bacterial diseases remained significant in the EUCLID model, while congestive heart failure, admitted with intestinal infection and proton pump inhibitors remained insignificant in the PSS model. All other variables were non-significant.

Results – Other risk variables

• Congestive heart failure, diabetes, admitted from assisted living or Emergency Department, proton pump inhibitors and chronic renal disease were significant in PSS (all p<0.005). In both EUCLID and PSS, admitted with other bacterial diseases were significant in EUCILD (p<0.005) but not PSS.

• As the PSS hospital has a large cancer patient population, there were differences in the number of controls with malignancy. The difference in patient mix between the singleton site (PSS) vs. multi-centre (EUCILD) cohorts was evident in the admission diagnosis. PSS cases were significantly more likely to have been admitted with renal failure, while EUCLID cases were significantly more likely to have been admitted with a ‘bacterial disease’. Patients with acute bacterial disease may be more likely to receive antibiotics and so be at risk of CDI, indeed, these patients had a CDI OR=5.37.

• Broad-spectrum antibiotics commonly associated with CDI were significantly more likely to have been prescribed to PSS cases than controls, cephalosporins, 3rd generation cephalosporins, β-lactam, β-lactamase, β-lactamase producing and monosporins (all 0.05), whereas in the EUCILD cohort cases only cephalosporins and β-lactam were more likely to be prescribed.

• In the PSS cohort, PPI use was associated with a CDI OR=1.8 (p=0.001), and there was significantly more PPI use in the cases (75.9%) than the controls (64.3%) (p=0.001). Duration of PPI use was also longer in cases in controls (all 10 vs. 8 days, p=0.001). However, in the EUCLID cohort there were no significant findings associated with the use of PPI. This may be a reflection of the smaller total number of cases in the cohort, and the different patient mix, as total. In the PSS cohort 68.6% of patients had PPI use, compared with just 39.4% of patients in the EUCILD cohort. As described previously, the role of PPI use in CDI is controversial and may reflect the potential impact of accentuation bias in the type of controls patients in studies of this nature.

• Although cases in both cohorts were significantly more likely than controls to have had surgery in the preceding 12 weeks, there were no significant differences in the type of surgery for the EUCILD cohort; however, PSS cases were associated with both elective and vascular surgery. Again, this may reflect patient mix in the two cohorts; more patients had surgery in the PSS vs. EUCLID cohorts (39.4% vs 23.2%).

Conclusions

• Only some CDI risk factors are consistent across datasets, emphasising the potential for patient mix bias in such analyses.

• Significant risk factors for CDI across both cohorts and all models were age >65 years, antibiotics and prior hospital admission.

• The odds of developing CDI increases with each additional prescribed antibiotic.

Acknowledgements

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References