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To cite this version:

Maja Ogielska, Philippe Lanotte, Cécile Le Brun, Anne Sophie Valentin, Denis Garot, et al.. Emergence of community-acquired Clostridium difficile infection: the experience of a French hospital and review of the literature. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases, 2015, 37, pp.36-41. <10.1016/j.ijid.2015.06.007>. <hal-01183893v1>

HAL Id: hal-01183893
https://hal.archives-ouvertes.fr/hal-01183893v1
Submitted on 11 Aug 2015 (v1), last revised 7 Dec 2015 (v2)

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Emergence of community-acquired *Clostridium difficile* infection: the experience of a French hospital and review of the literature

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**Article Info**

* Received 3 April 2015
* Received in revised form 10 June 2015
* Accepted 11 June 2015
* Corresponding Editor: Eskild Petersen, Aarhus, Denmark

**Keywords:**
* Clostridium difficile
* Community infection
* Clostridium Severity Index score
* Proton pump inhibitors

**Summary**

**Background:** *Clostridium difficile* infection (CDI) is a common cause of nosocomial diarrhoea. People in the general community are not usually considered to be at risk of CDI. CDI is associated with a high risk of morbidity and mortality. The risk of severity is defined by the Clostridium Severity Index (CSI).

**Methods:** The cases of 136 adult patients with CDI treated at the University Hospital of Tours, France between 2008 and 2012 are described. This was a retrospective study.

**Results:** Among the 136 patients included, 62 were men and 74 were women. Their median age was 64.4 years (range 18–97 years). Twenty-six of the 136 (19%) cases were community-acquired (CA) and 110 (81%) were healthcare-acquired (HCA). The major risk factors for both groups were long-term treatment with proton pump inhibitors (54% of CA, 53% of HCA patients) and antibiotic treatment within the 2.5 months preceding the CDI (50% of CA, 91% of HCA). The CSI was higher in the CA-CDI group (1.56) than in the HCA-CDI group (1.39). Intensive care was required for 8% of CA-CDI and 16.5% of HCA-CDI patients.

**Conclusions:** CDI can cause community-acquired diarrhoea, and CA-CDI may be more severe than HCA-CDI. Prospective studies of CDI involving people from the general community without risk factors are required to confirm this observation.

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1. Introduction

*Clostridium difficile* is an anaerobic, Gram-positive, spore-forming bacillus. These bacteria are found throughout the environment, are a widespread problem in healthcare settings, and cause healthcare-acquired *C. difficile* infection (HCA-CDI). *C. difficile* spores are resistant to gastric acid: following ingestion,
the spores germinate into their vegetative form in the small intestine and colonize the lower intestinal tract. Disturbance of the host’s microbiota favours the multiplication of C. difficile, leading to colonization, which in itself may become clinically symptomatic.

The biggest risk factor for colonization by C. difficile is antibiotic exposure within the 2.5 months preceding the CDI. Comorbidities favouring this infection include immunosuppression, diabetes, chronic renal failure, and recurring urinary tract infection. Chronic exposure to proton pump inhibitors (PPIs) is also a risk factor. CDI is associated with a high risk of morbidity and mortality. Symptoms range from mild diarrhoea to severe pseudomembranous colitis with associated toxic megacolon, colonic perforation, and multiple organ failure. Four risk factors for the severe form of CDI are used to calculate the Clostridium Severity Index (CSI) score to estimate the risk of severe disease: history of immunosuppression, hyperleukocytosis >20 × 10⁹ cells/l, acute renal injury, and an albumin concentration <30 g/l. The risk of CDI in the overall population is generally considered to be low. However, recent reports have shown that the incidence of this infection is continuing to rise among patients with no known risk factors because of changes in the community environment that have favoured the emergence of these bacteria in the general population. In addition, antibiotics and PPI drugs are prescribed increasingly and in large quantities in the outpatient healthcare setting, and these drugs favour community-acquired C. difficile infection (CA-CDI). As a result, C. difficile has started to spread to the general population. One study in the USA found no association between CA-CDI and food or animal exposure. However, other sources of C. difficile contamination may exist for people in the general population.

Most studies on CA-CDI have been carried out in the USA, Sweden, and the UK (Table 3). Few studies on CA-CDI have been performed in France; however risk factors such as the misuse of antibiotics and PPIs constitute a real public health problem in the French population.

The purpose of this study was to examine the epidemiology of CA-CDI in hospitalized patients in the University Hospital Centre of Tours, France between 2008 and 2012. The clinical and biological profile of CA-CDI and the health outcomes of these patients are described.

2. Materials and methods

2.1. Study design and population

This retrospective observational analysis was performed at the University Hospital of Tours, France.

Adult patients hospitalized between January 2008 and December 2012 who tested positive for the Clostridium difficile toxin were included.

2.2. Bacteriological diagnosis

The diagnosis was confirmed by microbiological testing: before July 2012, ImmunoCard Toxins A+B (Meridian Bioscience) was used; after July 2012, C. difficile Quick Check Complete (Alere) was used. Throughout the study period, a toxigenic culture was performed if the C. difficile toxin test was negative.

2.3. Data collection

Patient medical history was obtained from the electronic medical records. Laboratory tests and imaging tests were performed on the day of diagnosis. Variables such as sex, age, lifestyle, and diagnosis on hospital admission were collected. The following known risk factors for CDI were recorded: immunosuppression due to cancer, chronic corticoid therapy, dialysis, diabetes, recurrent urinary infection, antibiotic therapy less than 2.5 months before the CDI, chronic PPI therapy, history of abdominal or stomach surgery, chronic inflammatory diarrhoea, and history of CDI. The medical reason for the use of antibiotics within the 2.5 months before the CDI and the family of antibiotic used were also recorded.

2.4. The Clostridium Severity Index (CSI)

Following the confirmation of diagnosis with a positive toxin assay, the CSI score was calculated (on the same day) by analyzing four severity risk factors: history of immunosuppression, white blood cell count at admission >20 × 10⁹/l, blood albumin concentration <30 g/l, and acute renal injury (MDRD (Modification of Diet in Renal Disease) <60 ml/min or creatinine >1.5 times the baseline value). Each factor is awarded 1 point, which leads to a score of 0 to 4. The CSI predicts the severity of the CDI. According to the analysis of Lungulescu et al., patients with a high score are more likely to have a severe infection than those with a low score. The specificity of this index increases with each point: 0 = 0%, 1 = 23%, 2 = 65%, 3 = 92%, and 4 = 95%.

2.5. Definitions

Severe complications of CDI were defined as follows: severe dehydration with electrolyte disorders, acute renal injury due to dehydration, intestinal perforation, peritonitis, toxic megacolon, and death.

All patients who tested positive for Clostridium toxin in the first 48 h following hospitalization were defined as having CA-CDI (on the condition that the patient had not previously stayed overnight in a healthcare setting within the past 3 months).

The outcome of CDI was defined as favourable if diarrhoea subsided within 6 days of antibiotic therapy. Death, refractory CDI, and recurrent CDI were considered to be poor outcomes. Refractory CDI was defined as persistent diarrhoea after 6 days of treatment. Recurrent infection was defined as a new episode of diarrhoea commencing at ≥2 days after successful treatment of the primary episode.

2.6. Statistical analysis

A univariate analysis was conducted for the risk factors of CDI and the clinical and biological profiles of CA-CDI and HCA-CDI patients. The CSI score was used to classify the risk of severity as low (a CSI score ≤1), or high (a CSI score ≥2). The Chi-square test was used to compare categorical variables. A p-value of <0.05 was considered statistically significant. Multivariate analysis was conducted for the four variables used to calculate the CSI score (risk factors) in order to determine whether these factors affected the course of the disease. The outcome was a binary variable, therefore logistic regression was used (see Appendix 1).

3. Results

3.1. Patient demographics

Over the 5-year study period, 140 patients with diarrhoea tested positive for C. difficile toxins. However, it was not possible to determine whether the CDI was HCA-CDI or CA-CDI in four cases; therefore, only 136 patients (62 men and 74 women) were included in this study. Twenty-six of the 136 (19%) cases were CA and 110 (81%) cases were HCA. Only 48% (65/136) of the patients were aged >65 years. The mean age was 64.4 years. The mean age of patients with CA-CDI was 63.2 years and that of patients with HCA-CDI was 64.7 years. Infectious diseases were the main reason
for hospitalization. The proportion of patients admitted to the emergency unit because of diarrhoea was 19% (26/136).

3.2. Risk factors for CDI (Table 1)

Risk factors were found for 134 patients; two patients (1%) had no recorded risk factors for CDI. Risk factors were the following: 80% (110/136) of patients had been hospitalized within the last 3 months, 48% (65/136) were immunosuppressed (due to cancer, long-term steroid therapy, or dialysis), 26% (36/136) had a history of abdominal surgery, 84% (114/136) had received antibiotics within the 2.5 months preceding the CDI, and 53% (72/136) were receiving long-term PPI therapy. The long-term use of PPIs was a risk factor for 54% of CA-CDI patients (14/26) and 53% of HCA-CDI patients (58/110). Antibiotic use was a risk factor for 50% of CA-CDI patients (13/26) and 91% of HCA-CDI patients (100/110). Antibiotic therapy preceding the CDI had been prescribed to treat lower respiratory tract infection (n = 46), sepsis (n = 35), or urinary tract infection (n = 31). Beta-lactams were the most frequently prescribed antibiotics (n = 105), accounting for 84.6% of CA and 93% of HCA patients who had received antibiotics. Other antibiotics prescribed included fluoroquinolones (n = 34), aminoglycosides (n = 31), and macrolides (n = 14). In most cases (n = 77), the patient had received more than one antibiotic during the 2.5 months preceding the CDI. Twenty patients had received four or more drugs.

3.3. Severity of infection (Table 2)

Most patients (114/136) had at least one risk factor for severe infection (CSI score ≥1). Hyperleukocytosis and acute renal injury were more prevalent in the CA-CDI group than in the HCA-CDI group. However, immunosuppression was more frequent in the HCA-CDI group than in the CA-CDI group. The average CSI score was higher in the CA-CDI group (1.56) than in the HCA-CDI group (1.39). The proportion of patients with a CSI score ≥2 was significantly smaller in the HCA-CDI group than in the CA-CDI group (Figure 1). Similarly, the proportion of patients with a CSI score ≤1 was significantly larger in the HCA-CDI group than in the CA-CDI group. Overall, 15% (21/136) of all patients (8% in the CA-CDI group and 16.5% in the HCA-CDI group) had severe CDI requiring intensive care. The difference between the two groups was not significant (p > 0.05). Four patients experienced rectorrhagia (3%, 4/136) and two patients had toxic megacolon (1.5%, 2/136). Twenty patients died: 8% (2/26) of the CA-CDI group and 16% (18/110) of the HCA-CDI group.

3.4. C. difficile treatment

A total of 111 (82%) patients were treated with metronidazole alone, nine patients (7%) with vancomycin alone, and five patients (4%) with both antibiotics in combination.
3.5. Patient outcomes

CDI was treated successfully in 76% (103/136) of cases. Thirty-three (24%) patients had either refractory (n = 17) or recurrent disease (n = 16) (Table 2). An unfavourable outcome occurred more frequently in the HCA-CDI group (26%; 29/110) than in the CA-CDI group (15%; 4/26). The recurrence rate was slightly higher in the HCA-CDI group (13%; 14/110) than in the CA-CDI group (8%; 2/26). Risk factors for an unfavourable outcome were the following: a blood albumin concentration < 30 g/l and acute renal injury (MDRD < 60 ml/min or creatinine > 1.5 times the baseline value). Hyperleukocytosis > 20 × 10⁹ cells/l also had a negative effect on the course of disease, however this was not significant (p = 0.943) (see Appendix 1).

Table 3

<table>
<thead>
<tr>
<th>Year of the study; author</th>
<th>Type of study</th>
<th>Country</th>
<th>CA-CDI/total CDI (%)</th>
<th>CA−CDI/total CDI (n)</th>
<th>Risk factors for CA-CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983–1984; Riley et al. 13</td>
<td>Prospective</td>
<td>Australia</td>
<td>NAvi</td>
<td>89</td>
<td>-</td>
</tr>
<tr>
<td>1994; Hirschhorn et al. 16</td>
<td>Retrospective</td>
<td>USA</td>
<td>NA</td>
<td>51</td>
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</tr>
<tr>
<td>1995; Karlstrom et al. 20</td>
<td>Prospective</td>
<td>Sweden</td>
<td>28%</td>
<td>1437/5133</td>
<td>Yes</td>
</tr>
<tr>
<td>1995; Kyne et al. 21</td>
<td>Prospective</td>
<td>Ireland</td>
<td>11%</td>
<td>8/73</td>
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</tr>
<tr>
<td>1994–2004; Dial et al. 3</td>
<td>Prospective</td>
<td>UK</td>
<td>NA</td>
<td>1233</td>
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<tr>
<td>1999–2000; Beaugerie et al. 22</td>
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<td>France</td>
<td>NA</td>
<td>4</td>
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<td>2004–2007; Kunst et al. 7</td>
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<td>USA</td>
<td>44%</td>
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<td>2005–2006; Kutt et al. 14</td>
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<td>USA</td>
<td>20%</td>
<td>212/1046</td>
<td>Yes</td>
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<tr>
<td>2009–2010; Lessa 3</td>
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<td>USA</td>
<td>32%</td>
<td>3269/10342</td>
<td>NA</td>
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<tr>
<td>2008; Dumyati et al. 9</td>
<td>Retrospective</td>
<td>USA</td>
<td>18%</td>
<td>67/366</td>
<td>Yes</td>
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<tr>
<td>2009–2011; Chitnis et al. 4</td>
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<td>UK</td>
<td>2.1%</td>
<td>42/2000</td>
<td>Yes</td>
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<tr>
<td>2008; Wilcox et al. 13</td>
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<td>Netherlands</td>
<td>1.5%</td>
<td>37/2423</td>
<td>Yes</td>
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<tr>
<td>2014; Clohessy et al. 17</td>
<td>Retrospective</td>
<td>Australia</td>
<td>29%</td>
<td>38/129</td>
<td>Yes</td>
</tr>
</tbody>
</table>

4. Discussion

Among the 136 cases, nearly 20% of the CDI were considered to be community-acquired, and 8% (2/26) of these patients had no risk factor for CDI.

This study confirms that the use of antibiotics within the 2.5 months preceding C. difficile infection is a major risk factor for CDI, especially for HCA-CDI. The chronic use of PPIs was identified as a major risk factor for CA-CDI. PPIs were a risk factor in 54% (14/26) of CA cases and antibiotic therapy was a risk factor in 50% (13/26) of cases. Six patients received both PPIs and antibiotics. Among those with CA-CDI, patients received PPIs without antibiotics in 31% of cases (8/26) and antibiotics without PPIs in 23% of cases (6/26). Only 19% (5/26) of CA-CDI patients received neither antibiotics nor PPIs before CDI. Hence, the use of PPIs was the main risk factor for CA-CDI. PPIs modify intestinal pH; nevertheless the origin of the association between PPI and CDI remains unclear (Nerandzic et al. 13). Therefore, as with antibiotics, PPIs may also disturb the intestinal microbiota, which favours the emergence of C. difficile. These observations are consistent with those of Dial et al., 3 who also found that the long-term use of PPIs is a major risk factor for CA-CDI. Furthermore, the authors noted a decline in the prescription of antibiotics and an increase in the prescription of PPIs. Hence, PPIs may soon surpass antibiotics as the main risk factor for CA-CDI. On the other hand, a study carried out by Kutty et al. in North Carolina did not identify PPIs as a risk factor for CA-CDI. 14

Since the first description of CA-CDI 30 years ago, 15, 16 research teams across the world have been trying to understand this disease, and in particular to identify risk factors that could help to explain its occurrence. There are many discrepancies in the findings reported (Table 3). Some have described the overuse of

Figure 1. CA-CDI (n = 26)....HCA-CDI (n = 110).... Risk of severity - CSI score at diagnosis day CA-1: Community-acquired, CA−Clostridium difficile infection HCA-CDI: Health care acquired Clostridium difficile infection CSI: Clostridium severity index.

CDI: Clostridium difficile infection; CA−Community-acquired; ATB−Antibiotics; PPI−Proton pumps inhibitor; H2RA−Histamine H2 receptor antagonists; NSAIDS Nonsteroidal anti-inflammatory drugs; GERD−Gastroesophageal reflux disease; NA−Not applicable.
antibiotics as the only risk factor for CA-CDI. Others have reported that both antibiotics and chronic treatment with PPIs are risk factors. It is concluded that physicians in hospitals, but also general practitioners, should be more cautious in the prescription of antibiotics and PPIs to prevent patients from developing CDI.

Five patients with CA-CDI did not have any known risk factors. These patients may have been asymptomatic carriers before they became ill. The origin of Clostridium infection in these patients is unknown. The most probable source is exposure to spores by contact with animals, people, or contaminating environments. The environmental reservoir of this bacterium needs to be better explored if we want to stop the dissemination of CA-CDI. Chitnis et al. investigated food and exposure to animals as sources of C. difficile for community patients, but their findings were negative. However, they observed that the community patients who had received very little or no outpatient care had frequently been exposed to infants less than 1 year old. A similar study by Dumyati et al. was also unable to identify the source of CA-CDI. The present study was retrospective. Therefore, it was not possible to explore the source of CA-CDI or to identify the specific clones involved by molecular typing.

There are at least two explanations for the CDI in the patients without identifiable risk factors in the present study: (1) the patient had a risk factor for CDI (such as an illness) that could not be identified because of the retrospective nature of the study, or (2) the patient was susceptible to CDI because of some as yet unidentified risk factor. The role of healthy carriers in the dissemination of C. difficile spores and bacteria in the community setting may be underestimated. Appropriate prospective studies are needed to explore these possibilities.

CA-CDI patients were found to be more likely to develop a severe infection than HCA-CDI patients. Indeed, 54% of patients in the CA-CDI group but only 42% of those in the HCA-CDI group had a CSI score >2. A significantly higher proportion of patients in the CA-CDI than in the HCA-CDI group required intensive care unit management (36% vs. 11%, respectively). By contrast, Clohessy et al. did not find any differences between CA-CDI and HCA-CDI in terms of severity and outcome in Australian patients. Nevertheless, the present study did not explore patients with CA-CDI who were treated outside of a hospital setting.

Interestingly, although CA-CDI seemed to be more severe in the beginning, the rate of favourable outcome in this group was higher than that in the HCA-CDI group (85% vs. 74%, respectively). These findings are consistent with an American study by Lessa et al., which showed that the recurrence rate was higher in healthcare-associated than in community cases.

The proportion of immunosuppressed patients was higher in the HCA-CDI group than in the CA-CDI group. This is not surprising, given that hospitalized patients are highly exposed to and dependent on medical care. Immunosuppression also explains the lower white blood cell counts in the HCA-CDI group. Nevertheless, the proportion of patients with hyperleukocytosis and acute renal injury was higher in the CA-CDI group than in the HCA-CDI group. CDI may have been more severe in community patients than in nosocomial patients because: (1) community patients may have been more sensitive to C. difficile because of as yet unidentified risk factors, or (2) bacterial strains encountered in the general community may be more virulent than hospital-based strains. In addition, the medical management of CDIs may be delayed in community patients. Indeed, CDI is still considered to be a hospital-acquired infection, therefore it is not standard practice to screen for C. difficile in outpatient departments, even for individuals presenting with diarrhea and fever. Generally, other tests are performed first. Thus, community patients may be diagnosed at a late and more severe stage of infection. Alternatively, infection by very virulent strains may explain the severity of the diarrhoea and inflammation in CA-CDI patients. Unfortunately, it was not possible to perform PCR ribotyping on the isolates and thus it is not known whether the patients in the present study were infected with particular ribotypes such as 078, which has previously been associated with CA-CDI (Rodríguez-Pardo et al.). Further studies are needed to characterize the bacterial strains involved in CA-CDI and HCA-CDI cases and the changes occurring to the microbiota of CDI patients.

In conclusion, CA-CDI is an increasingly frequent occurrence in the French population. It is a real problem from both an epidemiological and an economic perspective. This increase in the incidence of CDI places a major burden on healthcare budgets and will necessitate a change in future management.

The careful monitoring of the prescription of antibiotics and PPIs would help to reduce the incidence of CA-CDI. This is especially true for the prescription of beta-lactam antibiotics. In this study, there were too few cases of CA-CDI to compare all variables between the community-acquired and nosocomial cases. A prospective study of CA-CDI is thus required to confirm our observations, in particular the finding that CDI is more severe in community patients than in nosocomial patients.

Acknowledgements

We thank the whole research team of the Infectious Diseases Unit of the University Hospital in Tours, France, for helping us with this work.

Funding: No financial support.
Conflict of interest: None of the authors has a potential conflict of interest to declare.

Appendix A

To analyze further the results shown in Table 2, a multivariate analysis was performed of the variables that had the largest effect on the outcome of the patients. Outcome is a binary variable, therefore logistic regression was used (‘logit’ model). Four major explanatory variables were tested in this model: acute renal failure, history of immunosuppression, albumin level <30 g/l, and hyperleukocytosis (>20 × 10⁹ cells/l).

Tests verifying the significance of the model rejected the null hypothesis at 99%. The choice of variables in our model is therefore relevant (Supplementary Material, data 1).

In theory, the four variables selected should have a negative value (and thus a lower odds ratio than 1) because they should negatively affect the chances of a favourable outcome (Supplementary Material, data 2). This was the case for the two variables found to be significant at the threshold of 5%: acute renal failure (p = 0.020) and serum albumin <30 g/l (p = 0.016). Hyperleukocytosis (>20 × 10⁹ cells/l) was estimated to have a negative effect on outcome, but this result was not significant (p = 0.412). A history of immunosuppression did not affect the course of the disease (p = 0.943).

The model was then expanded to only nosocomial patients and community patients. Unfortunately, due to the low number of community patients, neither the significance of the model nor the significance of variables was satisfactory, even at the threshold of 10%. Thus, the results obtained for nosocomial patients are similar to those obtained for the model including all patients.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2015.06.007.
References