Economic burden of Clostridium difficile in five hospitals of the Florence health care system in Italy

Introduction: Despite the awareness about the increasing rates of Clostridium difficile infection (CDI) and the economic burden arising from its management (prolonged hospitalization, laboratory tests, visits, surgical treatment, environmental sanitation), few studies are available in Italy on the economic costs directly attributable to the CDI. The Florence health care system has designed a study with the aim of describing the costs attributable to the CDI and defines the incremental economic burden associated with the management of this complication.

Methods: We conducted a retrospective study in five hospitals of the Florence health care system. The enrolled population included all patients who were hospitalized during the year 2013 with a diagnosis of CDI. Of the 187 total cases reported in 2013, 69 patients were enrolled, for whom the main cause of hospitalization was directly attributable to CDI.

Results: We enrolled 69 patients (19 males and 50 females), with a mean age of 82.16 years (minimum 46 to maximum 98). The total number of hospitalization days observed was 886 (12.8 per patient on average). The data from this study show that the mean total incremental cost for a patient with CDI was €3,270.52 per year. The hospital stay length is the most significant cost parameter, having the largest influence on the overall costs, with an impact of 87% on the total cost. The results confirm the costs for the management of CDI in five hospitals of the Florence health care system are in line with data from the international literature.

Conclusion: The economic impact of CDI is most evident in the extension of the duration of hospitalization and emergency recurrences requiring new therapeutic options with the need to develop and implement new diagnostic and therapeutic algorithms in clinical practice.

Keywords: cost of illness, burden of disease, pharmacoeconomics, cost analysis

Introduction

Clostridium difficile is one of many types of bacteria that are normally found in the colon. A large expansion of its population occurs after the consumption of antibiotics which kill off other indigenous bacterial flora. C. difficile infection (CDI) is one of the major causes of diarrhea in hospitalized patients and its incidence and severity are rising, often leading to death.1-3 Beside the recent increase in the use of antibiotics, other factors that influence the risk for CDI are gastrointestinal surgery, serious underlying illness, a weakened immune system (due, for example, to chemotherapy or HIV/AIDS), and advanced age.4 The prevalence of C. difficile spores in the environment is relatively high in hospitals, where subjects are frequently exposed to antibiotics.5,6

In recent years, CDI has become one of the most important public health problems worldwide; in fact, increases not only in the incidence of infections but also their severity, recurrence, and mortality have been observed.7 From a study conducted in
Patients and methods

We conducted a retrospective study in the five hospitals of the Florence health care system in Florence, Italy. The enrolled population included all patients who were hospitalized during the year 2013 (from January to December) with a diagnosis of CDI disease at admission. Sixty-nine patients of the 187 total cases reported in 2013 had a diagnosis of CDI confirmed (detection of toxigenic \textit{C. difficile}-specific – GDH antigen) and they were included in our analysis. The objective of the analysis was to describe the costs attributable to the CDI and to define the incremental cost associated with managing this important complication in terms of comorbidities and treatment options/adopted procedures. All data were collected from three different sources: from the Argos program (digital medical records), the Epi Info computer database system to collect data on CDI surveillance, and data from the Hospital Discharge Register (HDR). In accordance with Italian privacy law (code concerning the protection of personal data, 30 June 2003, n.196) patients were assigned identification numbers for the study, thus eliminating the patient health service codes and avoiding the risk of identifying patients personally.

**Cost analysis**

Cost analysis was completed under the hospital point of view. The costs analyzed were hospital stay, additional costs associated with other types of interventions (surgery, transfers to the intensive care unit, antibiotic therapy), and diagnostic tests (X-ray, ultrasound, magnetic resonance imaging, computerized tomography), as well as costs associated with other types of interventions directly attributable to the CDI episode. Surgery performed for the management of CDI (colectomy, ileostomy, colostomy) were also included in the used resources during the design phase of the study, but the analysis of medical records showed that no surgery was performed on enrolled patients. As shown in Figure 1 the main cost was represented by the hospitalization (87.2%).

Table 1 shows the breakdown of hospital direct costs due to hospitalization divided into inpatient hospital and intensive...
Table 1 Cost analysis of hospitalization and other health care costs in Clostridium difficile infection management

<table>
<thead>
<tr>
<th>Productive factors</th>
<th>Costs</th>
<th>Intensive care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical staff</td>
<td>€40.95</td>
<td>€229.32</td>
</tr>
<tr>
<td>Nurses and support staff</td>
<td>€114.05</td>
<td>€547.17</td>
</tr>
<tr>
<td>Hospital hotel costs</td>
<td>€20.61</td>
<td>€19.15</td>
</tr>
<tr>
<td>Amortization and maintenance</td>
<td>€14.01</td>
<td>€62.54</td>
</tr>
<tr>
<td>Other costs</td>
<td>€8.89</td>
<td>€15.77</td>
</tr>
<tr>
<td>Total costs</td>
<td>€198.51</td>
<td>€873.95</td>
</tr>
</tbody>
</table>

**Examinations**
- Detection of toxigenic C. difficile-specific GDH antigen: €12.00
- Colonoscopy – retrograde: €170.00
- Ileoscopy with biopsy: €62.00
- Right flexible colonoscopy or pancolonoscopy: €57.00
- Esophagogastroduodenoscopy: €26.00
- Abdominal radiography: €26.00
- Lower-abdomen computerized tomography: €95.00
- Whole-abdomen sonography: €60.00

**Antibiotic therapies**
- Vancomycin per gram: €7.69
- Metronidazole per gram: €0.20

**Other treatments**
- Blood transfusion: €158.00
- Plasma transfusions: €20.00
- Immunohematology exams: €25.00
- Transfusion and venipuncture: €30.00
- Specialist visit: €15.00

**Environmental sanitation**
- Patient unit: €6.25
- Room and bathroom: €14.20
- ICU cubicle: €15.93

Notes: Data from Nomenclatore Tariffario Regionale Delle Prestazioni Specialistiche Ambulatoriali, [Outpatient Formulary List of Medical Acts and Procedures]. Available from: http://www.regione.toscana.it/documents/10180/23313/Nomenclatore+tariffario+regionale/39bc54d6-6e6e-431e-98f6-1a60f2579721/1version=1.0.19

The treatment of the first episode of C. difficile colitis, mild and moderate forms, requires:
- oral metronidazole 0.250 g every 6 hours/0.5 g every 8 hours for 10–14 days; or
- oral vancomycin 0.125 g every 6 hours for 10–14 days; or
- combination therapy: oral vancomycin 0.125 g every 6 hours, oral metronidazole 0.5 g every 8 hours.

The treatment of relapsing forms is as follows. The first relapse is treated like the first episode. From the second relapse, treatment is set as vancomycin “tapered-pulsed dosing”:
- 125 mg four times a day for 14 days; then
- 125 mg two times a day for 7 days; then
- 125 mg per day for 7 days; then
- 125 mg every 2 days for 8 days (four doses); then
- 125 mg every 3 days for 15 days (five doses).21

Antibiotic therapy (vancomycin €7.69/g, metronidazole €0.20/g) was recorded as the number of grams used in a day multiplied by the duration of administration of the therapy (expressed in total days of hospitalization) (Table 1).21

Statistical analysis
The data for all patients were analyzed through descriptive analysis on the main parameters. Descriptive statistics on study variables used traditional numerical synthesis measurements: mean, standard deviation, median, and maximum and minimum values for the continuous variables, and frequency distributions for the categorical variables. The analysis of variance was used to compare the means of the quantitative variables between patient groups. The main investigated variables were: the patients’ demographic characteristics; stratification by age range; hospitalization; antibiotic therapy; visits; and environmental sanitation. Statistical analysis was conducted using the Statistical Package for the Social Sciences statistical software (SPSS Statistics version 14.0; SPSS Inc., Chicago, IL, USA).
Table 2 Patients’ characteristics

<table>
<thead>
<tr>
<th>Sex</th>
<th>Count</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>19</td>
<td>28</td>
</tr>
<tr>
<td>Female</td>
<td>50</td>
<td>72</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Count</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>69</td>
<td>82.16</td>
<td>10.21</td>
<td>84</td>
<td>46</td>
<td>98</td>
<td>52</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Length of stay (days)</th>
<th>Count</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>69</td>
<td>12.80</td>
<td>7.68</td>
<td>0.93</td>
<td>1</td>
<td>35</td>
<td>34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical area of hospitalization</th>
<th>Count</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical area</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Intensive area</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Medical area</td>
<td>58</td>
<td>84</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Short observation</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>100</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.

Results

Table 2 shows the main sociodemographic characteristics of the population included in the study. The mean age of the 69 patients examined (19 males [28.0%] and 50 females [72.0%]) was 82.16 years. Sixty-six patients were over 65 years of age, and three patients were under 65 years of age. Regarding the clinical area of hospitalization, 84.0% of the patients were hospitalized in the medical area; 6.0% were admitted to the surgical area; 4.0% to the short observation unit; 3.0% were hospitalized in the ICU; and, finally, 3.0% were hospitalized in the infectious disease area. The total number of hospitalization days observed was 886 (12.8 per patient on average), ranging from a maximum of 35 days to a minimum of 1 day (in this case, the patient died after 1 day of hospitalization).

Table 3 shows that the cost of a single inpatient day was €198.51; multiplied by the total days in hospital excluding ICU stays (855), it makes a total cost of €169,726.05. We added the cost of care per day in high-risk departments (€873.95), with a total ICU cost of €27,092.45 (31 days), and the total cost for the hospital was €196,818.50 (Table 3), with a mean cost per patient of €2,852.45 and a mean cost for LOS of €222.15 (hospitalization) (Table 5). The total cost of different antibiotic therapies was given by the unit cost of each therapy multiplied by the days of hospitalization and was €2,481.80 in total (Table 3), with a mean cost per patient of €35.60. The cost for sanitation was calculated by the number of days of hospitalization in inpatient hospitalization plus those in ICU departments multiplied by the daily cost for environmental sanitation, with a total cost of €17,978.58; the mean cost per patient was €260.56 (Table 5).

The total costs of transfusion therapy amounted to €2,580.00, with an average cost (divided by 48 patients) per patient transfused of €53.75. Table 4 also highlights the costs for diagnostic tests per patient and specialist advice (infectious diseases, surgery, and nephrology).

Table 3 Costs of length of stay, antibiotic therapies, and environmental sanitation per hospitalization in *Clostridium difficile* infection management

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Unit cost</th>
<th>Days of hospitalization</th>
<th>Mean days of hospitalization</th>
<th>Total cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>€198.51</td>
<td>855</td>
<td>886</td>
<td>€196,726.05</td>
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<tr>
<td>Intensive care department</td>
<td>€873.95</td>
<td>31</td>
<td></td>
<td>€27,092.45</td>
</tr>
<tr>
<td>Total</td>
<td>€1,072.46</td>
<td>886</td>
<td>12.80</td>
<td>€196,818.50</td>
</tr>
</tbody>
</table>

Antibiotic therapy

| Vancomycin             | €7.69     | 124                     |                              | €476.78    |
| Metronidazole          | €0.20     | 178                     |                              | €35.60     |
| Combination (vancomycin + metronidazole) | €7.89 | 777 | | €1,969.42|
| Total                  | €7.89     | 777                     |                              | €2,481.80  |

Environmental sanitation

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Unit cost</th>
<th>Days of hospitalization</th>
<th>Mean days of hospitalization</th>
<th>Total cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>€20.45</td>
<td>855</td>
<td></td>
<td>€17,484.75</td>
</tr>
<tr>
<td>Intensive care department</td>
<td>€15.93</td>
<td>31</td>
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<td>€493.83</td>
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<tr>
<td>Total</td>
<td>€26.38</td>
<td>886</td>
<td></td>
<td>€17,978.58</td>
</tr>
</tbody>
</table>

Notes: 124 days of hospital stay × 0.5 g = 62 g; 178 days of hospital stay × 1 g = 178 g; 475 days of hospital stay × 0.5 g = 237.5 g; 475 days of hospital stay × 1.5 g = 715 g.
Finally, Table 5 shows the total costs incurred by the patients participating in the study, divided into hospitalization costs, diagnostic exam costs, antibiotics costs, costs for blood transfusions/plasma infusion of fluids, specialist consultancy costs, and environmental sanitation costs. The analysis of medical records showed that nine patients were treated with vancomycin and 13 patients with metronidazole; 35 patients were put on a combination therapy of the two drugs; and 12 patients did not receive antibiotic therapy or were given different antibiotics other than those for the treatment of C. difficile. As shown in Table 5, the mean cost of CDI per patient was €3,270.52. The most significant cost driver was hospitalization, with a total of €196,818.50, followed by environmental sanitation at €17,978.58, costs of diagnostic procedures at €5,533.00, other treatments at €2,580.00, and antibiotic therapy at €2,481.80.

**Discussion**

Over time, cost-of-illness studies have become vitally important to the development of research and policy initiatives aimed at more cost-effectively treating and preventing illness. Despite limited data for Italy, studies to date have indicated that CDI has a significant burden on the health care system. For example, CDI may have resulted in as much as US $4.8 billion excess health care costs in acute-care facilities alone in 2008 in the USA. There are also additional costs for CDI that have yet to be quantified, such as increase in hospitalization rates. Those costs can be avoided if the patient with CDI is isolated in a semiprivate room, this can reduce the transmission of C. difficile and avoid new additional cases of CDI. Better understanding of the economic burden of C. difficile assists various decision makers. Hospital administrators, infection control practitioners, and policy makers could use this information to determine how much to invest in C. difficile prevention and control measures. This information can help policy makers and third-party payers to make insurance coverage and reimbursement decisions. Manufacturers and drug companies can use such information to develop and price C. difficile tests and treatments.

No significant studies on the economic impact of C. difficile in Italy had been carried out up to now, due to the difficulty in collecting data and developing and promoting studies for identifying the dynamics of the cost-of-illness trends based on the evolution of the epidemiological situation and on incidence and lifetime cost data. The results presented in this study demonstrate that the health care unit cost for the management of CDI (€3,270.52 per patient) is similar to those reported by other countries and in other systematic reviews. In particular, in a systematic review of 30 papers from 1980 to 2008, incremental cost estimate results in US-based studies ranged from $2,871 to $4,846 per case for primary CDI and from $13,655 to $18,067 per case for recurrent CDI. Non-US-based studies showed an estimated incremental cost of $5,243 to $8,570 per case for primary CDI and $13,655 per case for recurrent CDI. The economic health care costs of CDI were high for primary and recurrent cases. The high cost associated with CDI justifies the use of additional resources for CDI prevention and control.

There are some limitations to this study, and the results are likely to underestimate total disease costs for various reasons. The first possible limitation concerns the extrapolation of 12-month expenses and the total sample enrolled with
With the increasing popularity of burden-of-disease studies, the standardization of methods becomes more critical to permit policy makers and the general public to better understand our investment in health care and to drive decisions about future insurance benefits, efforts in curbing and controlling disease and injury, and development of programs to improve the health of the population.28

Despite advances in the diagnosis and treatment of CDI and prevention efforts to reduce the spread of C. difficile, CDI remains a significant challenge to health care systems worldwide. Further advances in prevention of CDI may need to focus on those who continue to be exposed to the organism and who are susceptible. Interventions directed toward this susceptible population, particularly hospitalized patients who receive antibiotics, may be effective. There is moderate evidence on the effectiveness of probiotics to prevent primary CDI, but there are few data to support use in secondary prevention of recurrent CDI.29 Multifaceted national prevention efforts in the UK, including antimicrobial stewardship, patient isolation, hand hygiene, environmental cleaning and disinfection, and audit, resulted in a 59% reduction in CDI cases reported from 2008 to 2012.29 Studies have shown that unrecognized cases of CDI are admitted to health care facilities or transferred from one facility to another and may spread it within a facility via health care workers' hands.30,31 However, CDI can be prevented. Environmental contamination stems from the fecal–oral transfer of C. difficile spores from the patient to the health care workers' hands and medical equipment leading to the ingestion of spores by other patients.30,31 Since CDI has been the cause of many large outbreaks in hospital settings, frequent hand washing by health care personnel and frequent cleaning and disinfecting of the patient’s environment are of utmost importance in preventing transmission.

Disclosure

AP has received research and educational grants from Astellas. GLC has served as a consultant on advisory boards for Astellas, LEO Pharma, Sanofi, Merck Sharp and Dohme, DOC Generici, Takeda, and Merck Serono Spa, and has received research and educational grants from Takeda, Gilead Sciences, Merck Sharp and Dohme, and LEO Pharma. The authors report no other conflicts of interest in this work.

References


