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An economic evaluation of *Clostridium difficile* infection management in an Italian hospital environment

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Abstract. – BACKGROUND AND OBJECTIVES: *Clostridium difficile* infection (CDI) accounts for the majority of nosocomial cases of diarrhea, and with recent upsurge of multidrug-resistant strains, morbidity and mortality have increased. Data on clinical impact of CDI come mostly from Anglo-Saxon countries, while in Italy only two studies address the issue and no economic data exist on costs of CDI in the in hospital setting. A retrospective cross-sectional study with pharmacoeconomic analysis was performed on the CDI series of the Policlinico Gemelli of Rome, a major 1400 bed Hospital.

PATIENTS AND METHODS: The clinical charts of 133 patients in a 26 month period were reviewed. All costs of the involved resources were calculated and statistical analysis was carried out with means and standard deviations, and categorical variables as number and percentages.

RESULTS: The results show the significant sanitary costs of CDI in an Italian hospital setting. The cost analysis of the various elements (exams, imaging studies, therapies, etc.) shows that none independently influences the high cost burden of CDI, but that it is the simple length of hospital stay that represents the most important factor.

CONCLUSIONS: Prevention of CDI is the most cost-effective approach. The major breakthrough in cost reduction of CDI would be a therapeutical intervention or procedure that shortens hospital length of stay.

Key Words:
Clostridium difficile, Cost evaluation, Hospital CDI.

Introduction

Clostridium difficile (*C. difficile*) is one of many types of bacteria that are normally found in the colon. A large expansion of it's (relative) population occurs after the consumption of antibiotics which kill off other indigenous bacterial flora. *Clostridium difficile* infection (CDI) is one of the major causes of diarrhoea in hospitalized patients and its incidence and severity are rising often leading to death[1-3]. Besides 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 among hospitals where subjects are frequently exposed to antibiotics[3,5,6]. According to an analysis of data from the Healthcare Cost and Utilization Project (HCUP) on CDI during U.S. hospital stays in 2009[7], patients with CDI as a secondary diagnosis were more severely ill than those with a principal diagnosis of CDI (68.3% had a major or extreme likelihood of dying compared to 40.5 percent of patients with CDI as the principal diagnosis). About 3 times more patients with a secondary diagnosis of CDI died (11.7%) compared to those with a principal diagnosis of CDI (3.7%).

Recent studies are focused on the comparison between different therapies for the treatment of CD infection[8,9]; others are focused on the economic aspects of CDI management[10,11]. Despite the awareness about the infection rates from *C. difficile* and the economic burden derived from the management of CDI (extended hospitalization, rehospitalization, laboratory tests, medications and surgical treatment) few studies are available about the economic costs of CDI, and a recent review investigating costs associated with CDI reported studies conducted from 1980 to present in only four countries, not including Italy (USA, Canada, UK and Ireland)[10]. In US-based studies, incremental costs were estimated to range between $2,871 and $4.846 per case of primary CDI. Non US-based studies reported incremental costs ranging

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from $5,243 to $8,570[10]. While recently the epidemiology of CDI was investigated in Italy by a retrospective study involving internal medicine wards in northern Italy[12], no economic evaluation was performed; therefore, there is no detailed information about the economic burden deriving from the onset of CDI.

In the present work we conducted a retrospective study on a population of 133 hospitalized patients who were admitted to the 1400 bed Gemelli Hospital, Rome, Italy, in different wards and for different admission diagnoses, and who developed CDI during their hospital stay (except 3 cases infected from home). The objective of the study was that of giving both a description of the sample in terms of concomitant illnesses, therapies and procedures adopted for the management of CDI, and a description of the costs likely attributable to CDI in order to have an idea of the incremental economic hospital burden associated with the management of this important complication.

Materials and Methods

Studied Sample

The study is a retrospective study involving 133 patients from different Departments of the Gemelli Hospital, Rome, Italy. Pediatric patients were not considered. Patients were admitted from November 2009 through February 2012 with different diagnoses. CDI was observed during their hospitalization period, except 3 cases diagnosed in Emergency Department before admission. Data were collected from two different sources: medical charts on one hand and the online Gemelli Hospital medical information system (SI) on the other. Because of the lack of a control group, for each of the 133 patients the hospitalization period was divided into two sub-periods, the first one referring to hospitalization before the diagnosis of CDI (i.e. before obtaining a positive culture test in a symptomatic patient) and the second one from the moment of diagnosis of CDI to the end of hospitalization. In this type of approach, the objective was the evaluation of the likely costs imputable to the occurrence of CDI.

Cost of the Involved Resources

Costs accounted for in the present study were inpatient costs: hospital stay, antibiotic therapy (vancomycin, metronidazole, meropenem), specific exams (test for CDI diagnosis, Magnetic resonance imaging, CT-scan), ad-hoc measures (transferal to Intensive Care Unit (ICU) or isolation measures) and surgical treatment performed for the management of CDI, as well as costs associated to other types of interventions directly imputable to the CDI episode. Because isolation measures sometimes were taken before obtaining a positive culture test (for diarrhea), isolation measures costs pre-CDI diagnosis were also attributed to CDI.

No outpatient costs or indirect costs were considered. Table I reports the list of the direct costs considered along with the respective amount expressed in euro.

Statistical Analysis

Continuous variables were reported as mean and standard deviations, categorical variables as number and percentages. Results related to the direct costs considered were reported as average cost per patient along with their standard deviation and as percentage of the single cost over the total cost. For each patient the total length of hospitalization (LOS) was compared with the average length of hospitalization stay computed for all patients admitted in the same ward in the year 2011. A paired sample *t*-test was used for the above comparison, whereas comparisons between particular sub-samples in terms of costs were performed by means of an independent *t*-test or an analysis of variance. A p value < 0.05 was considered as significant.

Results

Study Population Description

133 patients aged 70.24±15.01 (62 men, 46.62% and 71 women, 53.38%), from 31 differ-

Table I. Considered direct costs associated with CDI.

Associated Items	Cost (€)
One day Hospitalization	700
Toxin test (VIDAS®) for CDI diagnosis	6.06
CT-scan	173.99
Magnetic resonance	286.74
One day ICU stay	1200
One day Isolation stay	800
Antibiotic treatment with vancomycin per g	4.6
Antibiotic treatment with metronidazole per g	1.3
Antibiotic treatment with meropenem per g	12
Fluids	89.48
Total Colectomy	2622.04
Ileostomy	2277.23
Colostomy	2277.23
Blood transfusion	25.82

ent wards and with 113 different admission diagnoses, not including diagnosis of CDI, were studied. Figure 1A (white bars, secondary axis) reports the distribution of patients by main type of admission wards (Medicine, Surgery and ICU). The different admission diagnoses were instead aggregated in 12 macro-diagnosis and Figure 1B (secondary axis) reports the relative patients distribution.

All patients developed CDI during the hospital stay and the infection was confirmed by a positive toxin test on stool. For 129 (97%) patients out of 133, the event of interest was the first CDI event, for 4 (3%) patients it was a relapse. The average hospitalization stay was 40.13±47.26 days. The average hospital stay before and after CDI diagnosis were 20.23±23.91 and 19.94±38.03 respectively. The average CDI patient LOS (length of hospital

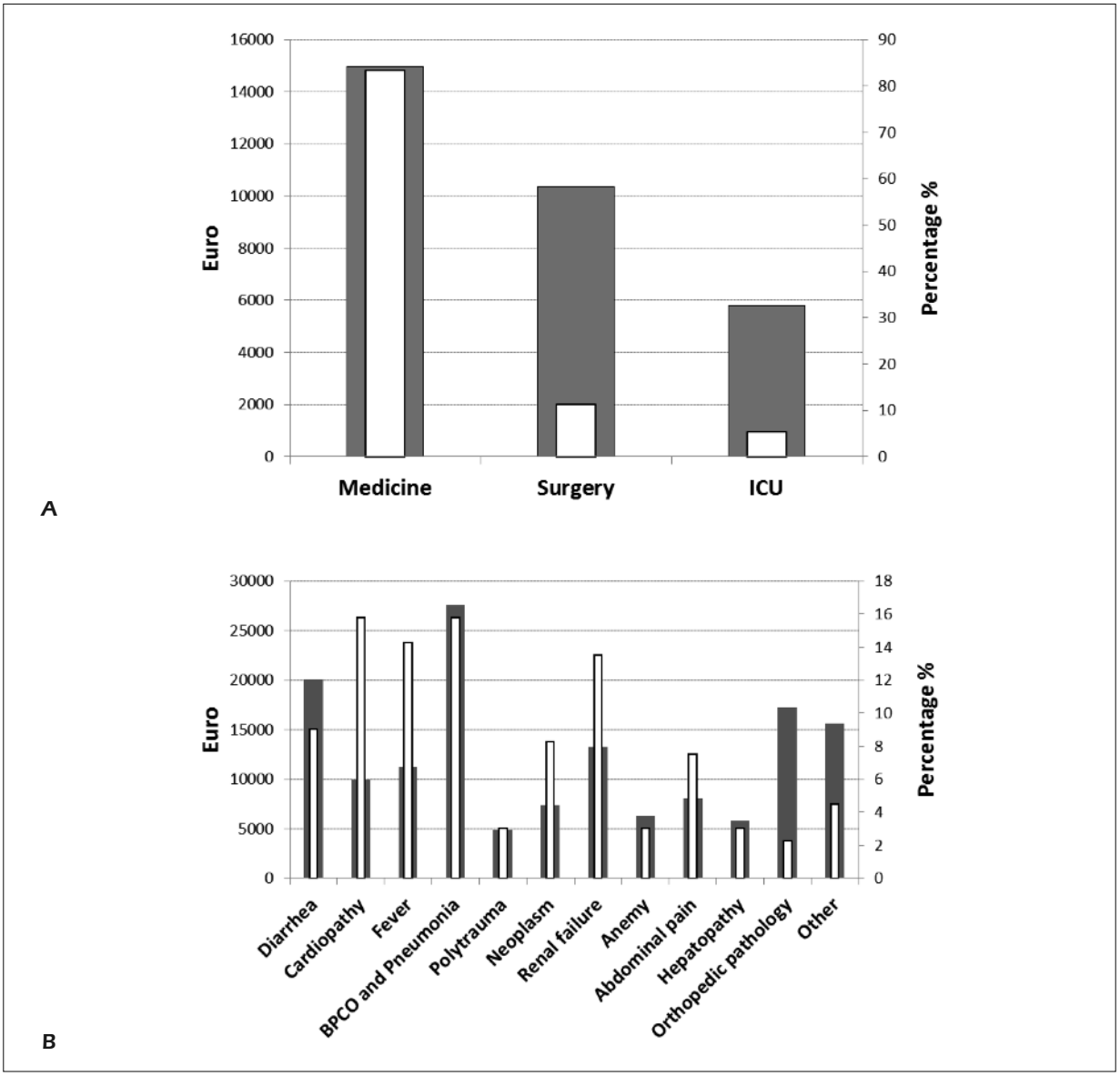

Figure 1. Panel A reports the distribution of patients according to the three main admission wards: Medicine, Surgery and ICU. On the principal axis are reported the average hospitalization stay costs per patient (*grey bars*) whereas on the secondary axis is reported the percentage distribution of the patients (white bars) in the three wards. In panel B patients were distributed according to twelve macro-admission diagnoses. Also in this case on the principal axis are reported the average hospitalization stay costs per patient (*grey bars*) and on the secondary axis is reported the percentage distribution of the patients (*white bars*) with respect to the considered aggregated diagnoses.

stay) was compared with the average LOS of all patients admitted in that ward in the year 2011 (paired sample *t*-test: 40.13±47.26 vs 15.49±7.65, $p < 0.001$). Twenty nine (21.8%) patients died during their hospitalization.

Specific Patient Status at Admission

28 patients (21.05%) presented with immune-depression: 3 (10.71%) were under chemo-therapy, 1 had undergone organ transplantation, 2 had undergone bone marrow transplantation and 22 (78.57%) patients reported other causes of immune-depression (steroid treatment). Moderate or severe chronic renal failure was present in 35 (26.3%) cases, neoplasms in 28 (21%), irritable bowel disease in 2 (1.5%), diabetes mellitus in 26 (19.5%), cardiovascular disease in 77 (57.9%) and chronic respiratory disease in 59 (44.4%).

Concomitant Therapy at CDI Diagnosis

117 patients (88%) were under concomitant therapy with antibiotics, with an average number of treatment days of 22.86±26.42, 117 (88%) were treated during hospital stay with proton pump inhibitors (PPI) (average number of length therapy equal to 28.52±40.13 days) and 29 (21.80%) with H2 blockers for an average duration of 4.96±18.27 days.

CDI Therapy, CDI-related Measures and Costs

Extra length of stay costs, due to CDI, amounted in average to 13,957.89 € per patient, with one day of stay in an ordinary ward being set at 700 €, one day in ICU being set at 1200 €. Multiple patients required intensive care: 5 patients were in ICU at moment of diagnosis; 6 patients (4.5%) were transferred to the ICU after diagnosis for the severe physiopathological disequilibrium and their average ICU stay was 10.33±10.44 days. Nineteen more patients (14.28%) were subject to isolation measures (800 € per day) in the ordinary ward for an average period of 19.58±13.05 days. The additional cost to the hospitalization stay for these two types of intervention resulted to be 233.08±1480.36 € and 279.70±839.71 € per patient in average respectively, and accounted for only 1.67% and 2.00% of the total cost.

Antibiotic therapy (vancomycin at 4.6 €/g, metronidazole at 1.3 €/g, meropenem at 12 €/g) was recorded as number of grams per day for the length of therapy administration. Medical charts recorded that 90% of the sample received antibiotic therapy, 65%, 30% and 5% of patients were treated sequentially with one, two and three different antibiotics respectively. Vancomycin and metronidazole were the most frequently administered drugs, meropenem was used rarely. The average cost per patient of antibiotic therapy amounted to 59.20 €, representing 0.42% of the total costs attributable to CDI hospitalization.

Transfusions were given in a subset of 7 patients (5.26%) and the average number of bags per patient amounted to 4±3.65. CDI-related relevant imaging were CT-scans (18.80% of cases) and magnetic resonance imaging (one patient).

The severe form (i.e. clinical situations of CDI with progressive rise of white blood count > 15.000, creatinine > 1.5 times pre-morbidity values) and the severe-complicated (organ failure, hypotension, etc.) occurred in 23 patients. The 8 patients satisfying criteria for severe-complicated form were treated surgically in 6 cases (while two were terminal): 4 patients underwent total colectomy, 1 colostomy and 1 ileostomy for lavage.

The cost of laboratory exams during the post-diagnosis stay amounted to 317.67±384.20 € in average, and impacted the total cost of CDI hospital stay by 2.28%. Table II reports, for each of the above considered costs, the average cost per patient, the standard deviations and the weights in terms of percentages of the cost of hospital stay.

Relations Between Costs and Specific Patient Status at Admission

Figures 1A and B report the average costs per patient over the three types of admission wards (Medicine, Surgery and ICU) and over the aggregated admission diagnoses (grey bars, principal axes). The largest average costs were recorded for the Medicine wards with 14,959±28,733 € and for the "BPCO and pneumonia" admission diagnosis with 27,600±56,738 €. For each patient presenting with one of the most two frequent admission diagnoses (myocardial disease and BPCO-Pneumonia) the difference between the recorded cost and the average cost related to an average admission (deltas) were computed. Deltas were tested by means of a One-Sample *t*-test and they resulted significantly difference from zero (13.170±40.938, $p = 0.027$).

Discussion

Clostridium difficile-associated disease is responsible for increased morbidity and a substantial

Table I. Estimated total cost per patient and percentage of each type cost over the total hospital stay cost.

Direct costs post diagnosis CDI	Average cost/patient (€)	SD	% with respect to total hospitalization stay cost
Hospitalization stay	13,957.89	26,619.77	–
Toxin test (VIDAS®) for CDI diagnosis	11.85	8.17	0.08
CT-scan for CDI management	47.10	111.55	0.34
Magnetic resonance for CDI management	2.16	24.86	0.02
ICU stay additional cost	233.08	1480.36	1.67
Isolation stay additional cost	279.70	839.71	2.00
Antibiotic treatment	59.20	76.16	0.42
Surgical treatment	113.10	523.47	0.81
Blood transfusion	5.44	30.60	0.04
Therapy fluid	2.02	13.34	0.01
Laboratory exams	317.67	384.20	2.28

economic burden[11]. Calculation of costs in different countries depends greatly on the degree of medical assistance, but also on the awareness and prompt response to the disease. In Italy, only two studies on epidemiology of CDI[12,13] have been published, one from an acute care teaching hospital and one from four internal medicine wards of a Northern Italian city, and no costs are reported.

Most accurate cost analysis come from Anglo-Saxon countries. Retrospective analysis of costs showed that from 2004 to 2008, in the USA, length of stay and costs for CDI soared passing from 4 days after diagnosis to 5.5 days with costs rising from $306 per case to $6,326[11]. A recent review in a multihospital cohort of academic medical centers shows an even more frightening situation. In fact, the adjusted mean cost for cases was significantly higher than that from controls ($55,769 vs $28,609) and adjusted mean length of stay was twice as long (21.1 vs 10.0 days)[14].

The most recent report[15] – that utilizes a computer simulation model to determine the costs attributable to healthcare-acquired CDI infection from the hospital, third-party payer and societal perspectives – shows that CDI is indeed costly not only to third-party payers and the hospital, but to society as well, with relative costs of $9,179 to $11,456, $8,932 to $11,679 and $13,310 to $16,464, with most of the costs accrued during a patient's primary infectious episode.

Study Limitations

Our Italian data from a major academic Hospital show that even if hospital costs for CDI basically follow those reported from other countries, length of hospital stay is the most significant factor influencing overall costs. Our data do not have a control group for patients admitted for similar disease, however the costs of an in hospital CDI have been calculated from the difference between the period previous to the diagnosis and the period successive to bacterial identification. In a few cases we have the admission to the hospital with an ongoing undiagnosed CDI, on the other we assist to an infection that occurs during hospital stay. Naturally these populations differ significantly but the costs depend greatly from the hospital length of stay, even if those patients (4.5%) that require a surgical intervention present very high costs. Our study, as well as those above, does not consider in the cost analysis the use of new drugs such as for example fidaxomicin[16] or prevention strategies such as vaccine development[17] or fecal transplantation[18]. These new therapies may be cost-saving reducing CDI incidence, duration, severity and transmission.

Conclusions

CDI is extremely costly once it occurs in hospitalized patients that usually have many risk factors such as age and comorbidities. Patients are usually chronically ill and even treated by invasive therapies (cardiosurgery, hip replacement, etc.). This makes prevention much more cost-effective. Infection control is the most essential component of an effective overall management strategy for prevention of nosocomial CDI[19], with cleaning of bedsteads, commodes, night tables and curtains in first line among prevention strategies. Even though all hospitals have procedures for cleaning, recent studies show that the best results are due to motivation of cleaning teams, protocols that imply a detailed attention to all the furniture and effects near the patient's bed.

Together with infection control, a more precocious antibiotic therapy would surely be advantageous, and this may depend in part from easier, quicker and more specific identification tests[20].

Costs of CDI will surely change in the future with the new antibiotics, that even if more costly will probably shorten hospital stay, reduce recurrences and the severity of the disease[9].

New and more costly antibiotics are surely justified by pharmacoeconomical data because as can be seen also from our study, antibiotics represent a minimal cost in the overall budget of CDI.

The diffusion of a new and less invasive surgical technique to treat severe and severe-complicated CDI with ileostomy and colonic lavage, also implies more specific and rapid delivery of antibiotics to the injured colonic mucosa and will benefit from new drugs[21].

This cost analysis from an academic major hospital in Italy takes into account all the computable costs of in-hospital stay. It may be biased by the fact, also underlined by others[15], that academy hospitals attract more serious cases and spend greater resources to achieve diagnosis, but consistency with international data show that CDI is truly a worldwide sanitary emergency in developed countries.

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