Evaluation of the cost and length of hospital stays related to the management of an intestinal *Clostridium difficile* infection

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Abstract

Introduction : **Intestinal Clostridium difficile Infection (CDI) treated in hospitals may concern patients whose reason for admission is CDI (primary diagnosis) or who have acquired CDI during their stay (secondary diagnosis).**

Objectives : **The objective of this study is to evaluate the cost for social security and hospitals and the length of hospital stays related to CDIs as the main reason for admission.**

Method : **This study was carried out in 2012 in 13 Belgian hospitals. Cases were selected by using diagnosis recorded in minimum discharge summaries. Pediatric stays are not part of the inclusion criteria (n= 86).**

Results : **The average length of stay (standard deviation) was 13.53 days (11.95). The average cost (standard deviation) covered by social security/hospitals was €5,019.51 / €6,286.39 (9,638.42/ 6,368.45). 7% of patients were admitted to the Intensive Care Unit during hospitalization, for an average duration (standard deviation) of 8.18 days (2.93). The mortality rate was 8.1%. 19.8% of patients used vancomycin during the stay, 43% were treated with metronidazole only, 12.8% used vancomycin and metronidazole and 24.4% do not received vancomycin or metronidazole. No patients received fidaxomycin.**

Conclusion : **This study made it possible to approach the cost of CDI as the main reason for admission. Such data should allow contributing to optimally assess both the pharmacoeconomic impact of the implementation of prevention strategies and also therapeutic management making use of more expensive medicinal products but associated with decreased risk of recurrence.** (Acta gastroenterol. belg., **2018**, 81, **263-268**).

Keywords : Clostridium difficile, cost, and charges.

Introduction

Clostridium difficile is a gram positive anaerobic bacterium most often responsible for nosocomial diarrhea that usually occurs during or after antibiotic treatment. Patients affected by a *Clostridium difficile* Infection (CDI), whether it is the main reason for hospitalization or complication, have worse outcomes of care than other comparable patients (length of stay, admission rates in an intensive care unit, hospital mortality or readmission rates) (1). Mortality observed in Belgium is estimated at approximately 3% of the cases, 7-8 deaths per million people, according to the Institute of Public Health Report (WIV-ISP) in 2015 (2). Deaths attributable to CDI ranged from 71 to 150 since 2003.

One of the specific characteristics of this infection is its high recurrence rate, estimated at approximately 20% when the patient is treated with vancomycin or metronidazole. CDIs represent significant costs, for social security, hospitals or patients.

Estimates for the treatment of these infections revolve around an annual cost of € 300 million in Europe (3). Vonberg et al. (4) evaluated the median extension of the length of stay of 7 days and an additional cost of €7,147 when such an infection is acquired in the hospital. The extension of the stay is even more important for some at-risk patients (immunosuppression, advanced age ≥ 65 years, chronic obstructive pulmonary disease, heart failure, diabetes, renal impairment) with extensions ranging from 12.58 days in the Netherlands to 16.09 days in England (5) . Le Monnier et al (6) have estimated the additional cost of these CDIs at € 163.1 million in French public hospitals, 12.5% of which are attributable to recurrence. The average additional cost per stay for the hospital was estimated at € 9,575. Patients aged above 65 years, with severe comorbidities, admitted to intensive care or immunocompromised are considered to be patients at risk of developing severe CDI (7). In 2014 (2), 108 acute Belgian hospitals participated in the registration of CDIs.

In 2014, in Belgian hospitals, 59% of cases of CDI were nosocomial. Nosocomial CDIs were diagnosed primarily in geriatric (31%), hematology-oncology (9%) or intensive care (7%) units. The average incidence as a nosocomial infection is 1.19 CDI per 10,000 days of hospitalization and 0.86 CDI per 1,000 discharges. In 2014, non-nosocomial episodes had an average incidence of 0.63 cases per 1,000 admissions. These rates can however vary depending on the source of data ranging, in 2012, from 1.97 per 1,000 admissions in minimum hospital discharge summaries to 1.50 per 1,000 admissions in compulsory registration by the Scientific Institute of Public Health (8).

Different treatments are currently being used. Oral metronidazole is the compound of choice for the treatment of mild to moderately severe forms (9). Recent

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studies show a higher efficacy of vancomycin compared to metronidazole in particular for the treatment of severe cases. Fidaxomicin, recently made available to clinicians, showed similar clinical efficacy to vancomycin but with superior efficacy in the prevention of recurrence. However, it is rarely prescribed in Belgium and is reserved for recurrent episodes. In cases of multiple recurrences, fecal transplantation appears to be a promising strategy (7, 10).

CDIs treated in hospitals may concern patients whose reason for admission is CDI (primary diagnosis) or who have acquired CDI during their stay (secondary diagnosis). Belgian medico-administrative data from 2012 shows that 25% of stays for a CDI concern CDIs as a admission primary diagnosis. These are patients from home, another hospital, long-stay institution, etc. These *community associated* CDIs have an incidence of 8.5 per 100,000 people (2).

Most of the articles in the literature are devoted to the assessment of additional costs or the extension of the length of stay attributable to nosocomial *Clostridium difficile* Infection. Whatever the matching method, it is often difficult to isolate, within hospital stays, the actual costs attributable to the CDI from those related to the initial diagnosis. Therefore, the objective of this study is to evaluate the cost for social security and hospitals and the length of hospital stays related to CDIs as the main reason for admission.

Methodology

Background

This study was carried out in 2012 in 13 hospitals in Belgium, in the Wallonia region (12 hospitals) or Brussels-Capital region (1 hospital). They were 12 general and one academic hospitals. Data from 219, 184 inpatient stays were analyzed representing approximately 12.98% (11) of inpatient stays in Belgium in 2012.

Selection of cases

Ninety eight stays were identified with an intestinal *Clostridium difficile* Infection as primary diagnosis. Two partial stays (hospitalizations spreading across two calendar years and for which only the part of quantitative data for the year 2012 was available) and 10 pediatric stays (1 to 3 years) were removed from the sample. It remains 86 inpatients stays for analyses. The primary diagnosis (12) is defined as the diagnosis that is the reason for hospitalization as determined considering all the performed diagnostic procedures at the time of discharge. Diagnosis are determined by the medical doctors in the medical file or in the discharge letter and are coded by the codification department by using the ICD-9-CM classification. The code 00845: INTESTINAL CLOSTRIDIUM DIFFICILE INFECTION was used to identify cases. Hospital stays were grouped into APR-DRGs (All patient refined diagnosis related groups), Version 15. Diagnosis Related Groups (DRGs) are a patient classification system used to relate the type of patients treated in the hospital to expenses incurred by the hospital to carry out such treatment.

APR-DRGs incorporate the concept of clinical severity (scope of physiological degradation or loss of function of a clinical system), risk of mortality (probability of death), and resource intensity (relative importance of diagnostic and therapeutic hospital services, used in the treatment of a particular diagnosis). Each APR-DRG is divided into 4 classes of clinical severity and 4 classes of risk of mortality. The assignment of clinical severity and mortality risk class is done in several steps, which take into account the primary diagnosis, secondary diagnosis (not the reason of admission but influencing the patient's stay), non-operating room procedures, age, etc. The identification of stays is anonymized and no longer allows access to medical files.

Economic data

Costs are evaluated with two different perspectives (social security and hospitals). The data used to create the database come from hospital billing data, accountancy data, and Minimum Clinical discharge Summaries (MCS). Pharmaceutical products were grouped according to the ATC classification (Anatomical, Therapeutic and Chemical).

Statistical analysis

The usual descriptive statistics were used for the description of all the variables. Given that the distribution of lengths of stay and costs are asymmetric, median, together with percentiles are presented and compared using the Mann-Whitney-Wilcoxon test. Some means together with their standard deviations are shown for comparison with the existing literature. The age of patients was grouped into two age groups (20-64 years, more than or equal to 65 years). Statistical analyses were performed using Microsoft Excel software *(version 2013)* and SPSS Version 23. The significance threshold retained was 0.05.

Results

CDI rate : In the 13 hospitals analyzed, 98 cases (Including partial stays and pediatric stays) of CDI were identified as a primary diagnosis of CDI and 353 cases were identified as a secondary diagnosis not present at the time of admission. CDIs as primary diagnosis therefore represent 21.73% of all reported cases and 0.04% of hospital stays in 13 hospitals, against 0.16% of hospital stays associated with a secondary diagnosis of CDI.

Characteristics of stays: All the 86 hospital stays are divided into five APR-DRGs. 95.3% of stays are grouped into the APR-DRG 250 OTHER DIAGNOSES OF THE

Table 1. — **APR-DRGs* of hospital stays for a CDI (n=86)**

APR-DRG	Frequency	Percentage	Cumulative percentage
250 OTHER DIAGNOSES OF THE DIGESTIVE SYSTEM***	82	95%	95%
139 SIMPLE PNEUMONIA	1	1%	97%
229 OTHER INTERVENTIONS OF THE DIGESTIVE SYSTEM	1	1%	98%
422 HYPOVOLEMIA AND ELECTROLYTIC DISORDERS	1	1%	99%
952 LESS IMPORTANT INTERVENTIONS NOT ASSOCIATED WITH THE MAIN DIAGNOSIS	1	1%	100%
Total	86	100.0	

* APR-DRG (all patient refined diagnosis related groups)
** clostridium difficile infection
*** There are 21 APR-DRG related to digestive problems in the **APR-DRG** classification: 220 MAJOR STOMACH, ESOPHAGEAL & DUODENAL PROCEDURES, 221 MAJOR SMALL & LARGE BOWEL PROCEDURES, 222 MINOR STOMACH, ESOPHAGEAL & DUODENAL PROCEDURES,223 MINOR SMALL & LARGE BOWEL PROCEDURES,224 PERITONEAL ADHESIOLYSIS,225 APPENDECTOMY,226 ANAL & STOMAL PROCEDURES,227 HERNIA PROCEDURES EXCEPT INGUINAL & FEMORAL,228 INGUINAL & FEMORAL HERNIA PROCEDURES,229 OTHER DIGESTIVE SYSTEM PROCEDURES,240 DIGESTIVE MALIGNANCY,241 PEPTIC ULCER & GASTRITIS,242 MAJOR ESOPHAGEAL DISORDERS,243 OTHER ESOPHAGEAL DISORDERS,244 DIVERTICULITIS & DIVERTICULOSIS,245 INFLAMMATORY BOWEL DISEASE,246 G.I. VASCULAR INSUFFICIENCY,247 G.I. OBSTRUCTION, 248 MAJOR G.I. BACTERIAL INFECTIONS, 249 NONBACTERIAL GASTROENTERITIS & ABDOMINAL PAIN, 250 OTHER DIGESTIVE SYSTEM DIAGNOSES.

Table 2. — **Severity index of APR-DRG attributed to hospital stays for a CDI* (n= 86)**

Severity index	Frequency	Percentage	Cumulative percentage
1	5	6%	6%
2	27	31%	37%
3	38	44%	81%
4	16	19%	100%
Total	86	100%	

* clostridium difficile infection

DIGESTIVE SYSTEM (Table 1). 76% of stays had a moderate (2) and major (3) severity of illness (SOI), associated with APR-DRG. Only 5.8% of patients had a minor SOI (1) (Table 2). The secondary diagnoses of patients were quite heterogeneous. Diagnoses of dehydration and hypopotassemia were however observed in 23 and 24 patients, respectively (Table 3). Seven per cent of patients were admitted into Intensive Care Unit (ICU) during their stay and 8.1% of patients died. Of the 7 patients who died, 4 had been hospitalized previously (between 6 and 34 days of readmission), 2 were hospitalized in ICU and 5 had an extreme SOI (4) (Table 4). The median age of patients (percentiles 25 and 75) was 78 years (62-83) (Table 5). Most of the patients came from their homes and were admitted in emergency while 16.3% of patients were from a nursing and/or care home. 64 patients (74.4%) had already stayed in the same hospital during the same year. Out of the 86 stays for which all the data is available, 10 patients had a previous hospitalization with an intestinal *Clostridium difficile* Infection as reason for admission (primary diagnosis). This previous hospitalization had taken place between 2 to 70 (median: 20 days) days after the patient was readmitted. 4 patients had had a previous hospitalization in the same hospital including an intestinal clostridium *difficile* Infection during the stay, coded as a secondary diagnosis in the MCS. These previous hospitalizations were for the 4 patients 15 days, 36 days, 49 days and 60 days prior to their admission.

Length of stay and cost: The average length of stay (standard deviation) is 13.53 days (11.95). The average cost covered by social security is €5,019.91 (9,638.42) and 6,286.39 for hospitals (6,368.45).The length of stay and cost (social security/hospitals) are quite heterogeneous and each has a coefficient of variation of 0.88 and 1.92/1.01, respectively. For this reason, percentiles are presented in the tables of results (Table 6).

Six patients were admitted into the Intensive Care Unit during hospitalization. For these stays, the average length of stay (standard deviation) was 22.76 days (11.76) and 8.18 (2.93) days in ICU. 19.8% of patients used vancomycin during the stay, 43% were treated with metronidazole only, 12.8% used vancomycin and metronidazole and 24.4% do not received vancomycin and metronidazole. No patients received fidaxomycin.

Discussion

The data extracted by exploiting the MCS of our study population was used to calculate a CDI incidence rate which can be compared to data collected in the national surveillance report that covers all hospital stays in Belgium, from laboratory data based on standardized microbiological definitions. It is the same for the distribution between primary and secondary diagnoses with approximately 20% of primary diagnosis. However, the diagnosis of *Clostridium difficile* infection remains dependent on microbiological techniques used, and our analysis of medico-administrative data does not make it possible to integrate these elements into the definitions used.

The primary character of the diagnosis does not rule out a direct link with health care institutions, since it

Table 3. — **The most common secondary diagnoses for hospital stays for a CDI* (present for at least 10 stays)**

Secondary diagnoses		Frequency	Percentage	Cumulative percentage
4011	|ESSENTIAL, BENIGN HYPERTENSION	34	40%	3.1
27651|DEHYDRATION		23	27%	5.3
2768	|HYPOPOTASSEMIA	24	28%	7.4
V070|REQUIRES ISOLATION		20	23%	9.2
2720	|PURE HYPERCHOLESTEROLEMIA	17	20%	10.7
4148	|CHRONIC ISCHEMIC HEART DISEASE, OTHER	17	20%	12.2
5533	|DIAPHRAGMATIC HERNIA	15	17%	13.6
V5866|LONG-TERM USE OF ASPIRIN		15	17%	14.9
5990	|URINARY TRACT INFECTION, WITHOUT FURTHER PRECISION	14	16%	16.1
V606|PERSON LIVING IN AN INSTITUTION		13	15%	17.3
2449	|HYPOTHYROIDISM, WITHOUT FURTHER PRECISION	11	13%	18.3
2689	|VITAMIN D DEFICIENCY, WITHOUT FURTHER PRECISION	12	14%	19.4
2639	|PROTEIN-CALORY MALNUTRITION, WITHOUT FURTHER	10	12%	20.4
PRECISION				
2859	|ANEMIA, WITHOUT FURTHER PRECISION	11	13%	21.3
V603|PERSON LIVING ALONE		11	13%	22.3
53011|REFLUX ESOPHAGITIS		10	12%	24.1

* clostridium difficile infection

Table 4. — **Patient characteristics and use of antibiotics (n=86)**

Variable	No. of stays	%
Age >= 65 years	63	73%
Emergency admission	69	80%
Readmission within a year	64	74%
Patient from a nursing home/rest and care home	14	16%
Patient from his (her) home	60	70%
Passage through an Intensive Care Unit	6	7%
Hospital mortality rate	7	8%
Use of vancomycin during stay	17	19,8%
Use of metronidazole during stay	37	43%
Use of vancomycin and metronidazole during stay	11	12,8%
No vancomycin or metronidazole during stay	21	24,4%

Table 5. — **Age of patients (n= 86)**

					Percentiles			
	5		10	25	50	75	90	95
Age		26	35	62	78	83	89	92

appears that the majority of hospitalizations for primary diagnosis of *C difficile* infection occur following a recent hospitalization (within the year) in the same hospital, and that at least 15% have a documented history of previous CDI infection. Given that the study methodology did not allow the identification of a previous stay in another health care institution as that which reported the primary diagnosis, this percentage is therefore probably undervalued.

The comorbidities associated with the diagnosis of primary *Clostridium difficile* infection illustrate the heterogeneity of the relevant patient group but the risk factors typically associated with this infection (age, hospital or long-stay institution stay, immunosuppression, cancer diseases, etc.). The presence of associated disorders such as dehydration or hypopotassemia reflects the state of severity of the clinical presentation. Given that *Clostridium difficile*-associated diarrhea can be treated by administering oral metronidazole outside the hospital, it is likely that patients admitted into emergency room for a CDI have a more severe picture than those who are not represented in the hospital and therefore require treatment with metronidazole and/or intravenous vancomycin. Unfortunately, we have no information on the outcome of care after discharge from the hospital.

Table 6. — **Length of stay and detailed cost of hospital stays for CDI* (n=86)**

	Percentiles						
	5	10	25	50	75	90	95
Length of stay (days)	1,13	2,50	4,79	9,51	18,94	29,96	43,67
Length of stay in the ICU** (days)	-	-	-	-	-	-	5,11
Cost covered by hospitals (€)	882,86	1.154,21	2.049,93	4.306,27	7.935,46	15.303,46	18.896,08
Cost covered by social security (€)	1.285,97	1.591,96	2.113,66	3.255,99	5.224,28	9.008,69	9.678,90
Cost of medical procedures covered by social security (€)	295,33	424,38	563,14	959,40	1.649,00	2.662,00	3.019,96
Clinical biology cost covered by social security (€)	137,08	161,75	239,92	411,60	613,08	1.026,88	1.220,42
Cost of pharmaceutical products covered by social security (€)	106,17	112,75	129,80	170,45	325,29	530,25	761,87
Cost related to the flat rate per admission (proprietary medicinal products) (€)	92,36	93,40	98,21	108,50	124,92	139,78	147,19
J_Anti-infectives for systemic use (€)	-	-	0,71	17,60	65,95	184,40	244,87
J01C_beta-lactam antibiotics, penicillins (€)	-	-	-	-	2,59	46,66	100,01
J01XA01_vancomycin (€)	-	-	-	-	34,08	109,98	159,94
Other costs covered by social security (€)	780,55	923,21	1.312,61	1.979,72	3.242,74	4.946,90	6.156,10

* clostridium difficile infection
** intensive care unit

It may seem challenging that 24.4% of patients do not seem to have received any antibiotic therapy. This data must be qualified by the following factors. It is likely that some hospitalized patients left before the final diagnosis through a bacteria culture and the detection of the toxin produced by *C. difficile* was made. They were therefore treated as outpatients or were not treated. In many cases, the discontinuation of prior antibiotic therapy may be sufficient to control the diarrhea symptoms that therefore no longer justified the administration of antibiotics. Finally, it cannot be ruled out that some patients are tagged as suffering from a CDI without a clinical picture that justifies antibiotic therapy, given the difficulties inherent in this pathology regarding diagnostic standardization and thus the inventory of the pathology.

Despite the limits outlined above, our study made it possible to approach the cost, for social security and hospitals, regarding the management of *C. difficile*-associated diarrhea, requiring hospitalization, with an average of respectively €5,019.51 and €6,286.39. The reader should bear in mind that the invoice paid by the patient is not evaluated in this study. This cost corresponds fairly well to incremental costs assessed in other very recent studies, for example a recent study by Ryan et al. with a median incremental cost of € 5,520 per stay in an Irish hospital, of which € 1,026 of variable costs (13). Similar costs have recently been evaluated in an English study evaluating the cost of a first infection at £6,294 and £7,539 when recurrence (14). This study, like ours, revealed heterogeneity of costs per patient (14).

This study allowed us to approach the costs of primary diagnosis of *C. difficile* infection in the financial context of health care in Belgium and, by extrapolation, could be used to approach the cost attributable to this infection when it occurs in the hospital. Little data exists on this subject, and this study should allow to contribute to optimally assess both the pharmaco-economic impact of the implementation of prevention strategies and also therapeutic management, making use of more expensive medicinal products but associated with a decreased risk of recurrence. This approach, based on administrative data and APR-DRGs, is an unfamiliar approach for most clinicians. However, they will have to familiarize themselves with it, because of the plans for reforming hospital financing based on lump sums by APR-DRG, and in particular the pay for performance reform envisaged in Belgium.

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