C H A P T E R 4

COST ANALYSIS OF AN OUTBREAK OF *CLOSTRIDIUM DIFFICILE* INFECTION RIBOTYPE 027 IN A DUTCH TERTIARY CARE CENTER

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Journal of Hospital Infection 2016; 95(4):421-425

ABSTRACT

Background

The economic impact of *Clostridium difficile* infection (CDI) on the healthcare system is significant. From May 2013 to May 2014, an outbreak of *C. difficile* ribotype 027 occurred in a Dutch tertiary care hospital, involving 72 patients. The primary aim of this study was to provide insight into the financial burden that this CDI outbreak brought upon this hospital.

Methods

A retrospective analysis was performed to estimate the costs of a one-year-long *C. difficile* ribotype 027 outbreak. Medical charts were reviewed for patient data. In addition, all costs associated with the outbreak control measures were collected.

Findings

The attributable costs of the whole outbreak were estimated to be €1,222,376. The main contributing factor was missed revenue due to increased length of stay of CDI patients and closure of beds to enable contact isolation of CDI patients (36%). A second important cost component was extra surveillance and activities of the Department of Medical Microbiology and Infection Control (25%).

Conclusion

To the authors' knowledge, this is the first study to provide insight into the attributable costs of CDI in an outbreak setting, and to delineate the major cost items. It is clear that the economic consequences of CDI are significant. The high costs associated with a CDI outbreak should help to justify the use of additional resources for CDI prevention and control.

INTRODUCTION

Clostridium difficile has increased in prevalence since 2000, and has caused outbreaks of nosocomial diarrhea worldwide.[1] The major cause of most recent outbreaks of *Clostridium difficile* infection (CDI) is *C. difficile* ribotype 027, a more virulent ribotype associated with significantly higher morbidity and mortality.[2] Despite prevention and control measures, hospital-acquired CDI is still a major problem, leading to increased morbidity, mortality and costs.[1]

The economic impact of CDI on the healthcare system is significant, because it doubles the average length of hospitalization and increases the cost of treatment.[3] Annual cost is estimated to be between $800 million and $3200 million per year in the USA and €3000 million in Europe.[4-6] With the ageing population and increased antibiotic resistance, the number of patients with CDI and related costs and morbidity are expected to increase further.

Several studies and reviews have focused on the annual cost for society in general incurred by CDI. However, to the authors' knowledge, data on costs specifically related to a CDI outbreak at a single center have not been published previously. From May 2013 to May 2014, an outbreak of *C. difficile* ribotype 027 occurred at the VU University Medical Centre, a 750-bed tertiary care center in The Netherlands.[7] The primary aim of this study was to provide insight into the financial burden that this CDI outbreak brought upon this hospital.

METHODS

General study outline

A retrospective analysis was performed to estimate the costs of an outbreak of *C. difficile* ribotype 027 that occurred between May 2013 and May 2014. The duration of the outbreak was defined as the time for which extra infection control measures were implemented.

Patients

The patient cohort of this CDI outbreak was described previously in a case-control study that investigated in-hospital risk factors associated with acquiring an infection with the outbreak strain.[7] The original case-control study included 79 consecutive patients with CDI due to ribotype 027, hospitalized on 19 different adult wards between May 2013 and March 2014. For the present study, nine of these 79 patients were excluded because they were diagnosed on the 'transfer ward' (ward where patients no longer in need of hospital care can rehabilitate before discharge), which is not officially part of the hospital. In addition to the previous cohort, patients diagnosed between March 2014 and May 2014 (N = 2) were also included. Therefore, 72 patients were included in this analysis. CDI was defined as the presence of diarrhea (three or more unformed stools per 24h) in combination with a positive stool culture for *C. difficile* ribotype 027.

The control group of the previous case-control study was used to calculate the attributable costs of a prolonged length of stay (LOS) of CDI patients during the outbreak.[7] Four controls were matched per case. The control patients were matched for age, attending specialty and stay on the ward within 48h of CDI diagnosis (excluding control patients who were matched to CDI patients diagnosed on the transfer ward).

Outbreak and data collection

In May 2013, an increase in the number of patients diagnosed with CDI due to ribotype 027 was noticed. During the ensuing months, *C. difficile* ribotype 027 spread to several wards, with an incidence of 8.7 cases per 10,000 patient-days between May and December 2013.[7] Several control measures were implemented to control this outbreak of *C. difficile* ribotype 027[8,9]: reinforcement of infection control measures (use of aprons and gloves, appropriate hand hygiene, contact isolation of every patient with diarrhea in single rooms, and the introduction of hydrogen peroxide as disinfectant); extra cleaning; optimization of CDI diagnosis (every patient with diarrhea was tested twice for toxin-producing *C. difficile* even when the diarrhea was likely attributable to an underlying condition or therapy); optimization of CDI treatment (most patients were treated with a combination of metronidazole and vancomycin instead of metronidazole alone); and antibiotic stewardship. To enable every patient with (suspected) CDI to be nursed in contact isolation in a single room, several beds had to be closed. It was not deemed necessary to close an entire ward. After the implementation of all these infection control measures, the incidence of CDI ribotype 027 decreased to approximately 1.5 cases per 10,000 patient-days in early 2014.[7] Medical charts were reviewed and the following data were retrieved for all CDI and control patients: demographic characteristics; date of hospital admission; date of CDI diagnosis; date of discharge; total hospital LOS; and hospital LOS after CDI diagnosis. All cost items associated with the outbreak control measures were collected. In addition, the costs of 12 meetings of the outbreak management team (OMT; consisting of five medical specialists, one infection prevention specialist, one care manager and two fellow workers of the facility management) were collected. Indirect in- and out-hospital costs (e.g. transfer to the intensive care unit for extra supportive care, costs from days lost due to absence or productivity losses), and costs of reinfection and re-admissions were not included.

Cost items and cost calculation

Cost items attributed to the outbreak and its containment were identified. Attributable costs per item (in 2014 Euros) were assessed over a one-year period. Data about the number of extra microbiological tests were retrieved from the medical microbiology database, and compared with the number of tests during the same period in the previous year. Data about extra workload, extra surveillance and infection control measures were based on interviews with the Department of Medical Microbiology and Infection Control, and calculated based on personnel costs per hour (gross salary including employer's costs). Costs of OMT meetings were calculated based on the personnel costs of OMT members per hour (€3294.10 per meeting). Costs made for contact isolation materials (aprons and gloves) of (suspected) case patients were calculated after internal evaluation (€111 per outbreak day). Additional cleaning costs were based on stored records as provided by the facility management (€790.53 per outbreak day). Missed revenue due to closed beds was based upon the difference in bed occupancy rates during the outbreak compared with the average bed occupancy rate (85%). Admission data were obtained from the general hospital database. Missed revenue due to prolonged LOS of CDI patients was estimated by comparing the LOS of CDI patients with the LOS of a control group (N = 280). The cost of one missed hospital admission due to closed beds or prolonged LOS of CDI patients was considered to be €1100. The cost of a 10-day course of metronidazole and vancomycin treatment was €6.69 and €431.48 respectively.

Missed revenue due to prolonged LOS of CDI patients, costs of the OMT meetings, extra surveillance, contact isolation materials (compared with the same period for the preceding year and following year) and additional microbiological diagnostics (compared with same period for the preceding year) were calculated directly from available data for the entire outbreak. Overall costs made for additional cleaning,

contact isolation of patients and missed revenue due to closed beds were extrapolated from the incurred costs during the last three months of the outbreak.

Calculations were made using Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA) and SPSS Version 22 (IBM Corp, Armonk, NY, USA).

RESULTS

Patient characteristics

The outbreak included 72 patients with CDI 027 over one year. The patients had a median age of 68 years (range 18-87 years). Thirty-five percent of the patients were female. Sixty-six patients (89%) received antibiotic treatment for CDI, of which 52 patients (79%) received a combination of oral metronidazole and vancomycin, 13 patients (20%) received metronidazole alone, and one patient (1%) received vancomycin alone. The mean total LOS of patients with CDI was 44 (standard deviation [SD] 35) days, compared with 23 (SD 24) days for the control patients. The mean LOS after the date of CDI was 24 (SD 24) days for CDI patients and 12 (SD 17) days for control patients. Thirty patients (41%) developed a recurrence (defined as a new episode of diarrhea with a positive stool for *C. difficile* after discontinuation of antibiotic therapy) within 90 days of the initial episode. The re-admission rate among CDI patients was comparable with the re-admission rate of the control group. Eleven patients (15%) died within 30 days of CDI diagnosis, compared with 9% in the control patients.

Cost analysis

The total identifiable costs of this *C. difficile* outbreak were €1,222,376, and are shown per cost item in Table I. The majority of costs (36%) were due to loss of revenue as a result of decreased hospital capacity because of the increased LOS of CDI

patients and the closure of multiple beds due to contact isolation of a single CDI patient. Twenty-five percent of the costs were due to extra surveillance and work of the Department of Infection Control; 24% for extra cleaning of the affected wards; 6% for extra microbiological diagnostics; 3% for OMT meetings; and 3% for the use of extra gloves and aprons. Extra antibiotic treatment of CDI patients accounted for 2% of the total costs.

Table 1. Cost items and respective costs of a one-year-long outbreak with *Clostridium difficile* ribotype 027

Cost items	Per patient (€)	Per outbreak day (€)	Total costs (€)
Extra microbiological diagnostics (compared to same period one year earlier)	1,020	201	73,443
Extra workload department of infection control (based on personnel costs per hour)	4,340	856	312,480
Additional cleaning costs	4,008	791	288,544
Twelve OMT meetings	549	108	39,529
Contact isolation material (compared to same period one year earlier and one year later)	563	111	40,540
Missed revenue due to closed beds	5,207	1027	374,880
Missed revenue due to prolonged length of stay of CDI patients	979	193	70,523
Extra antibiotic treatment	312	61	22,437
Total costs	**€16,978**	**€3,348**	**€1,222,376**

Abbreviations: OMT: outbreak management team; CDI: *Clostridium difficile* infection

DISCUSSION

Over this one-year-long outbreak of *C. difficile* ribotype 027, the main cost items that contributed to the total costs were identified. Closure of beds because of contact isolation requirements and prolonged LOS of CDI patients, leading to missed revenue, was the main contributor to the increased costs. A second important cost component was extra surveillance and activities of the Department of Infection Control; this accounted for one-quarter of the total costs. The total identifiable attributable costs of this outbreak were estimated to be €1,222,376.

To the authors' knowledge, this is the first study to provide insight into the main cost items and attributable costs of CDI in an outbreak setting. In previous studies, performed in endemic situations, mean costs attributable to CDI ranged from $3427 to $30,049 per CDI patient.[3,10-12] Reasons for this wide range of cost estimates are likely to be multi-factorial, reflecting the different methods used to calculate attributable costs, number of adjusted variables, the research population and the different healthcare systems.[11] However, in most studies, the increased length of hospitalization of case patients was the most significant contributor to the increased hospital costs. This is similar to the present findings: the mean length of hospital stay was twice as long for patients with CDI compared to patients without CDI.

Numerous cost analyses have been published on nosocomial outbreaks with different micro-organisms, including norovirus, Pseudomonas aeruginosa, methicillin-resistant Staphylococcus aureus, Acinetobacter spp. and vancomycin-resistant enterococci.[13-21] Although difficult to compare at best, costs of bacterial outbreaks seem comparable; costs made for norovirus outbreaks were much lower which is probably due to easier and quicker detection and shorter duration. Recently, Dik *et al.* reported a cost-analysis of multiple outbreaks in The Netherlands.[22] They showed that outbreak- and microorganism-specific characteristics (bacterial vs viral outbreaks) cause large variation in the total outbreak costs. Ward closure (and subsequent loss in revenue) is usually the major cost driver, just as for the outbreak described here, although it was not deemed necessary to close an entire ward.

It is suggested that prolonged hospitalization due to CDI is one of the major drivers of extra costs.[3] However, patients with CDI often have more comorbidities then patients who do not have CDI. Presumably, failure to adjust for underlying comorbidities has resulted in an overestimation of costs in previous studies. To disentangle the attributable costs due to severe comorbidity and the attributable costs due to CDI, a control group matched on age, attending specialty, and ward within 48 hours of CDI

diagnosis was used. This ensured that these patients had a comparable underlying comorbidity[7], and improved the accuracy of the cost estimation of attributable costs due to the prolonged LOS of CDI patients.

There are potential costs attributable to CDI that are difficult to quantify. Therefore, the costs presented above are likely to be an underestimation of the true costs related to this outbreak of CDI ribotype 027. Most importantly, the costs of re-infection and/or re-admissions of patients who developed a recurrence after the initial episode were not included, while it has been suggested that treatment costs of patients with recurrent CDI are approximately three-fold higher than the costs for primary cases.[23] In this outbreak cohort, over 30% of the patients with CDI ribotype 027 developed a recurrent infection within two months after initial CDI diagnosis. Secondly, the indirect in-hospital costs (e.g. costs of treatment for complications due to CDI, transfer to the intensive care unit for extra supportive care) and the general indirect costs (e.g. costs from days lost due to absence from work or productivity losses) were not calculated. Thirdly, the costs associated with patients with CDI-negative diarrhea were not calculated. These patients were also nursed in contact isolation, leading to missed revenue due to closed beds. Finally, a subset of the costs of this outbreak was estimated by extrapolating the costs of the last three months of the outbreak. On the contrary, it is acknowledged that the costs of staff who participated in the OMT meetings and staff of the Department of Infection Control would have been incurred regardless of whether or not the outbreak occurred. However, during these meetings, the OMT members and infection control specialists were not able to perform their normal activities. Therefore, it was considered that these costs should also be included in the cost analysis.

Several of the interventions that were implemented during the outbreak lack high-level evidence of efficacy and cost effectiveness. However, the main part of the costs was due to missed revenue (either because of increased LOS of CDI patients or

insufficient isolation capacity), additional cleaning and the extra activities of the Department of Infection Control; these costs are difficult to circumvent in the case of an outbreak. Currently, there are no definite conclusions regarding repeat stool sampling for the detection of toxigenic *C. difficile*. Therefore, the Department of Medical Microbiology and Infection Control evaluated the value of repeat *C. difficile* testing in this outbreak. They concluded that repeat toxin testing of stools is of value to control outbreaks of CDI.[24] Although it makes sense to undertake critical evaluation about whether all of the implemented interventions were justified and cost-effective, it is very difficult to disentangle the contribution of a single intervention in controlling the outbreak. Regarding the large numbers of patients affected, the authors believe that the need for these comprehensive infection control measures was evident. At present, over two years after the outbreak, the incidence of CDI in the study hospital remains very low (incidence of 0.7 patients with CDI ribotype 027 per 10,000 patient-days).

In conclusion, the economic consequences of CDI are significant. The high costs associated with a CDI outbreak should help to justify the use of additional resources for CDI prevention and control. To avoid unnecessary expense during an outbreak, it is important to follow evidence-based recommendations on control measures in order to limit pathogen spread at the earliest possible stage.

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