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The impact of *Clostridium difficile* infection on resource use and costs in hospitals in Spain and Italy: a matched cohort study

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SUMMARY

Objective: To assess the impact of *Clostridium difficile* infection (CDI) on hospital resources and costs in Spain and Italy.

Methods: CDI data were collected from institutions in Spain and Italy. Each patient was matched with two randomly selected uninfected controls in the same institution. Patient outcomes were assessed for the first and second episodes of CDI and for patients aged ≤65 and >65 years. The impact of CDI on hospital length of stay (LOS) was used to calculate CDI-attributable costs. A multivariate analysis using duration of stay as the continuous outcome variable assessed the independent effect of CDI on hospital costs and LOS.

Results: LOS attributable to CDI ranged from 7.6–19.0 days in adults and was 5.0 days in children; the increases were greater in adults in Italy than in Spain. Attributable costs per adult patient ranged from €4396 in Madrid to €14 023 in Rome, with the majority of the cost being due to hospitalization. For children, the total attributable cost was €3545/patient.

Conclusions: These data show that the burden of CDI is considerable in Spain and Italy. Treatments that can reduce LOS, disease severity, and recurrence rates, as well as effective infection control measures to prevent transmission, have the potential to reduce the burden of CDI.

1. Introduction

Clostridium difficile infection (CDI), which is caused by an anaerobic, Gram-positive, spore-forming bacillus, is the leading cause of infectious diarrhoea in hospitalized adult patients, causing infections ranging from mild diarrhoea to pseudomembranous colitis.[1–3] The most important risk factor for CDI is prior or ongoing antimicrobial therapy, which can disrupt the normal intestinal flora and allow *C. difficile* to colonize the gut.[1–3] Other risk factors include chemotherapy, solid organ and bone marrow transplantation, and chronic treatment with proton pump inhibitors.[2,4] Specific patient groups are also considered to be at risk, e.g. elderly, chronically ill, and immunocompromised patients.[2,3] However, CDI is becoming an increasingly common cause of community-acquired diarrhoea in low-risk populations, such as children, healthy adults, and pregnant women.[1,4]

Although viral infections (rotavirus, norovirus) remain the leading causes of diarrhoea in the paediatric population, CDI is also considered to be an increasingly common cause of hospital-acquired diarrhoea and an emerging cause of community-acquired diarrhoea in children.[2,5] In contrast to adults, no relationship with antibiotic exposure or comorbid conditions has been observed in children with community-acquired CDI.[2–4,6]

Many reports have shown that the incidence and severity of CDI are increasing and that it is associated with increasing morbidity and mortality; however, most studies have been performed in

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North America or northern Europe.[7–9] A pan-European study conducted by the European Centre for Disease Prevention and Control in 2008 showed that the incidence of CDI differs between countries; the reported rates in Italy and Spain were 3.6 and 4.3 episodes per 10 000 patient-days, respectively.[10] Although the study had a uniform design with a fixed 3-month follow-up, some studies have suggested that the diagnostic testing approach used causes variations in estimates of the incidence of CDI.[11–13] However, country-specific studies in Spain and Italy indicate that the prevalence of CDI is increasing: between 1999 and 2007, the prevalence rate increased from 3.9–12.2 per 100 000 population in Spain,[14] with more recent data indicating that rates remain high (13.4–22.5 per 100 000) and suggesting that CDI is under-diagnosed due to the diagnostic methods used;[15,16] in Italy, the incidence of CDI in five large hospitals in Rome increased significantly ($p < 0.001$) over the 6-year period between 2006 and 2011 (from 0.3–2.3 episodes per 1000 patient-days).[17]

The resource burden of CDI is considerable. A retrospective cohort study of infected ($n = 38$) and matched non-infected ($n = 76$) patients conducted during an outbreak of nosocomial CDI in Spain in 2006, demonstrated that patients who developed CDI were exposed to more antibiotics, had higher mortality, and were hospitalized for longer.[18] A retrospective cross-sectional study in Italy showed that CDI is associated with considerable costs in an Italian hospital setting, with length of stay (LOS) being the most important factor in determining costs,[19] although this study had methodological limitations. CDI in hospitalized children has been shown to increase the risk of death, extend hospital LOS, and increase hospital costs.[20] The general conclusion that CDI has a considerable resource impact is supported by a report showing that CDI is associated with a significant increase in attributable healthcare costs.[21] The increasing economic burden of CDI in healthcare facilities in Europe has been demonstrated, with incremental costs of infection in the range of €1857–€4266.[22] However, this study included only limited data from Spain and no information from Italy.[22]

As evidence regarding the impact of CDI on healthcare resources in southern Europe is generally scarce, the aim of this study was to analyse data on the burden of CDI in terms of hospital resources and costs, and in particular CDI-attributable LOS, in Spain and Italy.

2. Methods

2.1. Patient selection

Patients with CDI were diagnosed based on a positive *C. difficile* toxin immunoassay or positive culture for toxigenic *C. difficile* and signs and symptoms compatible with CDI (three or more unformed stools within 24 h). All patients with CDI diagnosed at the Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain (tertiary care referral hospital with a large solid organ transplantation programme and approximately 650 beds; period of data collection January 2011–November 2013), Hospital del Mar, Universitat Autònoma de Barcelona, Barcelona, Spain (tertiary care hospital with approximately 400 beds, including 18 in an intensive care unit; data collected February–November 2011), and Department of Translational Medical Science, University of Naples "Federico II", Naples, Italy (tertiary care hospital, including specialist paediatric medical and surgical departments with 50 beds; data collected 2006–2012) were included. Patients for inclusion in the study were selected randomly at the National Institute for Infectious Diseases "L. Spallanzani", Rome, Italy (tertiary care hospital with medical, surgical, and diagnostics departments and approximately 200 beds; data collected January 2011–August 2013).

2.2. Data extraction protocol

A protocol for data extraction from patient records was developed and used to collect data. For each institution, data for hospital-onset cases of CDI (infected cohort) and uninfected control patients (non-infected cohort) were collected. Hospital-onset was defined as >48 h after admission or <4 weeks after discharge from a healthcare facility (Naples only).

2.3. Matched cohort design

Each patient in the infected cohort was matched with two randomly selected uninfected control patients in the same institution. Patients were matched by ward and period of hospital admission (±15 days). For each patient in the infected and non-infected cohorts, data regarding main disease diagnosis at hospital admission, demographics, hospital department in which they were treated, and other factors potentially associated to LOS were collected. This matched cohort design was used to overcome the problem of how to assign hospital LOS data directly to *C. difficile*.

For the patients in the infected cohort, the index day was defined as the day of hospital stay when the patient was diagnosed with CDI. For those in the non-infected cohort, patients were selected randomly from those whose duration of stay was at least as long as that from the date of admission to the index day for the case with which they were matched. For these patients, the index day was defined as the same day of hospitalization as the index day of the case with which they were matched.

2.4. Data collected

To control for severity of illness before CDI infection, data required for the calculation of a modified Acute Physiology and Chronic Health Evaluation III (APACHE) score[23] were collected for all patients 48 h before the index day. The modified APACHE score did not include blood pH, pulmonary arterial oxygen saturation, pulmonary arterial gradient, urine output, or scoring for neurological abnormalities, because these data were not available for all patients in the study, particularly those not in the intensive care unit (ICU). To control for underlying disease, the Charlson comorbidity index was calculated using patient medical history.[24] It should be noted that while data for these two measures were collected for the paediatric patients, the validity of the measures for paediatric patients is uncertain.

To control for prognosis of primary disease, the McCabe–Jackson index was estimated.[25] Finally, information about previous antibiotic use was collected from the date of hospital admission to date of infection for cases, and from the date of hospital admission to the index day for controls.

The following data on CDI were collected: duration of diarrhoea, treatment for CDI, hospital LOS (including ICU and isolation days), whether sigmoidoscopy/colonoscopy was performed, and clinical outcomes, including cure, mortality at 30 days, attributable mortality, and recurrence. Based on the guidelines available at the time that patients were diagnosed,[26] recurrence was defined as a second episode of CDI based on clinical symptoms, a positive diagnostic test for *C. difficile*, or both, occurring within 2–8 weeks of the index case and within the hospital stay.

2.5. Treatment protocols

In Spain, adult patients with mild-to-moderate CDI received metronidazole 250 mg every 6 h for 10 days, whereas in Italy they received metronidazole 500 mg every 8 h for 10 days. Severe infections were treated using oral vancomycin 125–500 mg every 6 h for 10 days. Recurrences were treated using oral vancomycin