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Letter to the Editor

Epidemiology of *Clostridium difficile* infection in Portugal: Experience at a tertiary care hospital

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ABSTRACT

Background: Clostridium difficile is the main cause of healthcare-associated diarrhoea. Its incidence, severity and relapse rates increased over the past two decades.
Aim: To study epidemiologic characteristics and treatment of Clostridium difficile infection (CDI) and compare with a previous cohort from the same hospital.
Method: Retrospective analysis of clinical records of CDI diagnosed from 2010 to 2015 and comparison with data from 2004 to 2009.
Results: 259 cases were diagnosed, compared to 83 in 2004–2009. There was no difference in mean annual incidence (8.66 *versus* 7.11 per 1000 patients; $p = .116$), but a dramatic increase was observed in 2009/2010 (peak incidence: 21.63 cases per 1000 admissions). Females were more affected (61.4% *versus* 69.9%; $p = .177$). Median age was 80 and 83 ($p = .097$). We observed an increase in median number of antibiotics previously used (2 *versus* 3; $p = .147$) and in community-associated CDI (6% *versus* 19.7%; $p = .003$). There was a continued increase in the use of carbapenems and quinolones until 2010 and a high percentage of refractory cases in 2010. Female gender ($p = .043$), long-term care facility (LTCF) residency ($p = .022$) and a higher number of previous antibiotics (median of 3; $p = .025$) were independent predictors for refractory and recurrent CDI.
Conclusions: CDI incidence achieved a peak in 2009/2010 coinciding with the introduction of alcohol-based hand products, increase in quinolone and carbapenem prescription and a possible outbreak of an epidemic strain. Female gender, LTCF residency and exposure to three or more antibiotics are risk factors for refractory and recurrent CDI. We emphasize the need to restrict use of large spectrum antibiotics.

1. Introduction

The increase in *Clostridium difficile* infection (CDI) incidence and severity make *Clostridium difficile* the leading cause of infectious diarrhoea in healthcare settings [1]. While there is evidence that CDI rates have declined in England and other parts of Europe since their peak before 2010, rates have plateaued at historic highs in the United States since about 2010 [1]. A comparison within and also between countries is important so that prevention and control resources can be directed appropriately. The aim of our study was to study epidemiologic characteristics and treatment approaches of CDI and to compare with data from a historical cohort at the same tertiary care hospital in order to characterize its evolution [2].

2. Materials and methods

A retrospective study of all medical records of consecutive CDI cases between January 2010 and December 2015 from the Internal Medicine Department of the Centro Hospitalar e Universitário de Coimbra, a tertiary care hospital, was carried out. Only adult patients with consistent clinical manifestations and at least one laboratorial or histologic finding (identification of toxin A and/or B in stool samples by enzyme immunoassay or CDI compatible colonoscopy or histopathological evidence of pseudomembranous colitis) were included. We compared our data (referred as second study) with previous results from January 2004 to December 2009 (referred as first study) from the same department. Statistical analysis was performed using Statistical Package for the Social Sciences software version 23.0. Significance level was chosen at 0.05.

3. Results

From a total of 36,418 admissions between 2010 and 2015, we identified 259 patients admitted with the primary or secondary diagnosis of CDI. A historical cohort, carried out from 2004 to 2009, identified 83 patients from 9581 admissions. The overall incidence was 8.05 cases per 1000 patients and identical in both studies (8.66 *versus* 7.11 per 1000 patients; $p = .116$). However, we identified an annual increase of CDI until 2009, with a peak incidence of 21.63 cases per 1000 admissions (Fig. 1).

Female patients were more frequently affected in both studies (45.8% *versus* 61.4% with $p = .003$ in the first study and 52.2% *versus* 69.9% with $p < .0001$ in the second study). The median age was 80 in the first study and 83 in the second one.

Comparing community-associated CDI (CA-CDI) with healthcare-associated CDI (HA-CDI), we identified an increase in CA-CDI from the

Abbreviations: CDI, Clostridium difficile infection; CA-CDI, community-associated CDI; HA-CDI, healthcare-associated CDI; OR, odds ratio; LTCF, long-term care facilities

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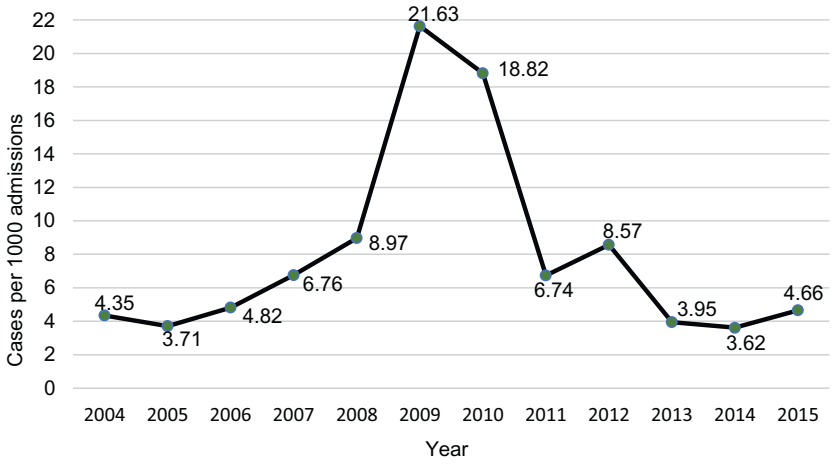

Fig. 1. Annual incidence of CDI in Coimbra, Portugal, 2004–2015.

first to the second study (6% *versus* 19.7%; $p = .003$) and a decrease of HA-CDI cases from 2010 on.

Previous exposure to antimicrobial drugs occurred in 100% of the cases in the first study and 95.8% in the second one ($p = .072$). The median number of antimicrobial drugs used previously to CDI was 2 in the first and 3 in the second study ($p = .147$). The most frequently prescribed antimicrobial drug class was beta-lactams in both studies, followed by quinolones and carbapenems. We observed a significant increase in the use of carbapenems (16.5% of all antibiotics) and quinolones (17.6% of all antibiotics) in 2010, compared to other antimicrobial drug classes ($p = .001$ and $p = .006$, respectively).

Oral metronidazole was the drug of choice for CDI treatment in both studies (88% in the first study and 64.9% in the second study; $p < .001$). This treatment was followed by oral vancomycin in 2.4% and 17.8%, respectively. In combination, they were used in 4.8 and 8.1%, respectively. Vancomycin was given as first-line drug in 1.2% and 8.9%. We identified 3 cases of successful use of fidaxomicin in recurrent CDI cases, in the second study. Molecular characterization of *Clostridium difficile* strains was not performed at our institution by then.

CDI was refractory to metronidazole in 2.4% in the first study and 17.8% in the second one. The highest percentage of all refractory cases (43.8% of 48 cases) was seen during the year 2010. A recurrence was identified in thirty-five cases (13.5%) in the second study (no data available for the first one). Regarding these difficult-to-treat CDI cases, there were more women affected ($p = .043$; odds ratio (OR) of 1.87 with a 95% confidence interval: 1.02 to 3.43), more patients from nursing homes and post hospital care units ($p = .022$; OR of 1.84 with a 95% confidence interval: 1.09 to 3.12) and a higher number of previous antibiotic exposure (median of 3 antibiotics; $p = .025$; OR of 1.19 with a 95% confidence interval: 1.02 to 1.39) in multivariate analysis. No case of fulminant CDI was described. The mortality rate decreased from 30.1% to 18.9% in the second study ($p = .031$).

4. Discussion

There are very few epidemiologic data about CDI in Portugal and about its extent in Europe [3,4]. The estimated incidence varied widely among European hospitals, from 3 to 80 per 10,000 admissions in 2008; most cases were healthcare-associated (80%), with only 14% of community-associated cases [4]. At our Department, CDI annual incidence achieved a dramatic increase in 2009/2010 and reached a plateau thereafter (Fig. 1).

A possible reason for the peak incidence in 2009 of our study could be the implementation of alcohol-based hand hygiene products in all wards from 2008 on, with a lesser use of soap and water. Although there is a theoretical possibility that these products increase the incidence of CDI because of their inability to eliminate *Clostridium difficile* spores from the hands, there have not been any clinical studies with evidence in favour of this association [5–7].

This peak incidence coincided also with the increase in quinolone and carbapenem prescription. Some studies described a higher risk for CDI in patients treated with carbapenems than with other antibiotic classes commonly related to CDI [8,9]. In the other hand, we could not link data with a possible outbreak of a clonal, epidemic strain which could explain the high incidences in 2009–2010. Another important risk factor for developing CDI was the use of multiple antibiotics [10]. CDI incidence increases with the number of antibiotics prescribed [10]. The increase in the median number of antimicrobial drugs from the first to the second study was first noted in 2008 and could have contributed to the increase in CDI rates.

As for CDI treatment, we observed a significant increase in the use of oral vancomycin from the first to the second study (3.6% *versus* 26.7%; $p < .0001$), with a peak of refractory cases registered in 2010 (43.8% of 48 cases). Our recurrence rate was similar to other published data (16%) [4]. Due to better results in clinical cure and recurrence rates, the Infectious Diseases Society of America guidelines recently recommend either vancomycin or fidaxomicin for first-line therapy over metronidazole for an initial episode of non-severe or severe CDI [1]. As shown in our study, fidaxomicin was successfully used in three cases of recurrence, which reinforces these recent orientations.

Female gender, long-term care facility (LTCF) residency and previous exposure to three or more antibiotics are risk factors for refractory and recurrent CDI. Therefore, the need to restrict the widespread and wholesale use of large spectrum antibiotics, in particular carbapenems and quinolones, and the importance of hand hygiene with soap and water should be emphasized. Controlled prospective studies and enhanced surveillance methods are needed to monitor the incidence, identify populations at risk and characterize the molecular epidemiology of strains causing CDI. Importantly, mandatory reporting of all cases should be considered in every country, in order to detect and control endemic and epidemic CDI.

Disclosure statement

The authors of this manuscript state that there are no actual or potential conflicts of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

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