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Original article

Clinical outcomes of *Clostridium difficile* infection according to strain type. A prospective study in medical wards

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ABSTRACT

Objectives: To describe clinical characteristics and outcome of *Clostridium difficile* infection (CDI) patients in Internal Medicine, to identify ribotypes (RTs); to evaluate the association between RT and patient clinical characteristics and report outcome.

Methods: One year prospective cohort study. Clinical data, Barthel Index (BI) and outcomes were collected for all inpatients suffering from CDI (n = 148) in hospital wards in Northern Italy. 84 fecal samples were analysed for molecular typing.

Results: 12 RTs were identified, predominantly RT018 (42.9%, n = 36/84) and RT356/607 (40.5%, n = 34/84). Patients with dementia were more frequent among those infected by RT018 [55.6% (n = 20/36) vs. 32.4% (n = 11/34), p = 0.05]. The median BI score of patients with RT018 was lower than BI score of patients with RT356/607 [10 (IQR 0–32) vs. 15 (IQR 5–50), p = 0.06]. RT018 infection was associated to higher levels of C-reactive protein [7.2 mg/dl (IQR 4.1–14.7) vs. 4.0 mg/dl (IQR 2.2–6.8), p = 0.01] and white blood cells ≥15,000/dl [33.3% (n = 12/36) vs. 14.7% (n = 5/34) of patients, p = 0.07]. Higher mortality was noted among RT018 infected patients. We found a continuous mortality increase according to the ATLAS score.

Conclusions: Our results confirm that RT018 and RT356/607 are the two major RTs causing CDI in older patients with a high degree of disability in Northern Italy and RT018 is associated with more serious outcomes.

1. Introduction

Clostridium difficile infection (CDI) is the most common cause of nosocomial diarrhea and one of the main healthcare associated infections (HAI) in the United States [1] and Europe [2]. In recent years diagnosis of CDI has dramatically increased worldwide [1,3] partly due to the spread of highly virulent strains, in particular those belonging to the BI/NAP1/RT027, responsible for the high rate of recurrence and mortality globally from 2001 [4,5].

The EUCLID study (European, multicentre, prospective, biannual, point-prevalence study of CDI in hospitalised patients with diarrhea) carried out between 2012 and 2013 found 125 different ribotypes (RTs) across 19 European countries. The most prevalent RTs were 027 (19%), 001/072 (11%) and 014/020 (10%), while RT078 accounted for 3% of isolates [6].

Literature indicates that the majority of CDI cases occur in medical

Abbreviations: CDI, *Clostridium difficile* infection; HAI, healthcare associated infection; RT, ribotype; PPI, proton-pump inhibitors; LOS, length of stay; CRP, C-reactive protein; SHEA-IDSA, Society for Healthcare Epidemiology of America-Infectious Diseases Society of America; CI, confidence interval; HRs, hazard ratios; IQR, interquartile range; NYHA, New York Heart Association; WBCs, white blood cells

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wards and infection is most prominent among the elderly. Advanced age is correlated with higher incidence, severity and adverse outcomes, including unresponsiveness to therapy and mortality [6–8].

RT018 is an emergent type that has been reported in Italy [9] and more recently in Korea and Japan [10]. In Italy it is becoming the prevalent strain along with RT356/607[11] and has been related to old age and complicated disease outcome [12,13]. Bauer et al. identified that old age, severe pulmonary comorbidity, previous use of fluoroquinolones and infection with RT018 are all associated with a more severe CDI [7]. Very little data are available regarding the association between strains and clinical characteristics in Italy. We conducted a prospective cohort study in medical wards in Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, a large referral hospital in Milan, Italy to describe strain types causing CDI and evaluate their association with patient clinical characteristics and outcomes. Aims of this study were to describe the CDI and to assess distribution of RTs. All cause 30, 60 and 90 day mortality rates and CDI severity defined by ATLAS score were also determined.

2. Materials and methods

2.1. Study design and definitions

A prospective cohort study was conducted between 15th March 2011 and 15th March 2012. This study involved three Internal Medicine wards (namely A, B and C respectively) and a Geriatric ward (namely D) with a total of 120 beds [14]. All cases diagnosed with CDI during the period of study were included. CDI cases were defined as a patient suffering either from diarrhea (> 3 episodes of loose stools in 24 h), ileus (vomiting, absence of stools and signs of bowel distension according to radiographic images) or toxic megacolon (distension of the colon according to radiographic images with signs of a severe systemic inflammatory response) [15], with the identification of *C. difficile* toxins or toxin-producing *C. difficile* in stool samples or pseudomembranous colitis identified by colonoscopy. Each time the microbiology laboratory found a stool sample positive for *C. difficile,* our team collected clinical data from the infected patient. Stool specimens were tested with an enzyme immunoassay for *C. difficile* toxins A and B and standard cultures were performed, however when the toxin test was negative but bacterial growth was observed in the stool cultures, a second toxin test was performed on them.

Community associated CDI was considered when symptoms started on or before the third day after admission into hospital, without contact with any healthcare facility during the previous 12 weeks. Hospital onset CDI was defined as symptoms that started after the third day from admission. Recurrent CDI was defined as an episode of CDI that occurred less than or equal to 8 weeks after the onset of a previous episode, determining that the CDI symptoms from the earlier episode had been resolved [16].

2.2. Clinical data collection and analysis

Clinical data were anonymously collected and manually reviewed and included: previous healthcare exposure (patients hospitalised for 2 days or more during the preceding 90 days, admissions from nursing home or other healthcare facilities), age, gender and comorbidities. Therapies administered during hospitalisation or during the previous 6 weeks, e.g. antibiotics and proton-pump inhibitors (PPI) and the use of medical devices were recorded. Patients' degree of disability was measured by Barthel Index: a 10-item ordinal scale used to measure performance in activities of daily living. The response categories of disability in an activity are defined and rated in scale steps dependent on the item, the overall score ranges from 0 to 100 with higher scores indicating greater independence [17].

Data for length of stay (LOS), defined as number of days spent from admission to discharge, and all cause mortality at 30, 60 or 90 days were also available for all hospitalised patients. Clinical parameters and laboratory tests were collected at the time of CDI diagnosis (or within two days) and used to assess CDI severity [18,19] and calculate ATLAS score (Table 1) [20]. We chose this score because it proved to be a validated tool and because it was consistent with the SHEA-IDSA severity classification for CDI: Mulherin et al. found that patients with an ATLAS score ≥6 were significantly more likely to have severe CDI and demonstrated moderate agreement between severe CDI, as defined by the SHEA-IDSA guidelines, and ATLAS scores ≥4 [20].

Table 1
ATLAS score [20].

Variable	0 points	1 points	2 points
Age, years	< 60	60–79	≥80
Treatment with systemic antibiotics during CDI therapy ≥1 day	No	–	Yes
Leukocyte count, cells/mm3	< 16,000	16,000–25,000	≥ 25,000
Albumin, g/dl	> 3.5	2.6–3.5	≤ 2.5
Serum creatinine, μmol/l (mg/dl)	≤ 120 (1.57)	121–179 (1.58–2.35)	≥180 (2.36)

No ethical approval is required for this study according to national law number 196, 2003 and regional law of Lombardia number 3, 2012 [21,22].

2.3. Microbiological analyses and PCR ribotyping

All fecal samples were analysed for *C. difficile* toxin A and B using the enzyme-linked immunosorbent assay (C. diff Quik Chek Complete TM, Alere) according to the manufacturer's instructions. *C. difficile* colonies were isolated on selective medium *C. difficile* agar (CDA; Oxoid) after alcoholic shock of stool samples and the commercial biochemical system Rapid ID 32A (bioMerieux) was used for *C. difficile* identification. *C. difficile* colonies were tested for the production of toxins using the same enzyme-linked immunosorbent assay mentioned above. The strains were then frozen in microvials to preserve for further analysis.

Out of 148 CDI patients, samples from only 84 patients were suitable for molecular typing: after gel electrophoresis, the banding patterns were visually examined and 24 strains, showing different RTs, were sent to the Department of Infectious Diseases at the Istituto Superiore di Sanità in Rome, Italy in order to assign a specific RT [23]. Isolates were characterised using the capillary gel electrophoresis-based PCR ribotyping described by Indra et al. [24] The WEBRIBO PCR-ribotypes were determined by submitting the data obtained from the web-based database https://webribo.ages.at, as already described [25].

2.4. Statistical analysis

To compare data from patients infected by RT018 or RT356/607 we used Wilcoxon-Mann-Whitney and chi-squared test for quantitative and categorical variables respectively. We calculated 90 day mortality rates (per 1000 bed-days) in each units and according to ribotype. Mortality at 30, 60, and 90 days after emergency admission was assessed with Kaplan-Meier failure function and the log-rank test. We then fitted univariable and multivariable Cox proportional hazard models to estimate hazard ratios (HRs) and 95% confidence intervals (CI) according to selected clinical characteristics. The analyses were performed using Stata 14 (StataCorp, College Station, TX).

3. Results

From 15th March 2011 to 15th March 2012 we identified 148 patients affected by CDI. Median age was 83 years (interquartile range, IQR 76-89) and 16 of the 148 patients were suffering from recurrent CDI. Clinical features, previous therapies, bed-days and 90 day mortality rate by units are shown in Table 2. More than a third of patients

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