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Impact evaluation of a Critical Pathway for patients with *Clostridium difficile* infection: A pre-post analysis in a Third Level Referral Center



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ABSTRACT

Background: Clostridium Difficile Infections (CDIs) have been increasing both in incidence and in severity, representing a big public health concern. *Aim:* The aim of this study was to evaluate the impact of a recently implemented Critical Pathway (CP) focused on patients with CDI in an Italian Teaching Hospital. *Methods:* The CP implementation consisted of intervention aimed to faster diagnosis and appropriateness

in admission and discharge point of care; activation of a multidisciplinary team; staff training; information to patients and caregivers.

In a pre-post retrospective observational study, volume, process and outcome indicators were analyzed. *Findings:* A total of 228 patients (128 in 2013 and 100 in 2016) were included. A decrease in the absolute number of access to the Emergency Department (p=0.02) and an increase in hospitalization in more appropriate ward (ie gastroenterology ward, p < 0.001) were found. The median hospital length of stay decreased from 20.5 (12.5–31) days in 2013 to 16.5 (7–31) days in 2016 (p=0.05). With regards to outcome indicators, an increase of discharge to home and a decrease of discharge to long term facilities were showed (p=0.01 both). Despite a reduction, no statically significant differences in mortality between 2013 and 2016 were revealed by the analysis.

Conclusion: In conclusion, we found quality improvement in patient hospital management. Our experience confirms that the implementation of the CP increases the appropriateness in hospital quality of care.

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Introduction

Over the past decade, infections related to *Clostridium difficile* – *Clostridium Difficile Infection (CDI)* – have increased in incidence and prevalence, becoming one of the leading causes of Antibiotic Associated Diarrhea in adult population (McFarland et al., 2016;

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Bartlett, 2006) and one of the major causes of infectious diarrhea in hospital (Pépin et al., 2004; Lessa et al., 2015).

As an example, USA-based studies showed that from 2001 to 2012, the annual incidence of CDI per 1,000 person-years increased by 42.7% (from 0.441 to 0.629 case) (Ma et al., 2017) and that among hospitalized adults the incidence of CDI nearly doubled between 2001 and 2010 (Reveles et al., 2014). In Quebec, Canada, among hospitalized patients, the incidence increased from 3 to 12 per 1000 persons (1991 to 2002) to 25 to 43 per 1000 persons (2003 to 2004) (Pepin et al., 2005). In Europe, according to the European Centre for Disease Prevention and Control (ECDC), the nosocomial spread of CDI has increased, from 0.039% in 1999 to 0.122% in 2007 (Anon, 2017).

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Also in Italy, the CDI incidence rates significantly increased from 2006 to 2014, up to 23.3 per 10,000 patients-days (Roncarati et al., 2017; Alicino et al., 2016; Di Bella et al., 2013; Mellace et al., 2013; Sansone et al., 2009). Furthermore, even the annual incidence of multiply recurrent CDI per 1000 person-years increased (from 2001 to 2012, by 188.8%, from 0.0107 to 0.0309 case), independently of known risk factors for CDI (Ma et al., 2017).

Looking at the burden of disease, CDI is associated with increased length of hospital stay, costs, morbidity and mortality in paediatric and adult (especially elderly) patients (Lessa et al., 2015; Gao et al., 2015; Magalini et al., 2012; Zhang et al., 2016; Petrosillo and Ravasio, 2017). According to Lessa et al., in 2011 CDI caused 29,000 deaths in the USA (Lessa et al., 2015), where it is responsible for at least \$1 billion in excess medical costs per year (CDC, 2013). A recent European analysis estimated the net cost for the CDI at around \in 3 billion (Jones et al., 2013). An analysis conducted in Italy in 2012 showed an average hospital cost for the treatment of a CDI episode of about \in 15,000, mainly due to the increase in length of hospital stay (Magalini et al., 2012). Furthermore, patients with CDI were almost twice as likely to be discharged to a long-term care facility (Lessa et al., 2015; Gao et al., 2015; Magalini et al., 2012; Zhang et al., 2016; Petrosillo and Ravasio, 2017).

Considering the described complex management and care, a Critical Pathway (CP) for patients with CDI was implemented in our Teaching Hospital, which since 2013 has been a regional centre for the treatment of CDI recurrence specialized in FMT (Ministero della Salute, 2015). Despite the high burden of disease, till now no studies have analyzed the impact of the implementation of a specific CP for patients with CDI and the overall effect of the improvement actions in a specific setting so far.

The aims of this study are to describe the CP focused on patients with CDI and to investigate the impact of the implementation of such CP in an Italian Teaching Hospital by comparing performance data in the pre- and post- CP implementation period through a selection of volume, process and outcome indicators.

Methods

Critical Pathway for patients with CDI

The critical pathways, also known as clinical or care pathways, are an evidence-based logical sequence (from a spatial and temporal - organizational - view point) affecting diagnosis, treatment and rehabilitation phases, which patients should follow from hospital admission until discharge in order to manage a specific health condition (Bucci and de Belvis, 2018), aiming to optimize patient outcomes (less post-operative complications and reduced length of stay) and team outcomes (better team communication, better documentation between professionals, better team relations and lower risk of burnout and task orientation), maximizing clinical efficiency while contributing to a better organized care processes (Campbell et al., 1998; Cheah, 1998; Bradshaw, 1999; Rotter et al., 2010; DUQuE Collaboration, 2014; Seys et al., 2017). Time required for a CP definition, design, implementation and management could vary (6-12 months) (Bucci and de Belvis, 2018).

Our CP was developed by a multi-disciplinary team (MDT) where healthcare managers, gastroenterologist, internal medicine specialist, nurses and all the professionals taking care of patients with CDI were actively involved in order to elaborate a shared path, suitable for our institution and local contest. The MDT:

- Started with the literature review focused on the health issue to apply Evidence-Based Medicine and Practice for CDI care.
- Defined patient inclusion criteria in the CP flow and the standardized, evidence-based algorithm for CDI diagnosis

(Bagdasarian et al., 2015), performed both in Emergency Department (ED) and in hospital wards. It included a real-time microbiological evaluation of the patient (Bagdasarian et al., 2015) and a multidisciplinary evaluation. In particular, to make the diagnosis in the ED timelier and appropriate a gastroenterologist consultant was called in selected cases.

- Continued with the detailed description of clinical episodes (Initial framing, Evaluation/Staging, Treatment, Rehabilitation, Follow-up/Monitoring) within different care settings, from domicile/residence, General Practitioner or Emergency Department to Hospital units/wards and long-term care facilities. In particular, the Gastroenterology unit was identified as the best pathology-related hospital setting of care, followed by Internal Medicine and Gerontology units.
- Described the patient care and management according to the diagnostic investigations and risk of recurrence. Treatment strategies, as a matter of fact, should be based on disease severity, history of prior CDI, and the individual patient's risk of recurrence. Vancomycin (for severe or complicated CDI) and metronidazole (for mild disease) are first-line therapies for most patients, although treatment failures and reoccurrence due to the reinfection or persistence of spores have been associated (Bagdasarian et al., 2015; Vardakas et al., 2012). Newer therapies, such as fidaxomicin and Fecal Microbiota Transplantation (FMT), show promising results, especially in these recurrent cases (Bagdasarian et al., 2015; Cammarota et al., 2015) and nowadays more than ever, referral FMT centres in proficient hospitals are encouraged through a more appropriate case selection (Cammarota et al., 2017).
- Pursued with the "real-life" CP development and implementation (daily utilization, development of information systems, monitoring and updating) in the hospital setting, including the continuous education of the professionals involved in patient CDI care.
- After a Gap analysis on the key points to improve quality in patient management, we identified improvement actions (Table 1) and specific periods/intervals for audit and evaluation (1 and 3 years, respectively the first and all the following).

Our CP, introducing rules of change management into the organization and reducing unnecessary variability (unwarranted variation), was aimed to respond to this specific health problem increasing quality of the assistance and services offered, achieving a faster and more appropriate diagnosis and treatment, improving patient outcomes and safety and guaranteeing a better coordination and continuity of care between settings.

Pre- and post-CP implementation study

Study design and setting

On December 2017, a pre-post retrospective cross-sectional study in a large (eg, with 1'600 beds) Italian Teaching Hospital, Fondazione Policlinico Universitario A. Gemelli IRCCS, located in Rome, was carried out in order to investigate the impact of a CP for CDI. Thus, we compared routine administrative data in the pre- and post-CP implementation period, respectively 2013 and 2016, through a selection of volume, process and outcome indicators.

The SQUIRE guidelines for reporting new knowledge about how to improve the quality, safety, and value of healthcare were used (SQUIRE, 2015).

Data collection and participants

According to the critical pathway rules, an audit to monitor (and eventually update) the CP for CDI was performed one year after the implementation period. Data used for the audit were collected from medical records retrieved from the hospital Data Warehouse and referred to:

Table 1

Improvement actions identified by the multidisciplinary team (MDT) and summarized in the CP for patient with CDI.

Observation/gap analysis	Improvement action
Absence of a MDT where all specialists would be involved for the follow-up treatment of patients with CDI Lack of timely diagnostics of patients with CDI	Activation of a MDT made up by gastroenterologists, infectious diseases physicians, nurses, microbiologists and surgeons involved for the patients' management Application a fast diagnostic algorithm for patient identification and apply protocols at the hospital admission and discharge point of care at the Emergency Department
	Activation of a prompt gastroenterologist consultation for a more timely and appropriate diagnosis in the ED.
Lack of shared criteria of critical classification	Implementation of a clinical stratification tool to standardize patient's management and therapy;
Inadequate training of health workers on CDI epidemiology and hospital management	Provision of dedicated educational training courses
Poor coordination of care between hospital and nursing home facilities	Implementation of evidence-based protocols at the hospital admission and discharge point of care
Lack of patients' knowledge of this specific health issue	Provide information and increasing communication with patients and their caregivers (eg a production of a <i>vademecum</i> to limit the spread of the CDI)

Abbreviations: MDT, multidisciplinary team; ED: Emergency Department; CDI, Clostridium Difficile Infection.

- All patients with diagnosis of CDI (ICD9-CM code: 008.45) admitted to our hospital
- Periods from January 1st, 2016 to December 31st, 2016 and from January 1st, 2013 to December 31st, 2013, the pre-and post- CP implementation period respectively. In fact, because CP was implemented between 2014 and 2015, we requested and collected data related to the years 2013 and 2016 to compare them and evaluate the CP impact.

The hospital medical records, according to the Italian law (Ministero della Salute, 2016) contain multiple information records, such as:

- Patient personal information: gender, date and place of birth, place (city and region) of residency, nationality, education, marital status;
- Hospital activity delivered to the patient: date of admission and discharge, admission from Emergency Department, diagnosis of admission, ward/unit of admission and discharge, diagnosis and procedure ICD9-CM codes to which the patient was subjected during the hospitalization, diagnosis related group (DRG) assigned to the patient.

Patient medical records not correctly registered according to hospital guidelines on medical file recording (i.e., correct clinical data reporting, ICD-9 codes, age, units etc.), including improper or missing information, were excluded.

Patients' data (medical records) were managed in conformity with the Italian Data Protection Act. The Hospital General Manager and the CP coordinator gave their consent to the study.

Statistical analysis and indicators

To estimate the impact of our CP, the following indicators were calculated through medical records related to the pre-and post- CP implementation period (patients admitted from January 1st, 2013 to December 31st, 2013 and from January 1st, 2016 to December 31st, 2016, respectively):

- 1 Number of discharged (hospitalized) patients with CDI (ICD-9: 008.45)
- 2 Percentage of patients with CDI registered as ED admission: number of hospitalized patients with CDI admitted from ED/ number of hospitalized patients with CDI
- 3 Percentage of patients transferred from ED to Gastroenterology ward: number of hospitalized patients transferred from ED to Gastroenterology ward/number of hospitalized patients admitted in ED
- 4 Percentage of patients transferred from ED to Internal Medicine ward: number of hospitalized patients transferred from ED to

Internal Medicine/number of hospitalized patients admitted in ED

- 5 Percentage of patients transferred from ED to Gerontology ward: number of hospitalized patients transferred from ED to Gerontology ward/number of hospitalized patients admitted in ED
- 6 Percentage of patients transferred from ED to other hospital units: number of hospitalized patients transferred from ED to other hospital units/number of hospitalized patients admitted in ED
- 7 Number of patients with one or more ward transfers: number of hospitalized patients transferred from one to other hospital units one or more time/number of hospitalized patients with CDI
- 8 Number of FMT procedures performed and number of patients who undergone one or more FMT procedures. This procedure is targeted towards patients with CDI treated inside and outside the hospital (e.g. in- and out-patients, respectively).
- 9 Median (and interquartile range) hospital length of stay (LOS)
- 10 Hospital mortality (crude and adjusted rate): number of patients with CDI who died in hospital/number of hospitalized patients with CDI
- 11 Percentage of patients discharged home (among patients alive at the discharge): number of patients with CDI discharged home/number of discharged patients with CDI
- 12 Percentage of patients discharged to long term facilities (among patients alive at the discharge): number of patients with CDI discharged to long-term facilities/number of discharged patients with CDI

A descriptive statistical analysis was performed using absolute and relative frequencies, mean and standard deviation (SD), median and interquartile range (IQR) when appropriate. Statistically significant differences were tested through t-test, Wilcoxon rank-sum (Mann–Whitney) test, Chi-square test, as applicable. The delta variation among volumes, percentages or median LOS was calculated to better analyze changes before and after the CP implementation. Uni- and multi-variate analysis were performed to evaluate the main appropriateness indicator of the CP (namely the indicator n. 3 according to the rules of our implemented CP) and the hospital mortality rate, the most important outcome indicator of our CP but less directly related to its impact.

The statistical significance level was set at p < 0.05 and all the analyses were carried out by using STATA software.

Results

Impact of the CP implementation: a pre- post-analysis

To estimate the impact of our specific CP through the comparison of the selected volume, process and outcome indicators, medical records of patients hospitalized with CDI related to the years 2013 and 2016 (respectively the pre-and post- CP implementation period) were collected.

The final sample consisted of 228 patients, 128 hospitalized in 2013 (patients admitted from January 1st, 2013, to December 31st, 2013) and 100 in 2016 (patients admitted from January 1st, 2016 to December 31st, 2016). The mean age was 76.4 (\pm 16.2) in 2013 and 76.7 (\pm 12.5) in 2016. The prevalence of CDI is higher among female and elderly. Demographic characteristics and diagnosis of admission of our sample are reported in Table 2.

Table 3 shows the indicators results utilized for evaluate the CP impact.

The percentage of patients registered as ED admission increased from 81.2% in 2013 to 92% in 2016 (+13.2%, p = 0.02), despite an overall decrease of hospital admission for patient with CDI diagnosis (-21.9%).

The percentage of patients with CDI transferred from ED to the Gastroenterology ward, the main pathology-related hospital unit indicated by the CP for the appropriate treatment and management of CDI, increased significantly (+329.3%, p < 0.001). A significant reduction in transfers from ED to Gerontology ward (-52.9%, p = 0.02) and to Internal Medicine ward (-40.8%, p = 0.01) were also registered. Instead, the percentage of patients transferred from ED to other hospital units, despite a reduction, seems not to be significantly influenced by the CP rules. Results from the multivariate analysis to investigate the capacity of the CP to appropriately and in a timely manner address patients admitted through the ED in the Gastroenterology unit (Table 4) showed that there was a significant improvement in the flow of patients through this specific ward over the two years considered (OR adj 6.59, 95% CI 3.01–14.40; p < 0.001).

The percentage of patients with one or more ward transfers increased between 2013 and 2016, but not in a statistically significant way.

The number of FMTs performed and number of patients who underwent one or more FMT procedures increased drastically between the two years considered.

Table 2

Characteristics of the study sample "patients hospitalized with CDI (ICD-9: 008.45)".

	2013	2016	p Value	
	N (%)	N (%)		
Patients sample Gender	128	100		
Male	42 (32.8%)	26 (26%)	0.27	
Female	86 (67.2%)	74 (74%)		
Years of Age (median, IQR) Age (class)	80.4 (71.5-85.2)	79.3 (72.1-84.7)	0.37	
<65y	18 (14.1%)	14 (14%)	0.99	
≥65y	110 (85.9%)	86 (86%)		
Region of provenance				
Lazio	120 (93.8%)	98 (98%)	0.12	
Others	8 (6.2%)	2 (2%)		

The average length of stay decreased, from 24.4 (\pm 18.4) days in 2013 to 20.7 (\pm 17.4) days in 2016, such as the median length of stay, from 20.5 (12.5–31) to 16.5 (7–31) (p = 0.05).

Although a reduction in hospital mortality was shown between 2013 and 2016 (-21.2%), no statically significant difference was revealed by the crude analysis (p = 0.41). Results from the multivariate analysis performed to better investigate the capacity of the CP implementation to have an impact on mortality according to gender, years of age, LOS, and complexity of care and treatment setting characteristics (Table 5) confirmed the absence of a statically significant difference in hospital mortality, but revealed that it was significantly negatively related to patient's age (OR adj 1.06, 95% CI 1.01–1.11; p = 0.01) and one or more intra-hospital transfers between wards (OR adj 5.96, 95% CI 2.04–17.45; p = 0.001) and positively related with the gastroenterology unit as recovery ward in comparison with internal medicine (especially), gerontology and other units.

Comparing 2013 and 2016 discharge data of patients, a decrease in the number of discharges to long term facilities (-50.0%)

Table 3

Results of the audit of CP for patients with CDI.

Indicators	2013	2016	Δ% '13–'16	p Value
Discharged patients with CDI diagnosis	128	100	-21.9%	
% of patients registered as ED admission	104 (81.2%)	92 (92.0%)	+13.2%	0.02
% of patients transferred from ED to Gastroenterology ward	10/104 (9.6%)	38/92 (41.3%)	+329.3%	< 0.001
% of patient transferred from ED to Internal Medicine ward	42/104 (40.4%)	22/92 (23.9%)	-40.8%	0.01
% of patient transferred from ED to Gerontology ward	24/104 (23.1%)	10/92 (10.9%)	-52.9%	0.02
% of patient transferred from ED to other hospital units	28/104 (26.9%)	22/92 (23.9%)	-11.2%	0.63
Number of patients with one or more ward transfers	28 (21.9%)	24 (24.0%)	+9.7%	0.7
FMT procedure (number of procedures, number of patients who undergone FMT)	9 (7 pts)	49 (30 pts)	+444.4% (+328.6%)	
Length of stay in days (median, IQR)	20.5 (12.5-31)	16.5 (7-31)	-19.5%	0.05
Hospital mortality (crude)	26 (20.3%)	16 (16.0%)	-21.2%	0.41
Discharge home among patients alive at the discharge	68/102 (66.7%)	70/84 (83.3%)	+25.0%	0.01
Discharge to long term facilities among patients alive at the discharge	34/102 (33.3%)	14/84 (16.7%)	-50.0%	0.01

Sampling: All patients of the reference time (from January 1st, 2013, to December 31st, 2013, and from January 1st, 2016 to December 31st, 2016). Sources: Medical records, hospital information system, hospital discharge chards (ICD-9: 008.45).

Table 4

Multivariate analysis to analyze the patients flow from ED to gastroenterology unit.

		Crude Odds Ratio (95% confidence interval)	Adjusted Odds Ratio (95% confidence interval)	p Value (adj)
Year	2013 2016	Rif 6.61 (3.05–14.33)	6.59 (3.01-14.40)	<0.001
Gender	Female	Rif	· · · ·	
	Male	0.55 (0.25-1.19)	0.67 (0.29-1.54)	0.34
Years of age		1.00 (0.98–1.03)	1.01 (0.98–1.04)	0.50

Table 5

CP impact on hospital mortality, multivariate analysis.

		Crude Odds Ratio (95% confidence interval)	Adjusted Odds Ratio (95% confidence interval)	p Value (adj)
Year	2013	Rif		·
	2016	0.75 (0.38-1.48)	0.90 (0.40-2.01)	0.80
Gender	Female	Rif	. ,	
	Male	0.69 (0.32-1.50)	0.58 (0.24-1.41)	0.23
Years of age		1.06 (1.02–1.10)	1.06 (1.01-1.11)	0.01
Length of stay (days)		1.01 (1.00-1.03)	1.00 (0.98-1.02)	0.99
Number of wards transfers	None	Rif	. ,	
	One or more	2.56 (1.25-5.27)	5.96 (2.04-17.45)	0.001
Patient recovery ward	Gastroenterology	Rif	. ,	
	Internal Medicine	4.50 (1.42-14.28)	4.66 (1.26-17.3)	0.02
	Gerontology	2.82 (0.79-10.14)	2.03 (0.48-8.69)	0.34
	Others	2.57 (0.78-8.50)	1.82 (0.43-7.73)	0.42

p = 0.01) and an increase of discharge home (+25.0%, p = 0.01) were showed.

Discussion

Our study described the CP for patients with CDI implemented in our Italian Teaching Hospital and investigated the impact of such a CP, showing a positive effect on patients' care and management, confirming that use of evidence-based practice, contextualization of the evidences, clinical involvement and implementation of a MDT, development of Information Systems according to "patient centered" analytics, Gap analysis, audit and feedback are fundamental components for an effective development and implementation of a CP (Rotter et al., 2010).

According to our knowledge this is the first research aiming at evaluating the impact of a CP focused on the management of patients with CDI analyzing process and outcome indicators.

The demographic characteristic of our sample corroborates the international literature epidemiology of patients with CDI: even in our sample the prevalence was higher in women than in men and in individuals aged \geq 65 years than in those aged <65 (Ma et al., 2017).

Our results showed an increased percentage in patients admitted from the ED and a reduction on patient discharged with a CDI diagnosis. This would be explained through a better management of patients in the ED thanks to the application of the diagnostic algorithm and timely management so to prevent hospitalization.

Passing through the comparison of the selected process indicators in the considered time interval, the CP application led to an increased and more appropriate access of patients from ED to Gastroenterology wards and a decrease of hospital mortality and length of stay, confirming literature evidence (Rotter et al., 2010; Bucci et al., 2016). These findings were also confirmed by applying multivariate analysis (Table 4). Beside the increased flow of patients with CDI diagnosis towards a more specialized hospital setting, a decrease in the number of patients admitted to other wards was observed in our study. We can suppose that this decrease has been due to the implementation of the CP, which had an impact on the patient care flow through Gastroenterology of patients previously directed to Gerontology, Internal Medicine and other wards. This choice was based on the highly integrated care needs of these patients. To treat patients with CDI in the Gastroenterology unit is also likely to be linked with a lower risk of mortality by applying a multivariate analysis to consider the role of demographic and care complexity variables. The Gastroenterologist is the preferable specialist of care for patients with CDI, especially in the severe/complicated infection and referral for FMT if multiple recurrences occur (Surawicz et al., 2013). It is reasonable to conclude that this could result in a less inappropriate use of hospital resources and, consequently, a wider availability of resources for other patients, which can be considered, without doubt, an important achievement of the CP. Of course, further analyses are needed to address this point.

The increase of patients treated through FMT would be explained by the leading role of our teaching hospital in FMT besides a more appropriate overall management. An appropriate and high safety and quality standard approach would encompass even the global management of patients, from CDI diagnosis to FMT procedure. Our research confirms that the application of a CP is likely to guarantee better quality in health care management towards in- and out-patients.

Regarding outcome indicators, we investigated mortality and hospital length of stay. According to our results, either mortality (crude data: 20.3% in 2013 to 16.0% in 2016), and hospital average and median length of stay have been reduced from the CP implementation, although no statically significant difference was revealed by the analysis. By adjusting according to demographic and complexity of care characteristics, our analysis found a lower risk in mortality in patients treated in Gastroenterology, if compared with Internal Medicine, thus confirming a more effective role in patient management of this setting.

Limits

This study has several limitations. First of all, it is a single-centre observational cross-sectional study, with a relatively small sample size, which describes the association between exposure and outcome, without the possibility to determine direct causation. Due to the lack of direct causation it is not possible to conclude that the CP by itself led to a better outcome. This study design, in fact, has the strength of temporality to be able to suggest that the outcome is impacted by the intervention, however, it does not have control over other elements that are also changing at the same time as the intervention is implemented. Therefore, changes in disease occurrence during the study period cannot be fully attributed to the specific intervention (Thiese, 2014). Regardless, the choice for a pre-post retrospective observational study design has already been successfully applied in other studies (Murri et al., 2016). Likewise, in this study it was considered most suitable to evaluate the likely improvements in CDI patient care and management and to reveal patient flow changes after the CP implementation. Moreover, although the design was monocentric, the quality improvement activity was implemented in one of the biggest third level referral Italian hospitals where the application of this CP led to a reduction in relevant measures in terms of quality of care (eg shorter lengths of stay, reduction in mortality rates). Secondly, we detected our metrics from the hospital medical records. Even if we excluded those which were not correctly recorded, it was not possible to assure the data reliability. Finally, current metrics for evaluating critical pathway impact do not consider patients' perspective as Patient Reported Outcomes Measures (PROMs) or Patient Reported Experience Measures (PREMs).

Conclusions

Our analysis seems to confirm a positive impact of the CP implementation for patient with CDI on patient flow, length of stay and appropriateness on the point of care. The success of CP is due to a multifaceted intervention based on organizational, training, technological and knowledge innovation. Such a challenge would represent a sustainable answer to the dramatic increase of CDI concern in health care organization. Future research is needed to re-evaluate the individuated and other indicators after a longer time period.

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Conflict of interest statement

We declare no conflict of interest.

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References

- Alicino C, Giacobbe DR, Durando P, Bellina D, Di Bella AM, Paganino C, et al. Increasing incidence of *Clostridium difficile* infections: results from a 5-year retrospective study in a large teaching hospital in the Italian region with the oldest population. Epidemiol Infect 2016;144:2517–26, doi:http://dx.doi.org/ 10.1017/S0950268816000935.
- Anon. European surveillance of *Clostridium difficile* infections surveillance protocol version 2.3. 2017 Stockholm.
- Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of Clostridium difficile in adults. JAMA 2015;313:398, doi:http://dx.doi.org/10.1001/jama.2014.17103.
- Bartlett JG. Narrative review: the new epidemic of *Clostridium difficile*-associated enteric disease. Ann Intern Med 2006;145:758–64.
- Bradshaw MJ. Clinical pathways: a tool to evaluate clinical learning. J Soc Pediatr Nurs 1999;4:37–40.
- Bucci S, de Belvis AG. Come organizzare l'assistenza del paziente per percorsi di cura L'esperienza presso la Fondazione Policlinico Universitario. Vita e Pensiero; 2018.
- Bucci S, de Belvis AG, Marventano S, De Leva AC, Tanzariello M, Specchia ML, et al. Emergency department crowding and hospital bed shortage: is Lean a smart answer? A systematic review. Eur Rev Med Pharmacol Sci 2016;20:4209–19.
- CDC. Antibiotic resistance threats in the United States, 2013. Current 2013;114: CS239559-B.
- Cammarota G, Masucci L, Ianiro G, Bibbò S, Dinoi G, Costamagna G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection. Aliment Pharmacol Ther 2015;41:835–43, doi:http://dx.doi.org/10.1111/ apt.13144.
- Cammarota G, Ianiro G, Tilg H, Rajilić-Stojanović M, Kump P, Satokari R, et al. European consensus conference on faecal microbiota transplantation in clinical practice. Gut 2017;66:569–80, doi:http://dx.doi.org/10.1136/gutjnl-2016-313017.
- Campbell H, Hotchkiss R, Bradshaw N, Porteous M. Integrated care pathways. BMJ 1998;316:133–7.
- Cheah TS. The impact of clinical guidelines and clinical pathways on medical practice: effectiveness and medico-legal aspects. Ann Acad Med Singapore 1998;27:533–9.
- DUQuE Collaboration. Seven ways to improve quality and safety in hospitals an evidence based guide. 2014.

- Di Bella S, Musso M, Cataldo MA, Meledandri M, Bordi E, Capozzi D, et al. *Clostridium difficile* infection in Italian urban hospitals: data from 2006 through 2011. BMC Infect Dis 2013;13:146, doi:http://dx.doi.org/10.1186/1471-2334-13-146.
- Gao T, He B, Pan Y, Deng Q, Sun H, Liu X, et al. Association of *Clostridium difficile* infection in hospital mortality: a systematic review and meta-analysis. Am J Infect Control 2015;43:1316–20, doi:http://dx.doi.org/10.1016/j. ajic.2015.04.209.
- Jones AM, Kuijper EJ, Wilcox MH. Clostridium difficile: a European perspective. J Infect 2013;66:115–28, doi:http://dx.doi.org/10.1016/j.jinf.2012.10.019.
- Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med 2015;372:825– 34, doi:http://dx.doi.org/10.1056/NEJMoa1408913.
- Ma GK, Brensinger CM, Wu Q, Lewis JD. Increasing incidence of multiply recurrent *Clostridium difficile* infection in the United States: a cohort study. Ann Intern Med 2017;167:152, doi:http://dx.doi.org/10.7326/M16-2733.
- Magalini S, Pepe G, Panunzi S, Spada PL, De Gaetano A, Gui D. An economic evaluation of *Clostridium difficile* infection management in an Italian hospital environment. Eur Rev Med Pharmacol Sci 2012;16:2136–41.
- McFarland LV, Ozen M, Dinleyici EC, Goh S. Comparison of pediatric and adult antibiotic-associated diarrhea and *Clostridium difficile* infections. World J Gastroenterol 2016;22:3078, doi:http://dx.doi.org/10.3748/wjg.v22. i11.3078.
- Mellace L, Consonni D, Jacchetti G, Del Medico M, Colombo R, Velati M, et al. Epidemiology of *Clostridium difficile*-associated disease in internal medicine wards in northern Italy. Intern Emerg Med 2013;8:717–23, doi:http://dx.doi. org/10.1007/s11739-012-0752-6.
- Ministero della Salute. Decreto 2 aprile 2015, n. 70. Regolamento recante definizione degli standard qualitativi, strutturali, tecnologici e quantitativi relativi all'assistenza ospedaliera. (15C00084) (GU n.127 del 4-6-2015). 2015 https:// dx.doi.org/10.1017/CB09781107415324.004.
- Ministero della Salute. Decreto 7 dicembre 2016, n. 261 Regolamento recante modifiche ed integrazioni del decreto 27 ottobre 2000, n. 380 e successive modificazioni, concernente la scheda di dimissione ospedaliera. (17G00015) (GU Serie Generale n.31 del 07-02-2017). 2016. https://dx.doi.org/10.1017/ CB09781107415324.004.
- Murri R, de Belvis AG, Fantoni M, Tanzariello M, Parente P, Marventano S, et al. Impact of antibiotic stewardship on perioperative antimicrobial prophylaxis. Int J Qual Heal Care 2016;28:502–7, doi:http://dx.doi.org/10.1093/intqhc/mzw055.
- Pépin J, Valiquette L, Alary M-E, Villemure P, Pelletier A, Forget K, et al. Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ 2004;171:466–72, doi:http://dx.doi.org/ 10.1503/cmaj.1041104.
- Pepin J, Valiquette L, Cossette B. Mortality attributable to nosocomial *Clostridium difficile*-associated disease during an epidemic caused by a hypervirulent strain in Quebec. Can Med Assoc J 2005;173:1037–42, doi:http://dx.doi.org/10.1503/ cmaj.050978.
- Petrosillo N, Ravasio R. Il Costo Ospedaliero di Trattamento di un Episodio di Infezione da Clostridium Difficile in Italia. Glob Reg Heal Technol Assess Ital North Eur Spanish 2017;4:, doi:http://dx.doi.org/10.5301/grhta.5000257 grhta.5000257.
- Reveles KR, Lee GC, Boyd NK, Frei CR. The rise in *Clostridium difficile* infection incidence among hospitalized adults in the United States: 2001-2010. Am J Infect Control 2014;42:1028–32, doi:http://dx.doi.org/10.1016/j. ajic.2014.06.011.
- Roncarati G, Dallolio L, Leoni E, Panico M, Zanni A, Farruggia P. Surveillance of *Clostridium difficile* infections: results from a six-year retrospective study in nine hospitals of a North Italian local health authority. Int J Environ Res Public Health 2017;14:, doi:http://dx.doi.org/10.3390/ijerph14010061.
- Rotter T, Kinsman L, James EL, Machotta A, Gothe H, Willis J, et al. Clinical pathways: effects on professional practice, patient outcomes, length of stay and hospital costs. Cochrane Database Syst Rev 2010;CD006632, doi:http://dx.doi.org/ 10.1002/14651858.CD006632.pub2.
- SQUIRE. Revised standards for quality improvement reporting excellence (SQUIRE 2.0). 2015 http://www.squire-statement.org/index.cfm?fuseaction=Page.View-Page&pageId=471. [Accessed October 16, 2018].
- Sansone S, Aschbacher R, Staffler M, Bombonato M, Girardi F, Larcher C, et al. Nosocomial diarrhoea in adult medical patients: the role of *Clostridium difficile* in a North Italian acute care teaching hospital. J Prev Med Hyg 2009;50:117–20.
- Seys D, Bruyneel L, Deneckere S, Kul S, Van Der Veken L, Van Zelm R, et al. Better organized care via care pathways: a multicenter study. PLoS One 2017;12:1–11, doi:http://dx.doi.org/10.1371/journal.pone.0180398.
- Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al. Guidelines for diagnosis, treatment and prevention of *Clostridium difficile* infections. Am J Gastroenterol 2013;108:478–98, doi:http://dx.doi.org/10.1038/ ajg.2013.4.
- Thiese MS. Observational and interventional study design types; an overview. Biochem Medica 2014;24:199–210, doi:http://dx.doi.org/10.11613/ BM.2014.022.
- Vardakas KZ, Polyzos KA, Patouni K, Rafailidis PI, Samonis G, Falagas ME. Treatment failure and recurrence of *Clostridium difficile* infection following treatment with vancomycin or metronidazole: a systematic review of the evidence. Int J Antimicrob Agents 2012;40:1–8, doi:http://dx.doi.org/10.1016/j.ijantimicag.2012.01.004.
- Zhang S, Palazuelos-Munoz S, Balsells EM, Nair H, Chit A, Kyaw MH. Cost of hospital management of *Clostridium difficile* infection in United States—a meta-analysis and modelling study. BMC Infect Dis 2016;16:447, doi:http://dx.doi.org/10.1186/ s12879-016-1786-6.