Research paper

Clostridium difficile outbreak: epidemiological surveillance, infection prevention and control

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Keywords

Clostridium difficile outbreak • Infection prevention • Epidemiological surveillance • Joinpoint regression • *Clostridioides difficile* infection

Summary

Introduction. *Clostridium difficile infection (CDI) is currently considered the most common cause of health care-associated infections. The aim is to describe the trend of CDI in an Italian hospital and to assess the efficacy of the measures adopted to manage the burden.*
Methods. *Data were retrieved in the San Salvatore Hospital of L'Aquila, from 1 January 2016 to 31 December 2018. Incidence rate of CDIs was calculated as the number of new infected persons per 10,000 patient-days. Changes in the CDI rate during the period considered were analysed using a Joinpoint regression model and related to the preventive strategies adopted. The strategies adopted focused mainly on patient isolation, reinforcement of proper hand hygiene techniques, antimicrobial stewardship and environmental disinfection.*
Results. *CDI/10,000 patient-days was 6.27 in 2016 and increased to 7.71 in 2017, then drastically decreased to 2.76 during 2018. The Joinpoint regression analysis identified three Joinpoints: Sep-2016, Jan-2017, and Sep-2017. There was a reduction from 2016/01 to 2016/09 (slope = -1.44; p = 0.67), then there was an increase from September 2016 to February 2017 (slope = 30.01; p = 0.29), both statistically not significant. Therefore, there was an important decrement from February 2017 to September 2017, statistically significant (slope = -15.84; p = 0.012).*
Conclusions. *Reports based on routine laboratory data can accurately measure population burden of CDI with limited surveillance resources. The adoption of multi-pronged strategies has proven effective in reducing CDI. It's important to keep attention high regarding preventive measures of CDI, also a continuous joint effort by all health professionals, caregivers and patients is needed.*

Introduction

Clostridium difficile (CD) is a Gram-positive anaerobic bacterium. This spore-forming bacillus can be found in a wide range of habitats, from soil and water to the intestines of animals, including humans (3-5% of human adults) and it is transmitted along the fecal-oral route. The principal virulence factors of the microorganism are exotoxin proteins, toxin A and toxin B, produced by the pathogenic strains of CD. Diseases caused by CD can range in severity from mild diarrhea to fulminant pseudomembranous colitis and, without suitable treatment, toxic megacolon and death. It has been associated mainly with hospitals, where it occurs both endemically and epidemically. *Clostridium difficile* infection (CDI) is one of the most important healthcare-associated infections in industrialized countries. In particular, it is considered the most common etiology of nosocomial diarrhea [1].
During the last few years, social and health changes led to an increase in this type of infection: over the past 20-years, hospital-acquired CDI has become more frequent, more severe, and more likely to recur or relapse after standard therapy. This increased severity has been attributed to the emergence of hypervirulent strains such as ribotype 027 or NAP1 or ribotype 078 which have been documented worldwide [2]. A recent systematic review and meta-analysis found a CDI incidence of 2.24 per 1,000 admissions per year and 3.54 per 10,000 patient-days per year; the rate of cases in the general population, for all ages, is 41.94 per 100,000 population per year [3]. The cases of CDI have led to an increase in mortality and morbidity, especially in older adults. Mortality is at least 6% within 3 months of diagnosis and 13% in patients > 80 years old. In addition, CDI has a significant economic impact on the healthcare system and is a cause of burden on healthcare institutions. The average length of hospitalization is increased by 14 days and the attributable cost per adult patient was about €10,000, with the majority of the cost being due to hospitalization [4]. Nosocomial transmission is the most frequent for this type of infection, in this context, practical measures for reducing infection are crucial to prevent and control the spread of CDI [5]. Thus, epidemiological surveillance and control measures take a central role in countering CDI.
The present study aimed to describe the trend of CDI in an Italian hospital, by investigating an outbreak which

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occurred between October 2016 and April 2017, and assessing the efficacy of the control measures adopted to manage the burden.

Methods

Data collection

Data were retrieved in the San Salvatore Hospital of L'Aquila, in Abruzzo, a region in the center of Italy, from January 1st 2016 to December 31st 2018. The study was authorized by the Hospital Management of San Salvatore Hospital, and the data were treated anonymously.

We analyzed the laboratory database to identify CDIs in patients over 18 years of age: we defined a "case" of CDI as a positive *Clostridium difficile* toxin assay from a stool specimen.

Data related to tests from outpatient facilities, extra-hospital facilities, and inappropriate tests were excluded. The latter were selected according to the European surveillance protocol for CD [6]: tests were repeated within 2 weeks of the first positive test. Therefore, positive tests during the 2-8 weeks after the first positivity were considered "recurrences".

Preventive protocol

On January 1st 2017 the Hospital Management of San Salvatore Hospital adopted preventive strategies to face the increasing cases of CDI. Strategies were categorized as: (1) diagnosis and surveillance; (2) hand hygiene; (3) patient isolation and personal equipment; (4) glove and protective clothing use; (5) reception, transport, transfer, and discharge of patients; (6) environmental cleaning; (7) management of medical devices, linen, dishes and waste; (8) antibiotic stewardship; and (9) education and information for staff, patients and caregivers. The indications contained allow for the prompt identification CDI cases and to guarantee correct management during hospitalization until discharge.

Diarrheal fecal samples from patients with suspected infection by CD were tested using an Intermedical CLOSTRIDIUM TRIO TOSSINA A/B/GDH kit, which detects both the presence of the glutamate dehydrogenase (GDH) antigen, and the presence of the A and B toxins. A positive test for the GDH antigen and one of the two toxins is sufficient to confirm the diagnosis of CDI.

Once the positive isolates were identified, the following interventions were implemented to reduce the incidence of CD colonization and infection:

- placing patients in contact isolation;
- soap and water hand hygiene;
- report the isolation to Hospital Management;
- development of an educational tool for patients and visitors;
- formulary restriction to prevent overuse of offending antibiotics.

The protocol provides that the room cleaning procedure be carried out by personnel equipped with adequate personal protection twice a day using chlorinated at 1,000 ppm. The cleaning procedure includes all lateral environmental surfaces frequently in contact with the patient and reusable medical equipment. Moreover, a patient who is suspected of CD infection is placed in contact isolation where there is room cleaned, and stool specimens are collected to determine if they are CD antigen positive.

Training courses and flyers were used to educate direct patient care staff regarding cross-contamination via the environment as a real possibility in this type of patient. In addition, patients and visitors are kept up to date with all the information regarding the transmission of the pathogen.

Statistical analysis

The incidence rate of CDIs was calculated as the number of newly infected persons for each month by the overall length of stay (incidence per 10,000 patient-days). In addition, positivity rates on the tested samples were calculated. The denominators were obtained through the SISWeb, a suite of interacting programs that allow for the management of the entire course of treatment of both outpatients and inpatients, and the collection of data from each health event, data for the clinical dossier. Changes in the CDI rate during the period considered were analyzed using a joinpoint regression model. Joinpoint regression model analyses rates, proportions, and any other measure that can be considered (e.g., counts), to study statistically significant changes in the trend and their locations within the model time [7]. We performed two models: in the first, the dependent variable was the CDI rate per 10,000 patient-days without log transformation and the independent variable was the time (months); in the second, the dependent variable was "crude rate x 100" (CDI/requests x 100) without log transformation and the independent variable was the time (months). We assumed that the random errors in the regression model were Poisson, and we estimated the regression coefficients by weighted least squares for the model $y = xb$, using the Joinpoint Regression Program (version 4.7.0.0 *https://surveillance.cancer.gov/joinpoint*).

Results

From January 2016 to December 2018, 1994 stool samples were tested for CD and 248 (12.4%) were positive. Positive tests corresponded to 186 CDI episodes, regarding 149 persons. Patient characteristics are summarized in Table I.

The number of stool samples tested increased from 597 in 2016 to 846 in 2017, then decreased to 551 in 2018. The numbers of infections were 70 in 2016, 85 in 2017, and 31 in 2018. The proportion of these samples tested as positive was stable in 2016 (11.7%) and 2017 (10.1%), then it was halved in 2018 (5.6%). The highest proportion of CDI episodes on tested samples was observed in surgical wards (10%), closely followed by medical wards (9.4%), whereas Intensive Care Units showed the lowest proportion (4.5%). However, the

Tab. I. Patient characteristics.

	2016, n(%)	2017, n(%)	2018, n(%)	Total, n(%)
Sex				
Male	25 (43.1%)	28 (37.9%)	16 (64%)	69 (46.3%)
Female	33 (56.9%)	38 (62.1%)	9 (36%)	80 (53.7%)
Average length of stay (days)	25.0	23.8	30.4	25.4
Ward				
Surgical	10 (17.2%)	14 (21.2%)	0	24 (16.1%)
Medical	48 (82.8%)	50 (75.8%)	24 (96%)	122 (81.9%)
Intensive care	0	2 (3%)	1 (94%)	3 (2%)
Age				
< 60 years	10 (17.2%)	4 (6.1%)	3 (12%)	17 (11.4%)
60 -75 years	18 (31.1%)	16 (24.2%)	6 (24%)	40 (26.8%)
> 75 years	30 (51.7%)	46 (69.7%)	16 (64%)	92 (61.8%)

raw number of cases in medical wards far outpaced others with a total of 157 CDI cases (84%). 84% of CDI occurred in medical ward, followed by Surgical (14%) and by Intensive Care Unit (2%).

The incidence during the considered period was 5.53/10,000 patient-days (95% CI: 4.73-6.32). During 2016, CDI/10,000 patient-days was 6.27 and increased to 7.71 in 2017, then drastically decreased to 2.76 in 2018, as shown in Figure 1.

The Joinpoint regression analysis identified three Joinpoints in the first model: sep-2016, jan-2017, and sep-2017 (Fig. 2). These points divided the trend line into four linear segments, each with a different slope. There was a moderate reduction during the time range 2016/01-2016/09 (slope = -1.44; p = 0.67), then there was an increase from September 2016 to February 2017 (slope = 30.01; p = 0.29), both statistically not significant. Therefore, there was an important decrement from February 2017 to September 2017, statistically significant (slope = -15.84; p = 0.012). Finally, in the last segment, the trend was fairly stationary with a not significant slope = 0.16 (p = 0.78).

In the second model, the Joinpoint regression analysis identified two Joinpoints: feb-17 and oct-17 (Fig. 3). These points divided the trend line into three linear segments, each with a different slope. There was an increment during the time range January 2016 - February 2017 (slope = 0.86; p = 0.043), then there was a decrement from February 2017 to October 2017 (slope = -1.54; p = 0.039), both statistically significant. Finally, in the last segment, the trend was fairly stationary with a not significant slope = 0.10 (p = 0.57).

Discussion

Several studies reported that the incidence and severity of CDI have been increasing in recent years across the United States, Canada, and Europe. It is now considered the most common cause of healthcare-associated infection: therefore, it requires continuous active surveillance. Public health surveillance is the ongoing systematic collection, analysis, and interpretation of data, closely integrated with the timely dissemination of these data to those responsible

Fig. 1. Incidence CDI/10,000 patient-days by month.

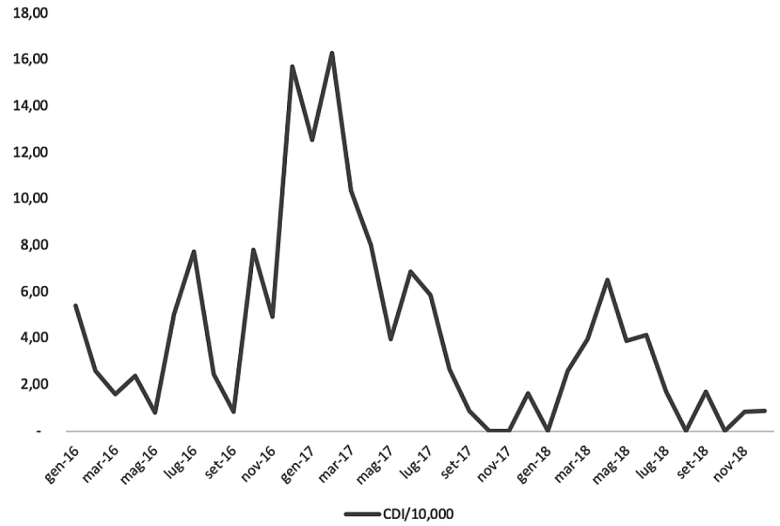


Fig. 2. Distribution of CDI/10,000 patient-days by month.

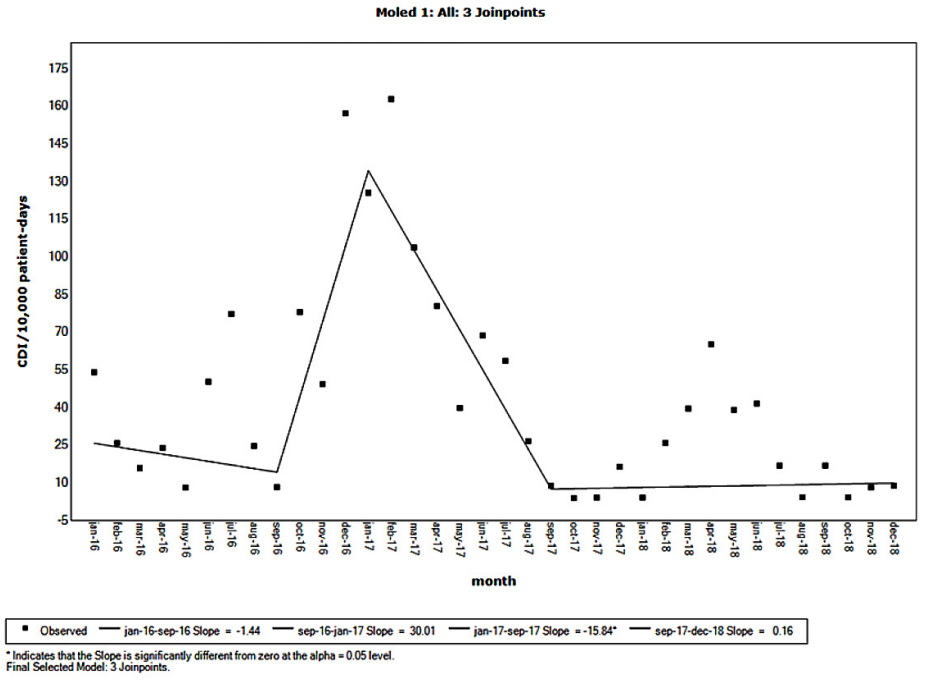
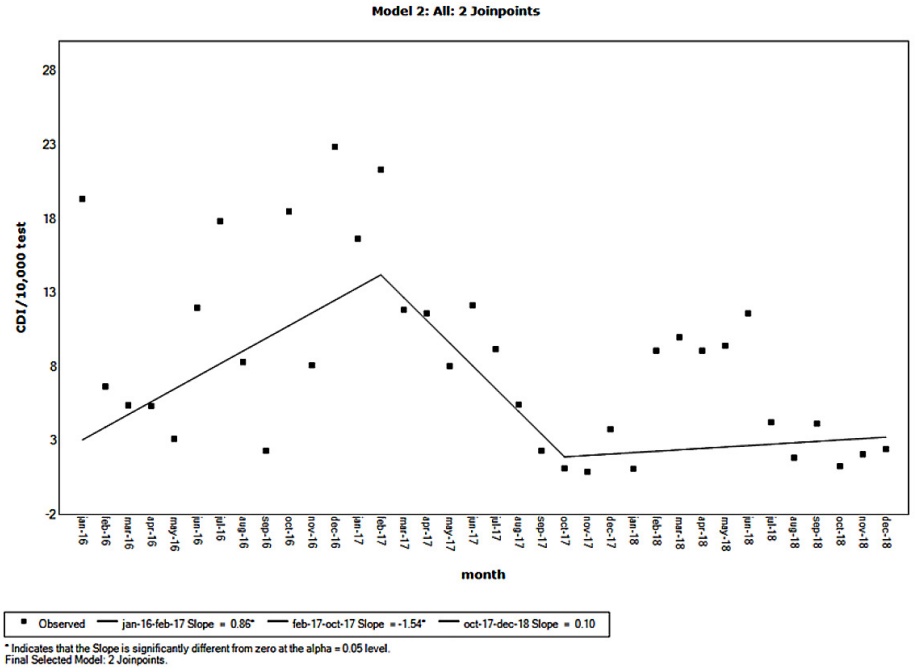


Fig. 3. Distribution of CDI/request x 100 by month.



for preventing and controlling disease and injury.[9] In particular, a laboratory-based surveillance system is an important cornerstone in the control of CDI: it allows for the detection of changes in local epidemiology and to provides information to guide decisions. Thanks to the surveillance activity it was possible to manage the outbreak that occurred between October 2016 and April 2017 by implementing new preventive strategies.

In particular, during 2016 and 2017 we reported an incidence of CDI episodes per 10,000 patient-days equal to 6.27 (CI 95%: 4.81-7.74) and 7.71 (CI 95%: 6.06-9.34) respectively. The increase in 2017 is mainly due to the high number of cases observed in the first three months of the year. These data are greater than those reported in the ECDC report, both for Europe and Italy, 3.98 (CI 95%: 3.45-4.51) and 2.76 respectively [8]. However,

the comparison with the reported Italian mean is not significant due to the poor adherence of Italian hospitals to the ECDC project (only two participants). Regardless, the episodes of CDI in San Salvatore Hospital were higher than the European average not only during the outbreak but also in the previous period. This situation has made it necessary to reaffirm the importance of prevention as a means of combating the spread of CDI and the need for a multidisciplinary approach in the management of CDI in hospitals. A previous study by Weiss et al. [9] showed that a multi-pronged intervention strategy is most effective in reducing the rate of healthcare CDI. Implementation of behavioral protocols, environmental sanitation, and antibiotic stewardship is considered the most effective strategies for the prevention and control of *C. difficile* infections. These interventions are aimed at identifying, isolating, and efficaciously treating patients affected by CDI to prevent the spread of infection [10]. The transmission of *C. difficile* and other pathogens particularly depends in particular, on the presence of other patients with infections, contaminated surfaces and hand carriage transmission by medical staff, that are the major route of the transmission of the infection [11-14]. An infected patient occupying the room can disseminate microorganisms and rapidly contaminate frequently touched surfaces in near-patient areas and these surfaces may remain contaminated for extended periods [15]. Consequently, *C. difficile* can be found on bedrails, bedsheets, commodes, call buttons, toilets, windowsills, blood pressure cuffs, electronic thermometers, floors, and any other surface that comes into contact with contaminated hands [16]. Indeed, there is a close correlation between hand contamination and the degree of environmental contamination, for this reason, proper hand hygiene is a crucial point in the prevention of nosocomial infections. Therefore, the use of hospital decontamination protocols and the correct disinfection of the contaminated surfaces and medical devices is essential to prevent the transmission of nosocomial infections [17].

According to a multi-pronged intervention scheme, the Hospital Management drew the attention of health professionals implementing behavioral protocols including hand hygiene, glove, and protective clothing use, and management of medical devices, linen, dishes, and waste. Moreover, particular attention has been paid to environmental cleaning, instructing cleaning staff, and strengthening communication between them and nursing staff. Those visiting infected patients were also taught to wash their hands and to limit contact only to the patient being visited. Indeed, the training of healthcare personnel, visitors, caregivers, and patients represents the best way to get adherence to the guidelines. Through this approach, numerous sessions of instruction/training for nursing staff and healthcare providers were developed. By modifying risk behaviors, these interventions certainly helped to control the outbreak: they were introduced on 1 January 2017 and both Joinpoint models show a statistically significant decrease in CDI since February. Such reduction remained constant until the last trimester of 2017. Both Joinpoint regression models suggest that the strategies implemented achieved good results, as shown by the trend of the last segment in the regressions: the regressions showed steady maintenance of the rates in the last segment with lower levels than the first segment for more than a year. The success of these measures has also led the company management to draft a new protocol to be adopted in all hospital facilities of the Local Health Unit 1 of Abruzzo. It is necessary to monitor the progress of these good practices and to implement new preventive techniques [18].

Moreover, our study indicates that reports based on routine laboratory data can accurately measure the population burden of CDI with limited surveillance resources. This activity can help target prevention programs and evaluate their effectiveness. Healthcare professionals assisting patients with CDI face the risk of infection in their facilities. In addition, we will use surveillance data to evaluate antibiotic stewardship and CDI prevention.

Conclusions

In conclusion, epidemiological surveillance for infection control is a very useful tool to identify sudden outbreak. However, in order to combat the spread of CDI, a continuous joint effort by all health professionals, caregivers and patients is needed. Our study shows not only the importance of a good surveillance system, but also the importance of keeping high attention on preventive measures of this type of infection.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

MM and CV contributed to the design, to the statistical data analysis and to the writing of the manuscript. GA and LM contribuited to data collection. LAR and MG carried out the preparation and implementation of preventive protocol. Necozione S planned and supervised the work, interpreting the results and working on the manuscript.

References

[1] Ofosu A. Clostridium difficile infection: a review of current and emerging therapies. Ann Gastroenterol 2016;29:147-54. https://doi.org/10.20524/aog.2016.0006

[2] Ramai D, Noorani A, Ofosu A, Ofori E, Reddy M, Gasperino J. Practice measures for controlling and preventing hospital associated Clostridium difficile infections. Hosp Pract (1995) 2019;47:123-9. https://doi.org/10.1080/21548331.2019.1627851

[3] Balsells E, Shi T, Leese C, Lyell I, Burrows J, Wiuff C, Campbell H, Kyaw MH, Nair H. Global burden of Clostridium difficile infections: a systematic review and meta-analysis. J Glob Health 2019;9:010407. https://doi.org/10.7189/jogh.09.010407

[4] Petrosillo N, Ravasio R. Il costo ospedaliero di trattamento di un episodio di infezione da Clostridium difficile in Italia. Glob Reg Health Technol Assess 2017;4:e77-e83. https://doi.org/10.5301/grhta.5000257

[5] Jullian-Desayes I, Pharmd CL, Mallaret MR, Brun-Buisson C, Pharmd B. State of the Science Review Clostridium difficile contamination of health care workers' hands and its potential contribution to the spread of infection: review of the literature. Am J Infect Control 2017;45:51-9. https://doi.org/10.1016/j.ajic.2016.08.017

[6] European Centre for Disease Prevention and Control. European Surveillance of Clostridioides (Clostridium) difficile infections. Surveillance protocol, version 2.4. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/clostridium-difficile-infections-EU-surveillance-protocol-vers2.4.pdf (accessed on 5 February 2020).

[7] Cofini V, Capodacqua A, Calisse S, Galassi I, Cipollone L, Necozione S. Trend analysis and factors associated with biological injuries among health care workers in Southern Italy. Med Lav 2018;109:308-15. https://doi.org/10.23749/mdl.v109i4.7245

[8] European Centre for Disease Prevention and Control. Healthcare-associated infections: Clostridium difficile infections - Annual Epidemiological Report for 2016. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2016-C-difficile_0.pdf (accessed on 5 February 2020).

[9] Weiss K, Boisvert A, Chagnon M, Duchesne C, Habash S, Lepage Y, Letourneau J, Raty J, Savoie M. Multipronged intervention strategy to control an outbreak of Clostridium difficile infection (CDI) and its impact on the rates of CDI from 2002 to 2007. Infect Control Hosp Epidemiol 2009;30:156-62. https://doi.org/10.1086/593955

[10] Società Italiana Multidisciplinare per la Prevenzione delle Infezioni nelle Organizzazioni Sanitarie. Prevenzione e controllo delle infezioni da Clostridium difficile. Available at: http://www.simpios.it/public/ufiles/Prevenzione%20e%20controllo%20delle%20infezioni%20da%20Clostridium%20Difficile.pdf (accessed on 5 February 2020).

[11] Perdelli F, Dallera M, Cristina ML, Sartini M, Ottria G, Spagnolo AM, Orlando P. A new microbiological problem in intensive care units: environmental contamination by MRSA with reduced susceptibility to glycopeptides. Int J Hyg Environ Health 2008;211:213-8. https://doi.org/10.1016/j.ijheh.2007.04.002

[12] Orlando P, Cristina ML, Dallera M, Ottria G, Vitale A, Badolati G. Surface disinfection: evaluation of the efficacy of a nebulization system spraying hydrogen peroxide. J Prev Med Hyg 2008;49:116-9

[13] Spagnolo AM, Orlando P, Panatto D, Amicizia D, Perdelli F, Cristina ML. Staphylococcus aureus with reduced susceptibility to vancomycin in healthcare settings. J Prev Med Hyg 2014;55:137-44.

[14] Spagnolo AM, Sartini M, Battistella A, Casini B, Lo Pinto G, Schinca E, Cristina ML, Hospital Infection Control Operating Group Galliera Hospital. A Clostridium difficile outbreak in an Italian hospital: The efficacy of the multi-disciplinary and multifaceted approach. J Prev Med Hyg 2018;59:132-8.

[15] Ali S, Muzslay M, Bruce M, Jeanes A, Moore G, Wilson AP. Efficacy of two hydrogen peroxide vapour aerial decontamination systems for enhanced disinfection of meticillin-resistant Staphylococcus aureus, Klebsiella pneumoniae and Clostridium difficile in single isolation rooms. J Hosp Infect 2016;93:70-7. https://doi.org/10.1016/j.jhin.2016.01.016

[16] Martinez FJ, Leffler DA, Kelly CP. Clostridium difficile outbreaks: prevention and treatment strategies. Risk Manag Healthc Policy 2012;5:55-64. https://doi.org/10.2147/RMHP.S13053

[17] Fawley WN, Underwood S, Freeman J, Baines SD, Saxton K, Stephenson K, Owens RC Jr, Wilcox MH. Efficacy of hospital cleaning agents and germicides against epidemic Clostridium difficile strains. Infect Control Hosp Epidemiol 2007;28:920-5. https://doi.org/10.1086/519201

[18] Revolinski S, Munoz-Price L. Clostridium difficile Exposures, Colonization, and the Microbiome: Implications for Prevention. Infect Control Hosp Epidemiol 2018;39:596-602. https://doi.org/10.1017/ice.2018.36

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