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ORIGINAL

Clostridioides difficile: relationship with previous use of antibiotics, risk factors and preventive measures to reduce transmission

Clostridioides difficile: relación con el uso previo de antibióticos, factores de riesgo y medidas preventivas para reducir la transmisión

Francy Ellen de Lima[1], Gerardo Erico Laube[1]

[1]Universidad Abierta Interamericana, Facultad de Medicina y Ciencias de la Salud, Carrera de Medicina. Buenos Aires, Argentina.

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Corresponding author: Francy Ellen de Lima

ABSTRACT

Introduction: Clostridioides difficile infection has emerged in recent years as one of the main hospital-acquired infections. This enteric pathogen is responsible for causing diarrhea related to prior antibiotic use in many healthcare settings, particularly hospitals, nursing homes, and rehabilitation clinics. This study aims to demonstrate the relationship between previous antibiotic use and Clostridioides difficile infection and determine the main risk factors and antibiotics associated with the infection, as well as the potential benefit of prevention strategies.
Method: a bibliographic search was carried out analyzing the database platforms of PubMed, Medline, Lilacs, Scielo and Cochrane during the period from May to September 2024. Articles were selected with a focus on risk factors, preventive measures and antibiotics related to the appearance of Clostridioides difficile infection.
Results: although any antibiotic is a potential risk factor for the development of CDI, the medications most commonly associated with the onset of the infection are Clindamycin, 2nd and 3rd generation Cephalosporins, Fluoroquinolones, Penicillins and Carbapenems.
Conclusion: it is extremely important to know the risk factors and the main antibiotics associated with CDI so that when a certain type of antibiotic is indicated for relatively serious processes, extreme preventive measures are initiated, prior to the possibility that this individual that triggers it does not be the origin of an in-hospital outbreak.

Keywords: Clostridium Difficile; Nosocomial Diarrhea; Antibiotics; Risk Factors; Prevention.

RESUMEN

Introducción: la infección por Clostridioides difficile (ICD) emerge en los últimos años como una de las principales infecciones intrahospitalarias. Este patógeno entérico es responsable por producir cuadros de diarrea relacionada al uso previo de antibióticos en muchos entornos de atención médica, particularmente en hospitales, centros de ancianos y clínicas de rehabilitación. Este estudio visa demonstrar la relación del uso previo de antibióticos con la infección por Clostridioides difficile y determinar cuáles son los principales factores de riesgo y antibióticos asociados a la infección, así como el potencial beneficio de estrategias de prevención.
Método: se realizó una búsqueda bibliográfica analizando las plataformas de bases de datos de PubMed, Medline, Lilacs, Scielo y Cochrane durante el período de Mayo a Septiembre de 2024. Fueron seleccionados artículos con enfoque en los factores de riesgo, medidas preventivas y antibióticos relacionados a la aparición de la infección por Clostridioides difficile.

Resultados: aunque cualquier antibiótico es un factor de riesgo potencial para el desarrollo de la ICD, los medicamentos más comúnmente asociados con la aparición de la infección son Clindamicina, Cefalosporinas de 2ª y 3ª generación, Fluoroquinolonas, Penicilinas y Carbapenémicos.
Conclusión: es de suma importancia conocer los factores de riesgo y los principales antibióticos asociados a la ICD para que ante la indicación de determinado tipo de antibiótico por procesos relativamente graves, ya se inicie medidas preventivas extremas, previo a la posibilidad de que este indivíduo que desencadena no sea el origen de un foco intrahospitalario.

Palabras clave: Clostridium Difficile; Diarrea Nosocomial; Antibióticos; Factores De Riesgo; Prevención.

INTRODUCTION

The Clostridioides difficile infection (CDI) has emerged in recent decades as one of the leading causes of healthcare-associated diarrhea, becoming a frequent complication in hospitalized patients and one of the most challenging nosocomial infections globally.[1,2,3] This anaerobic, gram-positive, and sporulated microorganism can survive in adverse conditions and spread rapidly in hospital environments, especially in contexts where environmental hygiene and rational use of antibiotics are not fully controlled.[4,5,6,7] The main risk factor identified for developing this infection is previous exposure to antibiotics, especially those of broad spectrum that alter the intestinal microbiota and allow the proliferation of toxigenic strains of Clostridioides difficile.[8,9,10]

In this context, changes in clinical practices, the aging of the population, the increase in the use of immunosuppressive treatments, the prolongation of hospitalizations, and the widespread use of antibiotics have generated a context conducive to an increase in the incidence of CDI.[11] This infection can have a broad clinical spectrum, from mild diarrhea to severe forms with toxic megacolon, sepsis, or even death.[12,13] The emergence of hypervirulent strains, resistant to multiple drugs and with high transmission capacity, has contributed to an increase in the severity and complexity of the management of this pathology.[14,15,16]

In Latin America, particularly in Argentina, information on the real prevalence of CDI is still limited and is hampered by the scarce implementation of standardized epidemiological surveillance systems, the unequal availability of diagnostic methods, and the lack of unified policies on the control of antibiotic use in the hospital setting.[17,18,19,20] In this context, it is necessary to deepen the study of this infection, identifying the associated risk factors, the classes of antibiotics with greater implications, and the most effective prevention strategies to reduce its impact.[20,21] Understanding the relationship between the use of antimicrobials and the occurrence of CDI is essential to implementing effective infection control measures and optimizing treatment protocols.[22] The present systematic review aimed to gather and analyze the available evidence on this problem, focusing primarily on the antibiotics involved and possible preventive strategies to reduce the prevalence and severity of this infection in the hospital setting.

What is the relationship between the use of antibiotics and the development of Clostridioides difficile infection (CDI), and what are the most effective strategies to prevent its occurrence and spread in the hospital setting?

Objective

To provide information on the effects of antibiotics on the intestinal microbiota and identify the main antibiotics associated with Clostridioides difficile infection (CDI) to promote preventive and isolation measures that reduce the risk of in-hospital outbreaks.

METHOD

A literature search was carried out to conduct this systematic review by analyzing the PubMed, Medline, Lilacs, Scielo, and Cochrane database platforms from May to September 2024. We searched for articles in full text, systematic reviews, clinical practice guidelines, and controlled clinical trials in English, Spanish, and Portuguese from the last 20 years, taking into account the relevance of the studies. The keywords used in Mesh format were Clostridium difficile, nosocomial diarrhea, antibiotics, risk factors, and prevention. The AND and OR operators were used to improve the search's sensitivity and precision.

Our search identified 637 publications relevant and adequate to the objectives of the systematic review. After removing duplicates and selecting study titles, 298 articles were selected according to their relevance to the study topic. The abstracts of these potentially relevant articles were read, and 34 were selected for full-text review according to topic. Twenty-one studies were included to describe the systematic review results according to the inclusion and exclusion criteria outlined below. The study selection process is described in figure 1.

Inclusion Criteria

- Patients older than 18 years of age.
- Patients of both sexes.
- Inpatients and outpatients.
- Patients with community-onset CDI are associated with the healthcare setting.
- Patients with a confirmed CDI diagnosis by detecting Clostridioides difficile Toxin in laboratory diagnostic methods.
- Patients with recurrent and duplicate CDI.
- Articles in the complete text, previous systematic reviews, controlled clinical trials, and meta-analyses.

Exclusion Criteria

- Patients with community-acquired CDI.
- Patients with CDI who did not have prior antibiotic use but suffered in-hospital contamination.
- Patients who have a chronic disease and make continuous use of antibiotics.
- Other causes of nosocomial diarrhea.
- Patients presenting with diarrhea before admission to the hospital.
- Articles directed to infants and children.

RESULTS

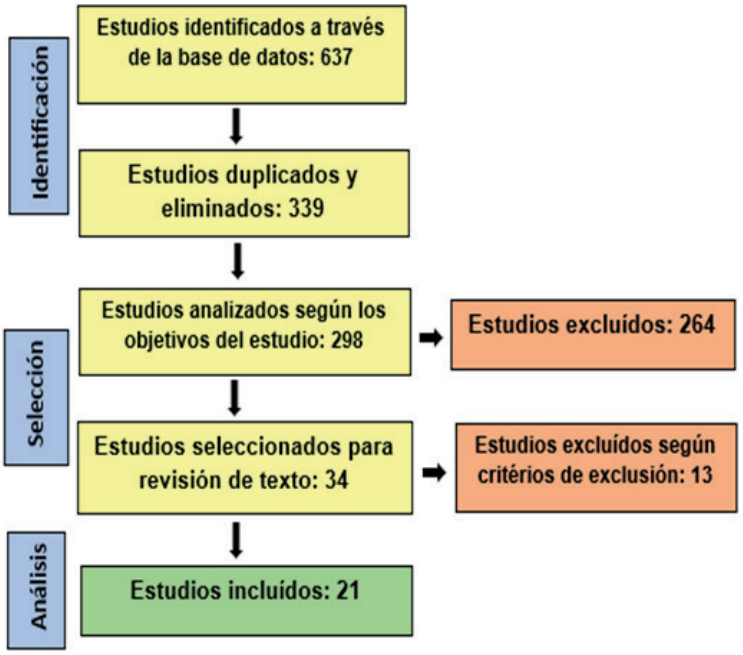

Figure 1. Study selection process

Antibiotics are substances capable of eliminating or preventing the multiplication of bacteria and are essential in treating various diseases. However, prolonged and indiscriminate exposure and use of antibiotics reduce the overall species diversity of the intestinal microbiota, leading to metabolic changes, increasing intestinal susceptibility to colonization, and stimulating the development of bacterial resistance to antibiotics. Together, these processes facilitate the successful invasion of enteric pathogens, making the intestinal epithelium more susceptible to damage.

Antibiotics can lead to bacterial overgrowth, such as toxigenic Clostridioides difficile, by altering the balance that normally exists between the different species of the microbiota.[19]

As already known, the most important risk factor for developing CDI is the use of antibiotics. This risk increases with the anti-anaerobic spectrum, with concomitant use of multiple antibiotics, and with prolonged duration of antibiotic therapy.[22]

Although any antibiotic is a potential risk factor for the development of Clostridioides difficile infection, the drugs most commonly associated with the development of infection are Clindamycin, 2nd and 3rd generation Cephalosporins, Fluoroquinolones, Penicillins, and Carbapenemics. Both the duration of antibiotic therapy and the dose and quantity of drugs used correlate positively with an increased risk of CDI. In addition, the risk also increases if the CD is resistant to the antimicrobial. This resistance varies between different classes of

antibiotics and different strains of CD.[18]

The following figure classifies the classes of antibiotics associated with CDI according to the degree of risk into high, medium, and low-risk.

Figure 2. Risk classification by grade[19-39]

DISCUSSION

Antibiotics are the primary treatment and risk factor for Clostridioides difficile infection. Broad-spectrum antimicrobials, administered either prophylactically or to treat infections, alter the intestinal microbiota, resulting in a dysbiotic state in which CD thrives.[19]

Each person's gut microbiota contains many unique strains, which makes the flora different for different individuals. Gender, ethnicity, and geographic location affect each person's microbiome's taxonomic composition; thus, the response to antibiotics is distinct and individual.[19]

The diversity of the intestinal microbiota also changes with age, increasing from infancy to adulthood and decreasing in older people—these gut changes in the elderly correlate with frailty, nutritional status, and markers of inflammation.[18] In addition, the presence of underlying comorbidities increases the risk of other infections, such as recurrent urinary tract infections or respiratory infections, and this may require even more antibiotics, making the elderly more vulnerable and susceptible to CDI.[23,24,25,26]

In addition to these factors that differ between patient populations, choice of antimicrobial therapy, prescription of multiple antibiotics, and long-term treatment are key risk factors.[27,28]

Empiric antibiotic use, either concomitantly or sequentially, is another risk factor. Since the etiologic agent is unknown, empiric antibiotic use usually involves the administration of more than one drug. This may explain why more antibiotics are associated with a higher risk of developing CDI.[29]

All classes of antibiotics can affect the intestinal microbiota in different ways. Antibiotics have different pharmacodynamics and pharmacokinetics and vary in their ability to reduce the total amount of bacteria in the gut. There is also variation in the impact of the antibiotic on specific dominant bacterial species in the microbiota.[25]

Epidemiological evidence suggests that different classes of antimicrobials are unequal in terms of the risk of producing CDI.[22]

Two risks are of interest because of how they relate to antimicrobial use:

- Relative risk of CDI: This is associated with using a specific antimicrobial drug.
- Attributable risk of CDI: incorporates the relative risk of an antimicrobial and the frequency with which this drug is used in a given population.[22]

Clindamycin was the drug with the highest risk in the 1970s, but its use decreased in US and European hospitals, consequently reducing the attributable risk of antibiotic-associated diarrhea and CDI.[30,31]

In the late 1980s and throughout the 1990s, Cephalosporins, particularly second—and third-generation, became the agents with the highest relative and attributable risk of CDI due to their frequent use in hospitals.[32,33]

Since 2001, the saga of CDI risk and association with antimicrobial use has extended to the Fluoroquinolone class. The other classes of antibiotics also present risks, but prescribing habits mean that the frequency of use is lower.[34,35]

The articles included in this systematic review were based on the inclusion criteria. However, these studies present heterogeneity because they have some variations and limitations that could influence the research's outcome.

The variability of the data may be related to the individual characteristics of the patients who present with different concomitant diseases and who use other medications in addition to the antibiotics prescribed during hospitalization.

Variations in the duration of antimicrobial therapy and antibiotic dosage and the use of more than one antibiotic simultaneously are also important sources of heterogeneity. This added to the different comorbidities, makes each patient's response different in relation to sensitivity and susceptibility to develop CDI.[36]

In addition, variations in the pharmacokinetic and pharmacodynamic properties of antibiotics limit class categorization in predicting the impact on the gut microbiota.[37]

Variations in CD strain may also explain the heterogeneity between studies, as the response to antibiotics differs according to the strain's virulence.[26]

One limitation is the lack of consensus on the appropriate time period to measure antibiotic exposure. Recent studies suggest that the greatest risk occurs in the first 30 days but remains increased until 90 days.[33,38,39]

One possible source of bias is sampling bias, meaning that commonly prescribed antibiotics were more frequently reported to be associated with CDI cases. Another source of bias could be misclassification of infection. Most studies define CDI cases using population-based administrative data rather than laboratory detection of CD toxins, which may underestimate or overestimate the number of cases.

Although the included articles vary and have limitations, all studies agree that antibiotics demonstrated the most significant association with the subsequent occurrence of CDI. Despite heterogeneity, our findings are supported by well-founded and adequately designed studies.

CONCLUSIONS

The evidence confirms a significant association between antibiotic use and the risk of developing Clostridioides difficile infection (CDI), especially with certain antimicrobial classes such as cephalosporins and fluoroquinolones. While antibiotic therapy is essential for treating bacterial infections, its indiscriminate use represents a significant risk factor for CDI. Careful antibiotic selection, duration, dosage, and consideration of individual patient factors are critical to minimize this risk. In addition, implementing preventive measures and infection control protocols is key to reducing the incidence, hospital costs, and mortality associated with this infection.

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FINANCING

None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

Conceptualization: Francy Ellen de Lima, Gerardo Erico Laube.
Data curation: Francy Ellen de Lima, Gerardo Erico Laube.
Formal analysis: Francy Ellen de Lima, Gerardo Erico Laube.
Research: Francy Ellen de Lima, Gerardo Erico Laube.
Methodology: Francy Ellen de Lima, Gerardo Erico Laube.
Project Management: Francy Ellen de Lima, Gerardo Erico Laube.
Resources: Francy Ellen de Lima, Gerardo Erico Laube.
Software: Francy Ellen de Lima, Gerardo Erico Laube.
Supervision: Francy Ellen de Lima, Gerardo Erico Laube.
Validation: Francy Ellen de Lima, Gerardo Erico Laube.
Visualization: Francy Ellen de Lima, Gerardo Erico Laube.
Writing - original draft: Francy Ellen de Lima, Gerardo Erico Laube.
Writing - proofreading and editing: Francy Ellen de Lima, Gerardo Erico Laube.