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ORIGINAL ARTICLE

# Metronidazole in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* infection in high-risk hospitalised patients☆

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**KEYWORDS**
Antibiotic-associated diarrhoea;
*Clostridium difficile* infection;
Chemoprophylaxis;
Metronidazole

**Abstract**
*Background:* In-hospital diarrhoea has a high impact on morbidity and mortality rates among hospitalised patients. Chemoprophylaxis with antibiotics in selected patients could be a cost-effective tool for prevention.
*Methods:* A prospective randomised, open-label study was conducted in a tertiary hospital in Mexico City, selecting patients at high risk of acquiring in-hospital diarrhoea and assigning them to a group taking metronidazole 500 mg orally every 8 h for seven days or an observation group. The primary endpoint was the presence of antibiotic-associated diarrhoea and *Clostridium difficile* (*C. difficile*) infection during the seven days of evaluation. The study was approved by the institutional ethics committee. Registration number (11.2017) of 14 March 2017.
*Results:* Of the 116 patients who met the inclusion criteria, 96 were analysed, 41 in the intervention group and 55 in the observation group: 4.9% of patients in the intervention group and 16.4% in the observation group developed antibiotic-associated diarrhoea (odds ratio [OR] 0.26 (0.05–1.29); $P = 0.109$). 0% of patients in the intervention group and 9.1% in the observation group developed *C. difficile* infection (odds ratio [OR] 0.91 (0.84–0.99); $P = 0.069$).

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*Conclusions:* Metronidazole prophylaxis did not result in a reduction in antibiotic-associated diarrhoea. It could, however, be an effective measure for preventing *C. difficile* infection in selected high-risk patients. This was the first prospective study designed for this purpose. New studies that involve a larger number of patients are required in the future.


**PALABRAS CLAVE**
Diarrea asociada a antibioticos;
Infección por *Clostridium difficile*;
Quimioprofilaxis;
Metronidazol

**Metronidazol en la prevención de diarrea asociada a antibióticos e infección por *Clostridium difficile* en pacientes hospitalizados de alto riesgo**

**Resumen**
*Antecedentes:* La aparición de diarrea intrahospitalaria supone un evento de alto impacto en la morbimortalidad de pacientes hospitalizados, la quimioprofilaxis con antibióticos en pacientes seleccionados podría resultar en una herramienta costo-efectiva para su prevención.
*Método:* Se realizó un estudio prospectivo, randomizado, abierto, en un hospital de tercer nivel de la ciudad de México, seleccionando pacientes con alto riesgo de adquirir diarrea intrahospitalaria, se asignó pacientes a un grupo de metronidazol 500 mg vía oral cada 8 h durante 7 días y un grupo de observación. El resultado primario fue determinar la presencia de diarrea asociada a antibióticos e infección por *Clostridium difficile (C. difficile)* durante los 7 días de evaluación. Aprobado por el comité de ética institucional. Número de registro (11.2017) del 14 de marzo de 2017.
*Resultados:* De 116 pacientes que cumplieron criterios de inclusión, 96 fueron analizados, 41 en el grupo de intervención y 55 en el grupo de observación, la diarrea asociada a antibióticos se presentó en un 4,9% de pacientes en el grupo de intervención y en un 16,4% en el grupo de observación (odds ratio [OR] 0,26 (0,05-1,29) p = 0,109). La infección por *C. difficile* se presentó en el 0% de los pacientes en el primer grupo y en el 9,1% en el segundo grupo (odds ratio [OR] 0,91 (0,84-0,99) p = 0,069).
*Conclusiones:* El uso de metronidazol para prevención de diarrea asociada a antibióticos no se relacionó con disminución en su aparición, mientras que para infección por C. difficile podría resultar en una alternativa efectiva en seleccionados pacientes de alto riesgo. Éste es el primer estudio prospectivo diseñado para este fin. Se requieren a futuro nuevos estudios que involucren mayor número de pacientes.


## Introduction

The onset of intrahospital diarrhoea (IHD) represents an event with a high impact on mortality and morbidity, which increases costs and days of hospital stay. One factor which fosters its onset is the use of broad-spectrum antibiotics.[1] Antibiotic-associated diarrhoea (AAD) is a common disease in hospitalised patients. Its main mechanism is disruption of the intestinal flora with subsequent changes in carbohydrate metabolism, short-chain fatty acids and bile acids.[2] It is usually a mild, self-limiting disease. However, 15–39% of cases are caused by *Clostridium difficile* (*C. difficile*) infection (CDI). These cases follow a more aggressive clinical course with high mortality.[3]

The first cases of CDI were reported in 1978.[4] Since then, the incidence of this disease has shown a marked increase, with the appearance of new strains such as NAP1/BI/027, which have greater virulence and complications.[5] The risk factors most commonly associated with its appearance in hospitalised patients are age >65 years, use of antibiotics (cephalosporins, clindamycin, beta-lactam antibiotics and fluoroquinolones) and suffering from serious diseases.[6] Other additional factors include suppression of gastric acid, enteral nutrition, gastrointestinal surgery, obesity, chemotherapy, hematopoietic stem cell transplantation and inflammatory bowel disease.[7–9]

Various measures to prevent its onset have been investigated, such as restricting prescription of antibiotics, particularly clindamycin, fluoroquinolones and cephalosporins[10]; washing hands with water and soap rather than alcohol-based disinfectants, which is associated with a greater likelihood of *C. difficile* eradication,[11] mainly with the use of chlorhexidine-based soaps.[12] Studies conducted with probiotics including a *Lactobacillus* combination have yielded variable results depending on the type and formulation used.[13,14] Recently, a study evaluated the use of actoxumab and bezlotoxumab, which are human monoclonal antibodies against *C. difficile* toxins A and B, respectively. The study found bezlotoxumab, but not actoxumab, to be associated with a decreased rate of disease recurrence versus placebo.[15]