

**Original**

# Factors associated with nosocomial diarrhea in patients with enteral tube feeding

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## Abstract

**Objectives:** Diarrhea is a frequent complication associated to enteral tube feeding (ETF) and it is a frequent cause of reduction or suspension of this type of nutritional support. Our objective was to evaluate the factors associated with nosocomial diarrhea in patients receiving ETF.

**Results:** The only significant factor associated with the appearance of diarrhea was antibiotic consumption, specially those patients receiving the combination of two or more antibiotics. We did not find any association between factors related to ETF, analytical parameters, nor other medications and diarrhea.

**Conclusions:** Our observational data supports the idea that ETF should not be seen as a primary cause of diarrhea, other possible causes should be considered before reducing or discontinuing ETF administration.

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**Key words:** Enteral nutrition. Diarrhea. Anti-bacterial agents. Cross infection.

## FACTORES ASOCIADOS A DIARREA NOSOCOMIAL EN PACIENTES CON NUTRICIÓN ENTERAL

## Resumen

**Objetivos:** La diarrea es una complicación frecuente asociada a la nutrición enteral (NE) y es causa habitual de reducción o suspensión de este tipo de soporte nutricional. Nuestro objetivo fue evaluar los factores asociados a la diarrea nosocomial en pacientes que recibían NE.

**Resultados:** El único factor significativo asociado con la aparición de diarrea fue el consumo de antibióticos, especialmente aquellos pacientes que recibían la combinación de dos o más antibióticos. No se encontró ninguna asociación entre factores relacionados a la NE, parámetros analíticos, ni otras medicaciones y la diarrea.

**Conclusión:** Nuestros datos observacionales respaldan la idea que la NE no debería ser vista como causa principal de diarrea, debiéndose considerar otras causas posibles antes de reducir o suspender la administración de NE.

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**Palabras clave:** Nutrición enteral. Diarrea. Agentes antibacterianos. Infección cruzada.

## Introduction

Enteral tube feeding (ETF) is a modality of nutritional support frequently used in hospital in-patients. It is defined as the nutrition provided through the gastrointestinal tract via a tube, catheter, or stoma that delivers nutrients distal to the oral cavity.<sup>1</sup> Diarrhea is a common complication associated to ETF, its incidence ranges from 2% to

63%.<sup>2</sup> Two main factors seem to be the cause of this wide range of reported incidences: the lack of a standard definition of diarrhea for patients receiving ETF and the disease state and seriousness of the patient.

Pathogenesis of nosocomial diarrhea is considered multifactorial and may have either an infectious or noninfectious source.<sup>3,4</sup> Toxigenic *Clostridium difficile* seems to be the most common cause for infectious nosocomial diarrhea.<sup>3</sup> While iatrogenic nosocomial diarrhea may be caused by hyperosmolar and lactose-containing feeding formulas, stool softeners, oncologic agents, sorbitol-containing medications, infusion rate of the feeding formula, contamination of containers and feeding tubes or the use of antibiotics.

Nosocomial diarrhea is a troublesome and costly condition, its reported complications include increased length of stay and higher costs and it is associated with

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considerable morbidity and mortality.<sup>5,6</sup> Even though the etiology of diarrhea in patients receiving ETF is diverse, it is still common to associate it with its administration before considering other potential causes.<sup>3</sup> In the appearance of diarrhea, the reduction or suspension of enteral feeding has been a common practice as a first step management, despite a lack of evidence to support it in many cases. Previously reported numbers for reduction or suspension of ETF account for 33.6% and 26.4% of patients with diarrhea, respectively.<sup>7</sup> Thus, knowing which can be the causes of diarrhea in these patients is of special interest to avoid unnecessary discontinuation of the nutritional support.

## Methods

The aim of this observational study was to assess the factors associated with nosocomial diarrhea in patients receiving ETF in general hospital wards. Analyzed data were a substudy from a prospective study of respiratory and infectious complications of tube feeding. From January 2003 until April 2004 all consecutive patients admitted in the Internal Medicine, Neurology, Neurosurgery and Infectious Diseases wards at the Hospital Clínic de Barcelona were assessed for inclusion criteria; patients receiving ETF during a period less than 48 hours were excluded. In order to collect the data, a specific data recording sheet was used, in which the researchers recorded the information obtained by direct observation of patients and by survey of the care documentation. There was a daily follow-up from the beginning of the ETF, finishing when the patient either went to exclusive oral diet, was transferred to an external institution or died. For patients coming from the Intensive Care Unit (ICU), only the period of stay in the general ward was monitored.

Tube feeding was performed either by bolus, drip or pump. The types of formulas used during the time of the study were as follows: normocaloric standard with or without fiber, high protein, diabetes, and high energy. In our study we considered diarrhea 3 or more bowel movements per day of liquid or semi-liquid consistency. Microbiologic analysis of stool was performed when the episode of diarrhea was not self-limited.

Conservative treatment was applied to patients that developed diarrhea, understood as using formulas without simple carbohydrates, temporary reduction of ETF and ruling out other possible agents that could contribute to diarrhea —i.e. prokinetics or sorbitol-containing medications. If there was not a remission of diarrhea, a soluble-fiber containing formula was used. The observer did not have any influence on the applied treatments, as patients received the feeding formula according to their needs, established by the nutrition support unit.

For data analysis, only days previous to the diarrhea event were considered. Continuous variables were analyzed as means and categorical variables were transformed to frequencies for each category. Comparisons between groups were performed using Student's *t*-test, Chi-squared test and non-parametric tests when required. A Cox-regression analysis model was used for multivariate analysis. A *p* value < 0.05 was considered as statistically significant. Data analysis was performed with the use of a statistical software (SPSS 12.0, Chicago, USA). The research protocol agreed with the requirements of the Research Ethics Committee of the Hospital.

## Results

The sample size of the study comprised 161 patients that received ETF through nasogastric tube or gastos-

**Table I**  
*Comparative data of patients with and without diarrhea*

	<i>Patients with diarrhea (n = 66)</i>	<i>Patients without diarrhea (n = 95)</i>	<i>p</i>
Age	72 ± 18	74 ± 15	0.43
Patients from ICU (%)	25.8	12.6	0.33
24 h ETF volume (ml)	1,368 ± 273	1,389 ± 204	0.58
Continuous perfusion (%)	78 ± 33	65 ± 36	0.01
Frequency of use (% days)			
Normocaloric std	36 ± 38	38 ± 39	0.86
High protein	15 ± 33	12 ± 29	0.95
Diabetes	31 ± 39	25 ± 39	0.38
Normocaloric fiber	14 ± 30	20 ± 33	0.22
High energy	5 ± 17	5 ± 19	0.90
Analytical parameters			
Total proteins	61 ± 8	62 ± 8	0.28
Albumin	34 ± 5	35 ± 5	0.33
Pre-albumin	0.19 ± 0.08	0.18 ± 0.08	0.50
Total cholesterol	166 ± 44	174 ± 69	0.56

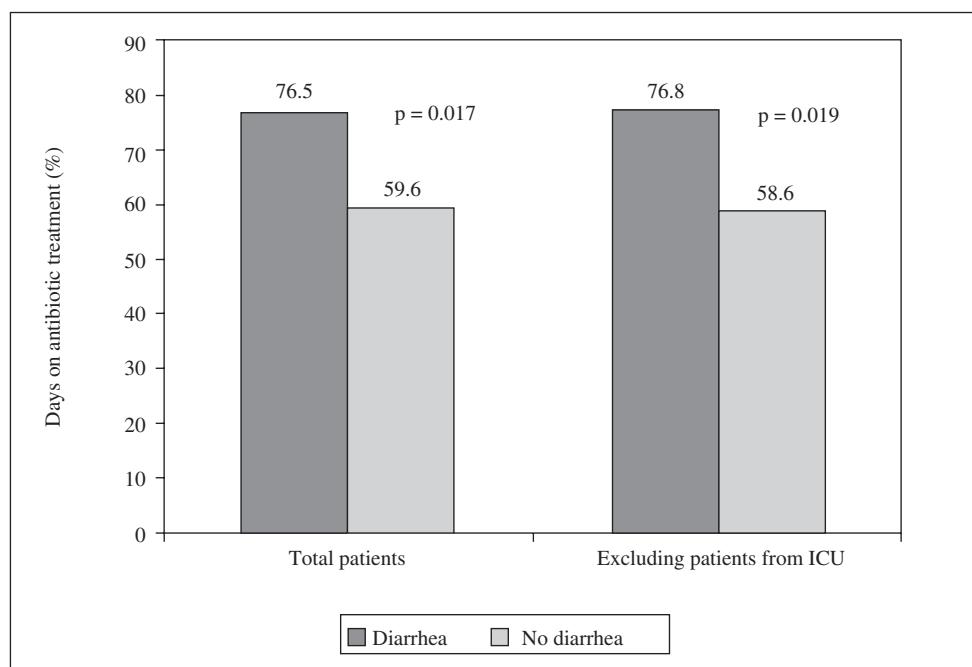


Fig. 1.—Diarrhea and antibiotic consumption.

tomy—only 2 patients at study entry. The mean age was  $73 \pm 16$  years, with a male/female ratio of 87/74. Eighty-two percent presented neurological pathology— cerebrovascular accident, craniocerebral trauma or dementia. The median length of feeding was 11 days. The type of enteral formulas used were as follows: normocaloric standard 37.1%, diabetes 27.4%, normocaloric standard with fiber 17.4%, high protein 13.4% and high energy 4.7%. Three types of perfusion were used: continuous 70.2%, drip 25.2% and bolus 4.6%. We accounted 8.51 days of diarrhea for every 100 days of ETF, affecting 41% of the patients. One hundred and fifty-six of 161 patients (96.9%) were free of diarrhea at the start of the study.

No differences were observed in age, consumption of opiates, antacids, anti-emetic drugs, the type of feeding formula used, the use of dilution nor the volume of formula administered between the patients that presented diarrhea and those who did not. Differences were not found either in the analytical parameters for total proteins, albumin and pre-albumin (table I).

For those patients with diarrhea, stool samples from 16 subjects (24.2%) were sent to the microbiology department for detection of *Clostridium difficile* toxin. The analysis tested positive in 2 of those patients.

In the group of patients with diarrhea, there was a higher proportion of patients coming from the ICU than in the group of those who did not have diarrhea (25.8% vs 12.6%,  $p = 0.03$ ). Also, continuous perfusion rate was more frequent in the group of patients with diarrhea ( $p = 0.013$ ).

In our study, antibiotic consumption was significantly greater in patients which developed diarrhea ( $p = 0.017$ ) (fig. 1). On the other hand, receiving a combination of 2 or more antibiotics was also related to a greater incidence

of diarrhea ( $p = 0.04$ ); we did not find an association with the days receiving monotherapy (fig. 2). We only found 10 patients without antibiotic treatment during the period of study. As the antibiotic consumption during ICU stay was not controlled, we repeated the same analysis excluding the patients originated from the ICU and similar results for the antibiotic consumption and their combined use were reproduced. In the multivariable model, the total consumption of antibiotics or their use in combination maintained the statistical significance.

When analyzing data by antibiotic groups, only the consumption of aminoglycosides, piperacillin-tazobactam and clindamycin/metronidazole showed a significant relation with a greater incidence of diarrhea (fig. 3). The last two groups maintained the significance in the multivariate analysis.

## Discussion

Diarrhea is a frequent problem in hospitalized patients and iatrogenic causes are often responsible for its appearance. Medical staff is usually unaware of what can originate diarrhea and few efforts are made then to eliminate the causes. Diarrhea causes a distressing state to the patients and carers, fluid and electrolyte abnormalities can occur and increases the risk of infection of surgical wounds.<sup>8</sup> All these factors can result in greater financial costs to the health care provider, therefore, increased attention should be paid to this condition.

One of the main problems found when comparing our results to previous studies was to find a consensus in defining diarrhea. Literature shows us 14 different definitions,<sup>9</sup> and previous research suggests an incidence of diarrhea in ETF patients of 2% to 63%.<sup>2</sup> This

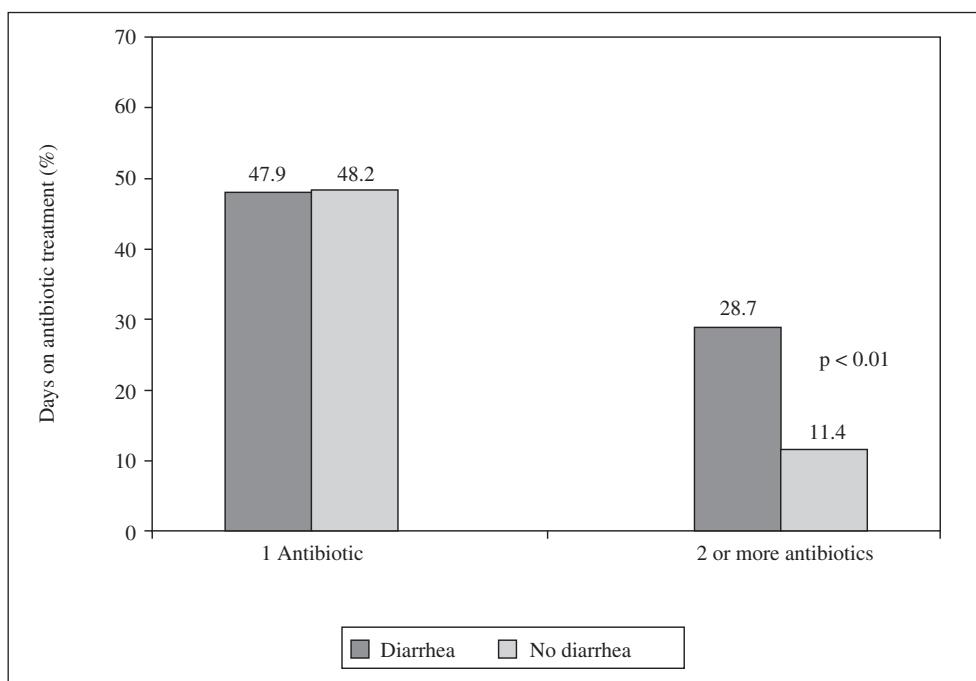


Fig. 2.—Diarrhea and antibiotic combination.

large variability in the incidence is influenced by the definition of diarrhea used and the number of days on which the patients are monitored, which hinders the comparison between studies. In a survey by Whelan et al. conducted in dietitians, gastroenterologists and nurses, fecal frequency and fecal consistency were considered to be more important over fecal quantity when characterizing fecal output and defining diarrhea in patients receiving ETF.<sup>4</sup> In our study, the information about diarrhea was gathered by nursing staff. In the absence of a gold-standard definition of diarrhea and to avoid inter-observer differences, we opted for a definition that seems to satisfy commonly accepted terms such as frequency and consistency.

Hypertonic feeding formulas or high perfusion rates can lead to ETF-related diarrhea, but in our study we could not associate any formula-related factors to this condition. Although it is usually accepted that diarrhea occurs more commonly in tube-fed patients who have low serum albumin levels,<sup>10</sup> the analysis of our data did not find any association between analytical parameters and diarrhea.

No association was observed either between diarrhea and patients receiving certain medications such as opiates, antacids and anti-emetic drugs. The only statistically significant pharmacological factor associated with the development of diarrhea was antibiotic consumption. Antibiotic-associated diarrhea (AAD) is a common complication of antibiotics and develops in 5% of patients.<sup>11</sup> The pathogenesis of AAD may be mediated through the disruption of the normal colonic microflora and overgrowth of pathogens, by increasing peristalsis, or by acting as colonic irritants.<sup>12,13</sup> In a study by Pancorbo-Hidalgo et al. with patients recei-

ving ETF, antibiotics were the most common administered drugs simultaneously with enteral nutrition. In that study, 32.8% of the patients had one or more episodes of diarrhea, although antibiotic treatment did not achieve statistical significance to associate it with diarrhea.<sup>14</sup> In our study, we associated the antibiotic consumption with a greater incidence of diarrhea. Further analysis also revealed an association when analyzing the combination of 2 or more antibiotics, but could not be established on the days on monotherapy.

We only found an association with certain antibiotic groups —aminoglycosides, piperacillin-tazobactam and clindamycin/metronidazole—, which are commonly given to severely ill patients and frequently used in combination. Also, the lack of association with other antibiotic groups, more commonly associated with diarrhea, may be owing to the fact that the study was not specifically designed to find differences between different groups of antibiotics.

Antibiotics do not necessarily cause diarrhea in the same way, but one of the most common is the disruption of colonic microflora. To this effect, *C. difficile* is reported to be the leading infectious cause of nosocomial diarrhea.<sup>15,16</sup> A recent study carried out in hospital in-patients reported that a possible pathogen was found in 71% of AAD cases —among them *C. difficile*—, the majority of patients were on multiple antibiotic regimens.<sup>17</sup> This was not our case, where only 2 patients tested positive for *C. difficile*. Even so, these numbers may not be fully representative because only 24.2% of the sample was tested. Distinguishing AAD from *C. difficile* diarrhea can also prove difficult. The first can sometimes present less severe symptoms than the second one, there is also a resolution of symptoms with

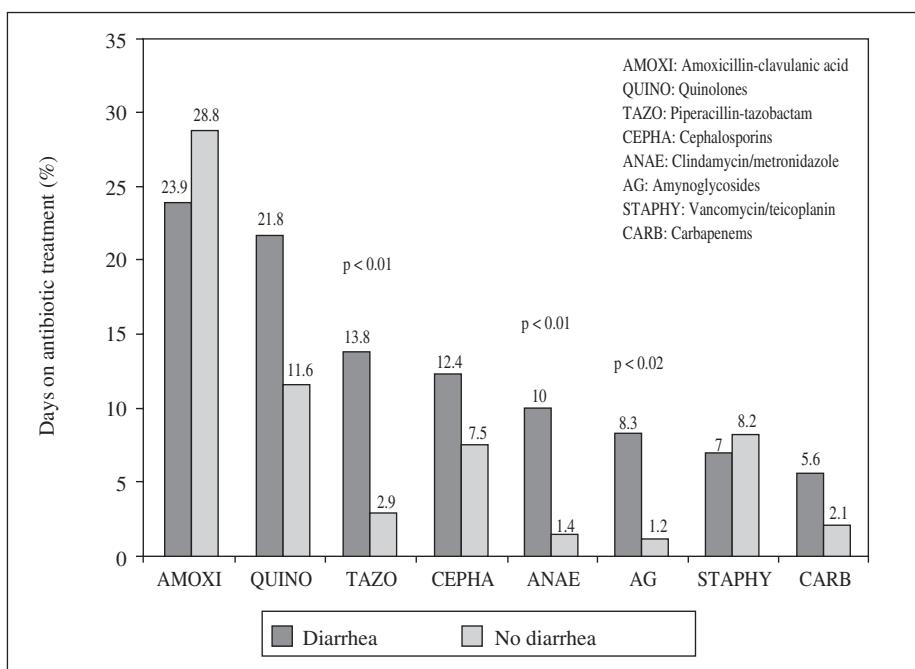


Fig. 3.—Diarrhea and type of antibiotics.

antibiotic withdrawal and diagnostic tests for *C. difficile* toxin are negative.<sup>11</sup>

In our study, antibiotic consumption was the main factor related with the occurrence of diarrhea. This association could not be demonstrated with factors related to ETF like the formula, the dilution or the administered volume. Even so, we have to acknowledge that our results can be influenced in some degree by the elevated mean age of the sample. It has to be taken into account that elderly patients are particularly vulnerable and have a higher incidence of infectious and iatrogenic diarrhea.<sup>18</sup> Also, patients with diarrhea were more severely ill, as shown by the higher proportion of patients coming from ICU and the higher frequency of use of continuous perfusion rate.

In summary, despite the limitations of this study due to its observational design, our results support previous data<sup>15,18</sup> and the idea that ETF should not be seen as a primary cause of diarrhea. Therefore, when evaluating diarrhea treatment, clinicians should consider other possible causes before reducing or discontinuing ETF administration.

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