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A Prospective, Double-Blind, Multicenter, Randomized Trial Comparing Ertapenem 3 Vs ≥5 Days in Community-Acquired Intraabdominal Infection

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Abstract Severe secondary peritonitis is diagnosed in only 20–30% of all patients, but studies to date have persisted in using a standard fixed duration of antibiotic therapy. This prospective, double-blind, multicenter, randomized clinical study compared the clinical and bacteriological efficacy and tolerability of ertapenem (1 g/day) 3 days (group I) vs ≥5 days (group II) in 111 patients with localized peritonitis (appendicitis vs non-appendicitis) of mild to moderate severity, requiring surgical intervention. In evaluable patients, the clinical response as primary efficacy outcome were assessed at the test-of-cure 2 and 4 weeks after discontinuation of antibacterial therapy. Ninety patients were evaluable. In groups I and II, 92.9 and 89.6% of patients were cured, respectively; 95.3% in group I and 93.7% in group II showed eradication. These differences were not statistically significant. The most frequent bacteria recovered were *Escherichia coli* and *Bacteroides fragilis*. A wound infection developed in seven patients (7.7%) and an intraabdominal infection in one patient (1.1%). There was a low

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frequency of drug-related clinical or laboratory adverse effects in both groups. Our study demonstrated that, in patients with localized community-acquired intraabdominal infection, a 3-day course of ertapenem had the same clinical and bacteriological efficacy as a standard duration.

Keywords Peritonitis · Ertapenem · Localized intraabdominal infection · Surgical and antibiotic therapy

Introduction

Recommendations published by the Surgical Infection Society and the Infectious Disease Society of America concerning the duration of antibiotic therapy in patients with intraabdominal infection were limited and not specific enough to inform treatment. The guidelines stated only "antimicrobial therapy for established infections should be continued until resolution of clinical signs of infection occurs, including normalization of temperature and WBC count and return of gastrointestinal function" and "that definition of the appropriate duration of antimicrobial therapy is perhaps the most pressing need".[1]

This lack of specificity is mainly because of a paucity of clinical studies addressing the optimal duration of therapy.[2,3] Many trials have adopted a fixed duration, ranging from 5 up to 14 days for all patients with community-acquired intraabdominal infection, irrespective of severity of the peritonitis.[4–6] It is well known that secondary peritonitis encompasses a number of diseases and can present with a wide range of severities.[7]

It has been shown that most patients with intraabdominal infection enrolled in antibiotic treatment trials present with acute illness of mild severity, which, in 35 to 55% (and in some studies, up to 70% of evaluable patients) of cases, is represented by acute appendicitis.[7–9] Additionally, many of these patients do not have a fully developed infection but rather a local initial infection or simple contamination.[5] In a nonrandomized trial, Schein et al. demonstrated that, by tailoring the duration of the antibiotic therapy according to the operative extent of infection, the same clinical results can be obtained in all patients, thus, minimizing antibiotic administration.[5] Another recent systematic review of 28 studies examining the duration of antibiotic therapy in advanced appendicitis in children showed that limiting the duration of antibiotic use to 3 days was not associated with higher rates of intraabdominal abscess or wound infection.[10] All these studies demonstrated many patients were treated unnecessarily for several days when using a fixed standard treatment period.

There is a need for randomized studies, as has been done in patients with pneumonia,[11,12] that consider whether shorter duration therapy is as effective as a standard therapy in patients with mild to moderate peritonitis. If this was the case, the resulting reduction in antibiotic consumption could represent an important achievement not only in the treatment of these patients, but in controlling the consequences of antibiotic overuse. It is well known that overuse of antibiotics is responsible for several important consequences such as increases in the cost of therapy and adverse effects, but the main concern is emergence of resistant pathogens. The selective pressure determined by inappropriate course of antibiotics favors the emergence of resistant isolates.

In the last SIS Guidelines, it is clearly indicated that antibiotics used for empirical treatment of community-acquired intraabdominal infections should be active against enteric Gram-negative aerobic and against obligate anaerobic bacilli.[1]

Moreover, for patients with community-acquired infections of mild-to-moderate severity, agents that have a narrower spectrum of activity and that are not commonly used for nosocomial infections, such as ampicillin/sulbactam, cefazolin or cefuroxime plus metronidazole, ticarcillin/clavulanate, ertapenem, and quinolones plus metronidazole, are preferable to agents that have broader coverage against Gram-negative organisms and/or greater risk of toxicity.[1] Cost is an important factor in the selection of a specific regimen.[1]

Ertapenem, a long-acting parenteral group I carbapenem, has shown a narrowed spectrum of activity in vitro against most aerobic and anaerobic bacteria generally associated with community-acquired infections.[13–16] Ertapenem is not active against most *Pseudomonas aeruginosa* or enterococci, but as underlined in the SIS Guidelines, coverage of these organisms is not routinely required for successful treatment of community-acquired intraabdominal infections.[1,3,5,16,17] In three earlier double-blind, randomized clinical trials, a standard duration therapy with ertapenem was comparably effective and as well tolerated as a standard duration therapy with piperacillin–tazobactam and ceftriaxone plus metronidazole.[17–19]

Demonstrating that short course of ertapenem is an effective monotherapy for community acquired intraabdominal infection is particularly important in the context of resistance and of cost.

The aim of the study was to compare the efficacy and safety of ertapenem administered according to a standard treatment regimen for 5 days or more vs a shorter regimen of 3 days in patients with community-acquired intraabdominal infection of mild to moderate severity.

Materials and Methods

Study Design

This was a prospective, open-label, multicenter, randomized clinical study of adult patients diagnosed with localized

Table 1 Reasons for Exclusion of Patients from the Study

Causes	Number of Patients	Percent
No pathogens found	14	66.7
No follow-up	2	9.5
Protocol violations	5	23.8
Total	21	100

community-acquired intraabdominal infections of mild to moderate severity, who required surgical intervention within 24 h of diagnosis/admission. The institutional review board at each site approved the protocol, and written informed consent was obtained from all participants.

Localized intraabdominal infections are defined as infection from diverse sources that extends beyond the hollow viscus into the peritoneal space as a consequence of the perforation (usually with localized pus formation), but is confined near the perforated viscus and does not affect the entire peritoneal cavity. A diagnosis consistent with intraabdominal infection in the eligible patients was based on clinical syndrome (history, complete medical and physical examinations, and laboratory evaluation) and intraoperative findings. Patients were required to present with either an oral temperature≥38°C, or a WBC≥10.5×10^3/mm, with symptoms and physical findings (e.g., abdominal tenderness and pain) and radiologic, ultrasonic, or radionuclide (if performed) changes consistent with intraabdominal infection.

All patients underwent operation within 24 h of diagnosis or enrollment in the study; during the operation, the surgeon was asked to check the diffusion of the peritonitis and to take a sample of the exudates present. In addition to an evaluation of the severity of the disease with the Apache II score, all patients had an intraoperative evaluation of the severity of the secondary peritonitis based on the Mannheim peritonitis index (MPI).[20–22] After 3 days of parenteral therapy, all patients had complete medical and physical examinations and laboratory evaluation. If clinical improvement was clearly demonstrated (i.e., the patient has temperature≤100°F or 37.8°C orally for ≥24 h, a diminution or a shift of the WBC, and an improvement in abdominal signs and symptoms), the patients were randomly allocated to short-duration therapy (3 days) or standard duration therapy. Those randomized into the short duration treatment group (group I) received placebo for the remaining course (up to day 5), whereas those randomized into the standard duration treatment group (group II) continued the antibiotic for no less than 5 days, Fig. 2.

Study Population

The study was conducted in ten surgery units responsible for the emergency surgery in Italy between March 2005–September 2006.

Only patients 18 years of age or older with localized intraabdominal infections extending beyond the organ wall but confined near the hollow viscus that were mild to moderate in severity but required surgical intervention within 24 h of diagnosis were included in this trial. Excluded were patients with traumatic bowel perforation requiring surgery within 12 h, perforation of gastroduodenal ulcers requiring surgery within 24 h, or other intraabdominal processes in which the primary etiology was unlikely to be infectious.

Also excluded were patients, lactating or pregnant, with a history of allergy, hypersensitivity, or any severe reaction to the study antibiotics or to any of the components of these products; with rapidly progressive or terminal illness; with a history or presence of severe hepatic or renal disease (e.g., creatinine clearance ≤0.5 ml min^{-1} per 1.73 m^2); or with a concomitant infection that would interfere with evaluation of response to the study antibiotics.

At the enrollment, the severity of the disease was evaluated with Apache II score and MPI before the operation. Diagnosis was based on the patient's clinical syndrome and intraoperative findings, including intraoperative cultures. The study drug was started before the operation. The patients underwent operation and were treated for 3 days with ertapenem (1 g per day). Only patients with an improvement in temperature (<37.8°C), WBC (returning to the normal range), and presence of abdominal sounds at the third day were randomized into either group I, short duration therapy for 3 days plus placebo for the remaining course, or group II, standard duration (ertapenem for no less than 5 days).

Table 2 Demographic Characteristics of Randomized Patient

		3 Days		≥5 Days	
		Number of Patients (%)	Mean Age	Number of Patients (%)	Mean Age
Appendicitis	Male	17 (77.2)	25.1	15 (65.2)	39.8
	Female	5 (22.8)	36.3	8 (34.8)	57.3
	Total	22 (52.4)		23 (48.0)	
Non-Appendicitis	Male	9 (45.0)	58.3	12 (48.0)	54.5
	Female	11 (55.0)	65.0	13 (52.0)	65.7
	Total	20 (47.6)		25 (52.0)	

Table 3 Distribution of Patients in the Two Groups

	Group I (3 Days)		Group II (≥5 Days)		Total
	Number of Patients	Percent	Number of Patients	Percent	
Appendicitis	22	52.4	23	48.0	45
Non-Appendicitis	20	47.6	25	52.0	45
Total	42	100	48	100	90

To achieve balance between the treatment groups, patients were stratified according to the site of infection (complicated appendicitis vs all other diagnoses). Enrollment into each stratum was closed when nearly 50% of cases were enrolled to limit the proportion of cases with complicated appendicitis. Criteria for complicated appendicitis were appendiceal perforation or periappendiceal abscess. Adequate surgical source control is a determinant key of the outcome in the intra-abdominal infections; thus, a panel of three surgeons was asked to review the adequacy of the surgical operation under blinded conditions.

Aerobic and anaerobic cultures of intraoperative specimens were obtained at baseline and processed in the clinical microbiology laboratory of the participating hospitals. All microorganisms isolated were cultured and tested for in vitro susceptibility to the study antibiotic ertapenem by disk diffusion or microtiter dilution according to guidelines of the National Committee for Clinical Laboratory Standards (NCCLS).[23,24] Routine susceptibility testing of strict anaerobes was not required per protocol.

Clinical and Laboratory Assessments

At enrollment, all patients underwent physical examination and laboratory studies, including a CBC with WBC and differential, platelet count, serum glucose, BUN, and serum creatinine. The same procedures were performed at day 3 and at the end of the study, at the post-treatment follow-up, or more frequently, as clinically indicated. Liver function studies, serum electrolytes, and urinalysis were performed as clinically indicated and at the discontinuation of intravenous study drug therapy. When clinically indicated during antibiotic therapy, blood, urine, and specimens from other clinically relevant intraabdominal sites were obtained for culture and susceptibility testing. Cultures were also performed at the end of antibiotic therapy, unless there was no material available to culture and/or no clinical evidence of infection.

In clinically and microbiologically evaluable patients, the clinical response considered the primary efficacy outcome was assessed at the test-of-cure (TOC) visit 2 and 4 weeks after discontinuation of antibacterial therapy as in previous trials comparing ertapenem with piperacillin–tazobactam and ceftriaxone/metronidazole.[17–19]

The clinical outcome of evaluable patients was classified into three groups: cure (no signs or symptoms of infection and no further antimicrobial therapy), failure (no improvement, infection progression, or death caused by infection), or late failure (recurrence between cessation of antibiotics and follow-up).

Microbiological responses were recorded for each baseline pathogen. Favorable microbiological responses included eradication of the pathogen(s) that was either documented or presumptive (no material available for culture in clinically cured patients); unfavorable microbiologic responses included persistence of the pathogen(s), whether documented or presumed (no material available for culture in patients who had clinical failure).

Data Analysis

Treatment groups were compared using a Pearson chi-square test or Fisher's exact test. Statistical significance was

Table 4 Site of Infections

	Group I		Group II		Total	
	Number of Patients	Percent	Number of Patients	Percent	Number of Patients	Percent
Appendix	22	52.3	23	47.9	45	50
Gallbladder and biliary tree	5	11.9	3	6.2	8	8.8
Colon	8	19	10	20.8	18	20
Stomach and duodenum	4	9.5	4	8.3	8	8.8
Small intestine	1	2.3	5	10.4	6	6.6
Others	2	4.7	3	6.2	5	5
Total	42	100	48	100		

Table 5 Value of the Score Systems

Apache II Score	Number of Patients (%)	Mean Value/ Mean Score
≤10	69 (87)	5
≥10 ≤20	10 (13)	14.1
	79 (87.7)	6.2
MPI score		
≤21	68 (79)	19.4
>21	18 (21)	28.6
	86 (95.5)	21.3

declared at the 0.05 level. All tests were two-sided. Two-sided 95% confidence intervals were calculated for the difference in efficacy parameters between the two groups.

Results

Patient Characteristics

Of 111 patients enrolled in the study, 90 were evaluable. The remaining 21 (19%) patients withdrew from the study because of the absence of pathogens in the culture taken at operation (n=14), because they were lost at follow-up (n=2), and because of protocol violations (n=5; Table 1).

The most important characteristics and the distribution of the patients between groups I and II are shown in Tables 2 and 3. There was no difference between the two groups with regard to either the number of men and women or the mean age. However, an analysis showed that, in men with appendicitis, the mean age was very low (25.1 years) compared with women without appendicitis (65.7%). A slight difference was noted between non-appendicitis patients treated for 3 days compared to the group treated for 5 days (47.6 vs 52%); all the differences between the two groups were not statistically significant.

The decision to stop randomization of patients with acute appendicitis allowed us to have two identical groups with regards to the site of infection (Table 4).

The mean Apache II score for all treated patients was 6.2%, and the MPI was 21.3%, indicating that the severity of the disease was always mild to moderate, which also explains why no important differences were noted between the two scoring systems (Table 5).

The two groups were well matched for concomitant diseases, present in one third of the evaluable patients, the

Table 6 Pathogens Recovered and Their Susceptibilities to Ertapenem

	Group I (3 Days)					Group II (≥5 Days)					
	Appendicitis		Non-Appendicitis			Appendicitis		Non-Appendicitis			
	S	R	S	R		S	R	S	R		
Aerobes Gram-positive											
Staphylococcus capitis		1									
Staphylococcus coagulase-negative						1	2				
Staphylococcus haemolyticus							1				
Other staphylococci	1		1					2			
Streptococci			3			1		1			
Enterococcus faecium									2		
Enterococcus faecalis									1		
Other enterococci	1		1			2		1			
Aerobes Gram-negative											
Escherichia coli	17		7		**24**	15		16		**31**	**55, 46.20%**
Enterobacter cloacae			1								
Enterobacter faecalis				1							
Pseudomonas				1		1	4				
Klebsiella				1				1			
Other *Enterobacter* spp								2			
Proteus								1			
Serratia						1					
Citrobacter								1			
Acinetobacter baumanii		1									
Anaerobes											
Bacteroides fragilis	3		5		**8**	4		9		**13**	**21, 17.60%**
Clostridium spp	1										
Fusobacterium frigens			1								
Peptostreptococcus						2					

Table 7 Incidence of Postoperative Complication

	Group I (3 Days)		Group II (≥5 Days)		Total
Infection	Appendicitis	Non-Appendicitis	Appendicitis	Non-Appendicitis	
Wound	2	1	2	2	7
Intraabdominal		1			1

most common being heart and lung disorders and neoplasms. The mean average duration of antibiotic therapy in group II was 5.7 days with a range from 5 to 10 days. The intervention was considered inadequate to control the source of infection detected intraoperatively in only one patient.

A total of 119 isolates were obtained from the 90 evaluable patients. The most important pathogens isolated were *Escherichia coli* from 55 patients (46.2%) and *Bacteroides fragilis* from 21 patients (17.6%); both pathogens were more frequent in group II. There were 15 resistant isolates represented mainly by Gram-negative aerobes and enterococci (Table 6).

A post-operative infection was recorded in eight patients: seven had a wound infection and one an intraabdominal abscess drained without reoperation. In three patients from group I, the wound infection was drained on an outpatient basis after hospital discharge. In the other four patients from group II, the wound infection was discovered in the hospital and was treated without antibiotic therapy. The intraabdominal infection was discovered while the patient was undergoing antibiotic, and the treatment was continued after the drainage (Table 7).

Clinical and Bacteriological Outcomes

The clinical and bacteriological outcomes are shown in Fig. 1. Thirty-nine patients in group I (92.9%) and 43 patients in group II (89.6%) were cured at the test of cure. The difference between the two groups was not statistically significant (Fig. 2).

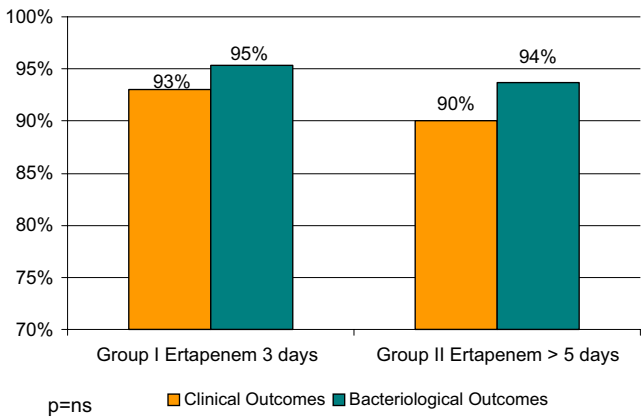


Figure 1 Clinical and bacteriological outcomes.

Complete eradication was achieved in 95.3% of patients in group I and 93.7% of patients in group II. This difference was not statistically significant. In the eight patients with a postoperative infection, cultures of the drainage material from the site of the infection were performed. The same pathogens as those present in the cultures taken at the operation were found in four patients in the cultures taken at infection site and were represented in three cases by *Staphylococcus* and in one case by *Klebsiella*, whereas in the other four patients, no germs were recovered. None of these germs were resistant to the study drug.

Safety

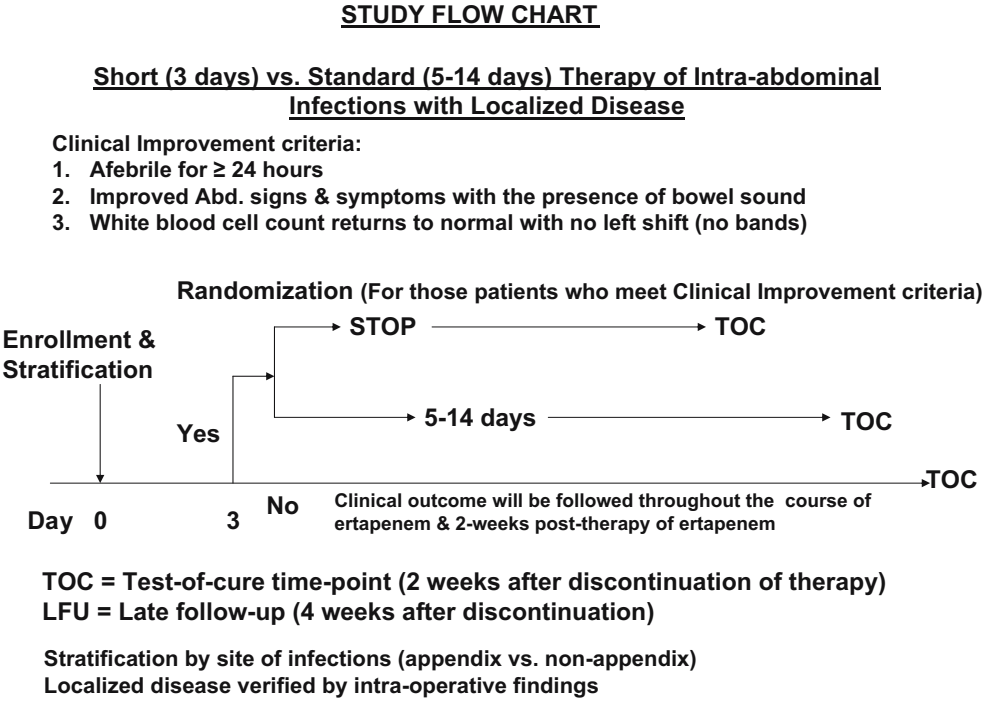
All 111 patients who received study medication were evaluated for clinical and laboratory adverse experiences. The presence of bowel movements was one of the parameters to assess the improvement of patients at day 3, and thus, specifically recorded by the investigators. None of the patients suffered from diarrhea up to day 3, whereas one case was observed in the group in a patient treated for more than 5 days. The most common drug-related adverse event was a local allergic erythema; digestive disorders were the second most common drug-related adverse event followed by mild increase of hepatic enzymes.

Discussion

The results of this study indicate that in patients with localized community-acquired intraabdominal infection (appendicitis and non-appendicitis), a short course (3 days) of ertapenem had the same clinical and bacteriological efficacy as a standard duration (≥5 days) of ertapenem. Clinical cure was achieved in 92.9% of patients in group I and in 89.6% of those in group II, whereas bacteriological eradication was achieved in 95.3% in group I and in 93.7% in group II. These differences in clinical and bacteriological outcome between the two treatments were not statistically significant. Our study demonstrated that, in patients showing clinical improvement after 3 days of treatment with ertapenem, discontinuation of antibiotic therapy was prudent and there were no differences in clinical success rates compared to patients treated with a standard duration therapy.

Our study validates for the first time the assumption that clinical parameters, such as normalization of temperature,

Figure 2 Study flow chart.



WBC count and return of gastrointestinal function, are reliable measures that can be used to monitor when to stop antibiotic therapy.[33] After discontinuation of the therapy at 3 days, none of the patients receiving placebo required another course of antibiotics. These data confirm also that the risk of subsequent treatment failure appears to be quite low for patients who have no clinical evidence of infection at the time of cessation of antimicrobial therapy.[10]

The previously reported observation that, in a certain number of patients, mainly those with acute appendicitis, there is contamination rather than an infection, as shown by the presence of negative cultures, is confirmed by our study in which sterile cultures were obtained from about 25% of patients with acute appendicitis.[4,6,9]

In these patients with non-perforated, uncomplicated appendicitis, a 24–48 h of antibiotic therapy is sufficient if a sound operative treatment has been performed.

There were no mortalities in this study, and the morbidity was represented mainly by wound infection (−n=7; 7.7%) and an intraabdominal infection (n=1; 1.1%). These figures are in line with those published in previous studies of patients with mild to moderate community-acquired intra-abdominal infections.[4,25–27]

The mild severity of the disease was also demonstrated by the low Apache II and MPI scores, although the median rates were close to those reported in published trials.[4,9]

As reported in previous studies, the bacteria recovered most frequently in this study were *E. coli* and *B. fragilis*. A number of enterococci were also present, and the majority were resistant to ertapenem.[28,29] However, we were unable to demonstrate whether they were responsible for causing postoperative wound infections. The same observation was made in other studies in which, despite the absence of coverage of bacteria present in the culture by the antibiotic regimen, the clinical success rate was similar to the other group treated with a broader-spectrum antibiotic.[30]

The bacteriological outcome was not significantly different between the two treatment groups. Eradication of the infecting organisms was observed in nearly 96% of all patients. In the four patients (4 of 90) who experienced bacteriological persistence after treatment with ertapenem, no ertapenem-resistant organisms were found. Persistence of *Staphylococcus* and *Klebsiella* spp. was recorded in those patients. None of these patients required an antibiotic course to treat the complication.

The frequency of adverse events was low in both groups and mainly represented by a local irritation and a mild elevation of hepatic enzyme. In the 3 days group was difficult to correlate this hepatic adverse event with the antibiotic treatment because of the administration of drugs concomitantly during the surgical procedure.

The conclusion of our study can be applied only to those patients with localized community-acquired intraabdominal infection who showed, after 3 days of treatment, a clinical improvement, thus, excluding patients with more severe form of peritonitis.

However, it is important to underline that the majority of patients admitted in the hospital with secondary peritonitis

present such a mild-to-moderate form of severity of the disease and that these patients are unlikely to need further parenteral antibiotic after 3 days of therapy.

Despite our study demonstrating that a 3-day course of ertapenem is as effective and safe as a standard course of ertapenem (≥5 days), additional larger prospective trials might be useful to support our results.

This reduction of antibiotic consumption may have important effects not only on the bacterial resistance[31] and but also on the cost of the health care. The possibility to discontinue the antibiotic treatment after 3 days results in a saving of the drug acquisition cost, of the cost associated with the labor (nursing time) and above all, in a shorter hospital stay (3 vs 5.6 days).

An analysis of the cost effectiveness of this trial would be worthwhile and is under evaluation.

The potential for reduced antibiotic use should be regarded as important support for the emerging concept that less antibiotic therapy to decrease antibiotic overuse may be used for less severe infections.[7,31] In such patients the fewer drugs used and the shorter the duration of treatment, the better.[7,32]

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