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SCIENTIFIC LETTERS

Ertapenem failure as therapy for nosocomial spontaneous bacterial peritonitis

FALLO DE ERTAPENEM EN EL TRATAMIENTO DE LA PERITONITIS BACTERIANA ESPONTÁNEA NOSOCOMIAL

Nosocomial spontaneous bacterial peritonitis (SBP) accounts for one third of all SBP episodes and is caused by microorganisms resistant to third generation cephalosporins (3rdGC) up to 40% of cases, mainly due to extended-spectrum β-lactamases (ESBL) *Escherichia coli* and *Klebsiella pneumoniae* producing strains, other *Enterobacteriaceae* spp. and some gram positive bacteria.[1] In this setting, 3rdGC must not be used as empirical antibiotic therapy in nosocomial SBP. Carbapenems have been recommended based in bacteriological data reported in these cases.[2,3] Ertapenem, a parenteral broad-spectrum 1-beta-methyl carbapenem was approved by FDA in US and in Europe for complicated intra-abdominal infections. We are treating nosocomial SBP with ertapenem provided that 93% of isolated bacteria in nosocomial SBP of our center were sensible in vitro to this carbapenem. We report three cases of nosocomial SBP caused by ertapenem-susceptible, ESBL-producing *E. coli* and *K. pneumoniae* with a microbiological and clinical failure to recommended standard doses of 1 g/24 h.

Case 1

A 62-year-old male cirrhotic patient was admitted because of refractory ascites and hepato-renal syndrome (HRS). He presented with anasarca and a MELD score of 24. After HRS recovery, he developed hepatic encephalopathy and fever with a creatinine of 66 μmol/L, albumin of 22 g/L and bilirubin of 121 μkat/L. He was receiving prophylaxis with norfloxacin. Ertapenem 1 g every 24 h was initiated. An ESBL-producing *K. pneumoniae* was isolated in ascitic fluid culture with a MIC < 0.5 mg/L for ertapenem, however after 48 h ascitic fluid (AF) PMN count was higher and culture was still positive. After changing therapy to meropenem 500 mg/8 h, the AF culture become negative and PMN count normalized.

Case 2

A 41-year-old female patient was admitted for fever and ascites 9 months after orthotopic liver transplantation. Creatinine was 110 μmol/L, albumin 36 g/L and bilirubin 12 μkat/L. She was immunosuppressed with tacrolimus. Ertapenem 1 g/24 h was begun. AF culture yielded an ESBL-producing *K. pneumonia* with a MIC <0.5 mg/L. During the following days, PMN count decreased but ascitic fluid culture remained positive. After 6 days, although the patient improved clinically, we changed antibiotic therapy to imipenem 500 mg/6 h and AF culture became negative after 24 h of therapy.

Case 3

A 65-year-old male was admitted due to acute variceal bleeding. Patient was treated following our standard protocol. He developed a hepato-renal syndrome and was treated with terlypressin and albumin. Creatinine was 152 μmol/L, albumin 29 g/L and bilirubin 121 μkat/L. AF analysis was diagnostic of SBP and ascitic and blood culture grew ESBL-*E. coli* with a MIC < 0.5 mg/L for ertapenem. In the following days, patient improved and the PMN count in ascitic fluid decreased; however AF culture remained positive until day 6 of therapy. We stopped antibiotic therapy at day 13 with normal PMN count and ascitic fluid culture finally negative. A summary of all AF analysis and cultures are shown in Table 1.

Carbapenems are considered the drugs of choice for serious infections due to ESBL-producing bacteria.[4] Ertapenem is a good option when coverage against *Pseudomonas aeruginosa* or *Acinetobacter baumannii* is not needed,[5] and it is recommended for the treatment of complicated intra-abdominal infections.[6] It is noteworthy that despite a good sensibility in vitro measured by a MIC of <0.5 mg/L, treatment failed to resolve infection in patient 1 and 2 and delayed SBP resolution in case 3. Verdier et al.[7] studied ertapenem concentration in plasma and peritoneal fluid from patients with severe intra-abdominal infections. The study showed that ertapenem at 1 gr/day achieved highly variable plasma and peritoneal antibiotic concentrations. Ertapenem had a good peritoneal diffusion, but concentrations were frequently below the susceptibility breakpoint for ESLB-*Enterobacteriaceae*. Data in cirrhotic patients with

Table 1 Asctic fluid, blood culture and polymorphonuclear count and antibiotic therapy in the three cases.

Case 1	Day 0	Day 2	Day 3	Day 7
AF* PMN&	200/μL	600/μL		200/μL
AF* culture	*Klebsiella pneumoniae*-ESBL	*Klebsiella pneumoniae*-ESBL		Negative
Blood culture	Negative	Not done		Not done
Antibiotic therapy	Ertapenem 1 g/24 h		Stop ertapenem. Meropenem 500 mg/8 h	Meropenem 500 mg/8 h

Case 2	Day 0	Day 2	Day 6	Day 7
AF* PMN&	5478/μL	1496/μL	525/μL	200/μL
AF culture	*Klebsiella pneumoniae*-ESBL	*Klebsiella pneumoniae*-ESBL	*Klebsiella pneumoniae*-ESBL	Negative
Blood culture	Negative	Not done	Not done	Not done
Antibiotic therapy	Ertapenem 1 g/24 h		Stop ertapenem. Imipenem 500 mg/6 h	Imipenem 500 mg/6 h

Case 3	Day 0	Day 2	Day 4	Day 6	Day 9	Day 13
AF* PMN&	7221/μL	4590/μL	2960/μL	560/μL	330/μL	<100/μL
AF* culture	*Escherichia coli*-ESBL	*Escherichia coli*-ESBL	*Escherichia coli*-ESBL	*Escherichia coli*-ESBL	Negative	Negative
Blood culture	*Escherichia coli*-ESBL	Not done	Not done	Not done	Not done	Not done
Antibiotic therapy	Ertapenem 1 g/24 h					Stop ertapenem

* Ascitic fluid.
& Polymorphonuclear count.

ascites are not available. Host factors as hypoalbuminaemia may have a profound effect on ertapenem pharmacokinetics producing a decreased concentration in plasma and tissues.[8] This may be relevant in cirrhotic patients. As others β-lactams, time above MIC is a key point to achieve good clinical and microbiological results and prevent resistance.

Resistance to ertapenem in ESBL-producing isolates during therapy may occur due to concurrent loss of porins and has been described in both *K. penumoniae*[9] and *E. coli*.[10] Nevertheless, in our three cases, MIC for ertapenem did not change during therapy in AF isolated bacteria.

Appropriate antibiotic empirical therapy in nosocomial SBP is unknown. Other carbapenem, imipenem and meropenem, and piperacillin–tazobactam alone or associated with glycopeptides have been suggested although randomized clinical trials are scanty.[11] Knowing prevalence and susceptibility of bacteria involved in nosocomial SBP in each center is mandatory to choose the best option. Pharmacokinetic studies of new therapies are needed. In critically-ill cirrhotic patients, ertapenem at 1 g/day may be insufficient due to hypoalbuminaemia and a low AF antibiotic concentration and 1 gr twice day may be more suitable for nosocomial SBP treatment.

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Solitary rectal ulcer in a teenage patient☆

Úlcera rectal solitaria en paciente adolescente

Solitary rectal ulcer syndrome (SRUS) is an exceptional disorder in paediatric and adolescent patients. It is often confused with other conditions, such as inflammatory bowel disease (IBD), delaying its diagnosis for years after the first consultation. We describe the case of a teenager with symptoms of tenesmus and rectal bleeding initially classified as ulcerative proctitis but who was later, in view of refractoriness to treatment, diagnosed with SRUS.

The patient was a 15-year-old boy with a history of bronchial asthma and a 1-year history of diarrhoea with up to 7 small-volume stools daily with mucus and haematochezia associated with colicky abdominal pain. Laboratory tests were normal. Colonoscopy revealed an erythematous inflamed erosive ring in the rectum with undamaged distal rectal mucosa and rest of the colonic mucosa normal; histological study reported non-specific chronic rectitis. With a presumed diagnosis of ulcerative proctitis, he initiated treatment with topical mesalazine and was referred to the IBD clinic for follow-up.

The patient was shy and withdrawn and reluctant to provide any information, so his mother described the symptoms. Due to the persistence of symptoms despite the treatment initially described, he was treated with a combination of both topical mesalazine with topical budesonide, and topical mesalazine with oral mesalazine, also with no response. Oral corticosteroids were also tried, similarly with no improvement observed.

At that time, in view of the refractoriness to treatment and the non-typical appearance of the ulcerative proctitis in the initial colonoscopy, we reconsidered the diagnosis and decided to repeat the endoscopic and histological study, observing persistence of a circumferential ring around 7–8 cm from the anal margin, polypoid, erosive and friable, but not affecting the distal rectal mucosa (Fig. 1). Biopsies reported benign border and base of the ulcer with development of granulation tissue, regenerative epithelial changes, and fibromuscular proliferation in the lamina propria, with no changes indicative of IBD, suggesting the possibility of a lesion associated with prolapse.

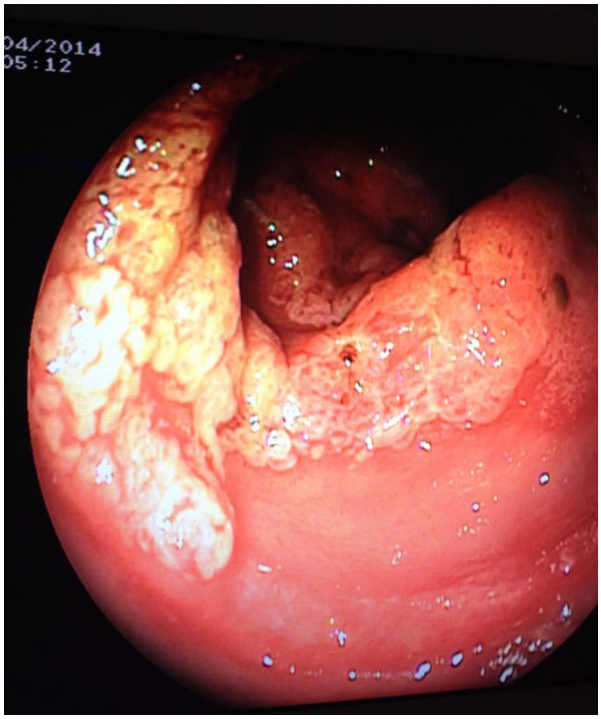

Figure 1 Rectoscopy: circumferential ring in mid-rectum with an erosive polypoid appearance.

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