



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 $\mu\text{mol/L}$, albumin of 22 g/L and bilirubin of 121 $\mu\text{kat/L}$. 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 $\mu\text{mol/L}$, albumin 36 g/L and bilirubin 12 $\mu\text{kat/L}$. She was immunosuppressed with tacrolimus. Ertapenem 1 g/24 h was begun. AF culture yielded an ESBL-producing *K. pneumoniae* 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 $\mu\text{mol/L}$, albumin 29 g/L and bilirubin 121 $\mu\text{kat/L}$. 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 ESBL-*Enterobacteriaceae*. Data in cirrhotic patients with ascites are not available. Host factors as hypoalbuminaemia

Table 1 Ascitic 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/ μ L	600/ μ L		200/ μ L		
AF [*] culture	<i>Klebsiella pneumoniae</i> -ESBL	<i>Klebsiella pneumoniae</i> -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/ μ L	1496/ μ L	525/ μ L	200/ μ L		
AF [*] culture	<i>Klebsiella pneumoniae</i> -ESBL	<i>Klebsiella pneumoniae</i> -ESBL	<i>Klebsiella pneumoniae</i> -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/ μ L	4590/ μ L	2960/ μ L	560/ μ L	330/ μ L	<100/ μ L
AF [*] culture	<i>Escherichia coli</i> -ESBL	<i>Escherichia coli</i> -ESBL	<i>Escherichia coli</i> -ESBL	<i>Escherichia coli</i> -ESBL	Negative	Negative
Blood culture	<i>Escherichia coli</i> -ESBL	Not done	Not done	Not done	Not done	Not done
Antibiotic therapy	Ertapenem 1 g/24 h					Stop ertapenem

* Ascitic fluid.

‡ Polymorphonuclear count.

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. pneumoniae*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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Úlcera rectal solitaria en paciente adolescente



Solitary rectal ulcer in a teenage patient

El síndrome de úlcera rectal solitaria (SURS) es un trastorno excepcional en pacientes pediátricos y adolescentes. Es habitual que se confunda con otras afecciones, como la enfermedad inflamatoria intestinal (EII), demorando su diagnóstico hasta años después de la primera consulta. Describimos el caso de un adolescente con clínica de tenesmo y rectorragia, inicialmente catalogado como proctitis ulcerosa, y que ante la refractariedad al tratamiento fue diagnosticado con posterioridad de SURS.

Se trata de un paciente de 15 años con antecedentes de asma bronquial, con clínica de diarrea de un año de evolución, con hasta 7 deposiciones diarias de escasa cuantía, con moco y hematoquecia, asociado a dolor abdominal cólico. Las determinaciones analíticas fueron normales y en la colonoscopia realizada se observó un rodete inflamatorio eritematoso y erosionado a nivel rectal con mucosa rectal distal indemne y resto de la mucosa colónica normal; el estudio histológico informó de rectitis crónica inespecífica. Con el diagnóstico de presunción de proctitis ulcerosa inició tratamiento con mesalazina tópica y fue remitido a la consulta monográfica de EII para seguimiento.

Recibimos en la consulta a un paciente tímido y retraído, del que era difícil sonsacar información, siendo la madre la que relataba los síntomas. Ante la persistencia de la clínica a pesar de tratamiento inicialmente prescrito, fue tratado con combinación tanto de mesalazina tópica con budesonida tópica, como de mesalazina tópica con mesalazina oral igualmente sin respuesta. Se ensayaron también corticoides orales igualmente sin observar mejoría.

En este momento, ante la refractariedad al tratamiento y el aspecto no típico de proctitis ulcerosa en colonoscopia inicial, nos replanteamos el diagnóstico y decidimos repetir el estudio endoscópico e histológico, observando persistencia de un rodete circunferencial a unos 7-8 cm desde margen anal, polipoide, erosionado y friable, respetando la mucosa

rectal distal (fig. 1). Las biopsias se informaron de borde y fondo de úlcera de naturaleza benigna con desarrollo de tejido de granulación, cambios epiteliales regenerativos, y proliferación fibromuscular en lámina propia, sin cambios indicativos de EII, sugiriendo la posibilidad de lesión asociada a prolapso. Reinterrogando al paciente sobre la clínica, con las dificultades antes mencionadas, parecía tratarse más de un cuadro de tenesmo y urgencia defecatoria con deposiciones de escasa cuantía, evacuación incompleta, y todo ello asociado a dolor abdominal cólico que mejoraba tras la defecación, suscitando la posibilidad de una alteración



Figura 1 Rectoscopia: rodete circunferencial en recto medio de aspecto polipoide y erosionado.