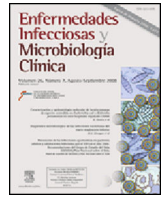




# Enfermedades Infecciosas y Microbiología Clínica

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## Scientific letters

### Ertapenem-induced neurological toxicity in a patient with stage IV chronic kidney disease<sup>☆</sup>



### Toxicidad neurológica por ertapenem en paciente con enfermedad renal crónica estadio IV

Dear Editor,

Ertapenem is a broad-spectrum antibiotic of the carbapenems class widely used in infections due to multi-resistant microorganisms.<sup>1</sup> Eighty per cent of its metabolization takes place in the kidneys, but there is still not enough information when it comes to its safety/effectiveness in situations of severe renal failure (SRF) with levels of creatinine clearance (CrCl) between 5 and 30 ml/min/1.73 m<sup>2</sup>,<sup>2</sup> which is why its label does not recommend its use in patients with these characteristics and in the absence of the necessary information to be able to make dose recommendations; for this reason contemplating other therapeutic alternatives in this situation is the most reasonable approach.

This is the case of a seventy-three-year-old male with a history of Parkinson's disease and chronic renal disease (CRD) with baseline creatinine levels of 4 mg/dl and CrCl levels of 12.6 ml/min/l using the MDRD-4 IDMS equation. Prior to the actual hospitalization the patient was treated out-patiently with IV ertapenem 1 g/24 h for four days following a urinary tract infection due to *Escherichia coli* – producer of extended-spectrum betalactamase. After completing the therapy, the patient developed the clinical manifestations of an acute confusional state, with temporal spatial disorientation; progressive lack of recognition of family and friends; visual and auditory hallucinations; generalized myoclonies; and persistent persecutory and occupational delusions. Initially, the patient was managed systematically through the administration of neuroleptics but the visual hallucinations did not cease, and his pre-existent stiffness and tremors worsened. He did not have a fever and both the axial computed tomography (CT) scan and the electroencephalogram did not show any signs of significant structural affection. The analysis conducted including the B<sub>12</sub> vitamin; the luetic serology; and the thyroid profile was normal. Similarly, the possibility of uremic encephalopathy as a contributing factor was ruled out, since the renal function was stable from the very moment of symptom onset.

Given the timeline of the clinical picture seen once the ertapenem course was completed, and after reasonably ruling out other causes, the diagnosis of acute ertapenem poisoning was suggested since the transience and dose accumulated in patients

with known CRD was consistent with what has previously been reported in the medical literature,<sup>1,3,4</sup> and followed the criteria of likely adverse drug reaction after using the algorithm by Naranjo et al.<sup>5</sup> The patient was then treated with levomepromazine for symptomatic control and hemodialysis was ruled out since ertapenem has both a large volume of distribution and a high percentage of plasmatic protein binding.<sup>6</sup> Progressively, during the next few days the patient improved gradually until reaching ad integrum functional recovery three weeks after completing the therapy with ertapenem, and without any objective neurological effects.

Nonepileptic neurotoxicity due to ertapenem is rare as we can see in the cases described by the medical literature,<sup>1–3,7</sup> but actually one of these cases has been reported in our own country. So far, almost all the disclosed cases have occurred in patients with stage IV CRD (some of them on hemodialysis), who were over 70 years of age, and with a prior accumulated dose of up to 4 g of ertapenem. The appearance of this clinical picture may still happen even after dose titration aimed at reducing the dose administered (500 mg/day) in 50 per cent of the patients.<sup>8</sup> Typically, the neurological clinical manifestations occurred 5–7 days after the administration of the last dose and persisted for another 10–15 days with subsequent complete symptomatic resolve. From the neurological point of view, the patients showed an acute confusional state and clinical manifestations of mood changes that were regarded as psychotic outbreaks, at first, in most of the cases.<sup>1–3,9</sup> The prior neurological condition seems to promote the development of this toxicity that is associated with ertapenem; in our case, the patient had a prior history of Parkinson's disease.<sup>10</sup>

In our patient we were able to see all the circumstances and situations described by the medical literature as well as the temporal correlation between the use of the drug and the appearance of symptomatology compatible with the aforementioned symptoms. This aspect is essential if we want to establish causality between the antibiotic and the described clinical manifestations. We should also say that the time elapsed until ad integrum recovery was achieved was longer than expected based on the cases published so far.<sup>1</sup>

Although the appearance of neuropsychiatric symptoms after the administration of ertapenem is extremely rare, it seems reasonable to be extra careful when titrating the dose and estimating the total accumulated dose in elder patients with CRD.

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DOI of original article: <http://dx.doi.org/10.1016/j.eimc.2016.12.003>

<sup>☆</sup> Please cite this article as: Almorza T, Muñoz-Hernández M, Lalueza A. Toxicidad neurológica por ertapenem en paciente con enfermedad renal crónica estadio IV. *Enferm Infecc Microbiol Clin.* 2017;35:607–608.

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2529-993X/

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## Age distribution of acute respiratory infections caused by enteroviruses in the child population<sup>☆</sup>



### *Distribución etaria de las infecciones respiratorias agudas causadas por los enterovirus en la población infantil*

Dear Editor,

Acute respiratory infections (ARI) are an entity that primarily affects the child patient population. Out of all the different viruses involved here, the enteroviruses (EV) have been reported to have an incidence of 3–7 per cent.<sup>1,2</sup> EVs are transmitted through the fecal-oral route, and they can be sporadic or community outbreaks. We attribute them their etiologic participation in the ARIs of the upper (rhinitis and pharyngitis) and lower respiratory tracts (bronchiolitis, bronchitis, and pneumonia).<sup>1–3</sup>

Although their preference for child age is widely known (<15 years old) probably due to their scant immunity, there are very few studies establishing a correlation between age of presentation and type of EV found.<sup>4–6</sup>

We hereby present a retrospective study on the age distribution of ARIs due to EVs in the child patient population in the Balearic Islands, Spain. During the study period, November 2015 through June 2016, one respiratory sample was collected from all children presenting to the ER with clinical suspicion of ARI.

Viral detection took place using one real time RT-PCR genomic amplification technique capable of detecting both simultaneously and differentially 16 different types of viruses (Allplex<sup>®</sup> Respiratory Full Panel Assay; Seegen, South Korea). This technique allows us to distinguish between enteroviruses and rhinoviruses, but it won't help typing the different kinds of enteroviruses that exist. The samples that tested positive for enterovirus were taken to the National Center of Microbiology (Madrid, Spain) for the ultimate typing process.

Across the study 2754 samples were analyzed, out of which 1461 (53 per cent) tested positive. In this period, we found 115 cases of ARIs due to EV, which amounts to 4.1 per cent of all the samples collected, and 7.8 per cent of the ones that tested positive. The *Echovirus* was responsible for 17.3 per cent of the infections, the

*Coxsackievirus* type A of 33 per cent of the ARIs, the *Coxsackievirus* type B of 9.5 per cent, the EV-D68 of 33 per cent of the infections, and the EV-A71 of 6.9 per cent of all the ARIs (Table 1). Twenty (20) different types of viruses were found being the following ones the most common of all: EV-D68 (38 cases – 33 per cent), *Coxsackievirus* A6 (14 cases – 12.1 per cent), EV-A71 (8 cases – 6.9 per cent), and *Coxsackievirus* A10 (8 cases – 6.9 per cent).

The patients' main clinical presentations were: cold (44.3 per cent); bronchiolitis (20 per cent); pharyngotonsillitis (10.5 per cent); bronchitis (9.5 per cent); bronchospasm (9.5 per cent); and pneumonia (6 per cent).

22.6 per cent of the cases debuted <6 months old, 55.6 per cent >1 year old, and 75.6 per cent <2 years old (Table 1). Fifteen (15) cases were found in the neonatal stage, most of them due to *Echovirus* and EV-D68. Fifty-three (53) per cent of the cases were found between 6 and 24 months old. Sixty (60) per cent of *Echoviruses* were found <6 months old, 50 per cent of *Coxsackievirus* type A between 6 and 12 months old, 45.4 per cent of *Coxsackievirus* type B between 6 and 12 months old, 50 per cent of EV-D68 <12 months old, and 50 per cent of EV-A71 between 6 and 12 months old.

The average age of patients with *Echovirus* was 12.7 months old (range: 17 days–4 years), the average age of those with *Coxsackievirus* type A, 21.5 months old (range: 14 days–5 years), the average age of patients with *Coxsackievirus* type B, 30.8 months old (range: 1 month–9 years), that of patients with EV-D68, 32.4 months old (range: 1 month–9 years), and the average age of patients with EV-A71, 17 months old (range: 5 months–3 years).

We were able to confirm that *Echoviruses* are predominant during the neonatal stage and in patients under 6 months old. How-

**Table 1**

Age distribution of respiratory infections due to enterovirus.

	Echo	CoxA	CoxB	D68	A71	Total
<1 m	8 (53.3) <sup>a</sup>	1 (6.6)	1 (6.6)	5 (33.3)	0	15 (13)
1–6 m	4 (36.3)	0	0	6 (54.5)	1 (9)	11 (9.5)
6–12 m	2 (5.2)	19 (50)	5 (13.1)	8 (21)	4 (10.5)	38 (33)
12–24 m	2 (8.6)	10 (43.4)	2 (8.6)	7 (30.4)	2 (8.6)	23 (20)
2–4 a	4 (23.5)	6 (35.2)	1 (5.8)	5 (29.4)	1 (5.8)	17 (14.7)
>4 a	0	2 (18.1)	2 (18.1)	7 (63.6)	0	11 (9.5)
	20 (17.3)	38 (33)	11 (9.5)	38 (33)	8 (6.9)	115

Echo: *Echovirus*; CoxA: *Coxsackievirus* type A; CoxB: *Coxsackievirus* type B; D68: EV-D68; A71: EV-A71.

<sup>a</sup> Number of cases (percentage on the total number of cases).

DOI of original article: <http://dx.doi.org/10.1016/j.eimc.2016.12.007>

<sup>☆</sup> Please cite this article as: Reina J, Cabrerizo M. Distribución etaria de las infecciones respiratorias agudas causadas por los enterovirus en la población infantil. *Enferm Infecc Microbiol Clin.* 2017;**35**:608–609.