Última serología (ELISA): IgG 1 U (positivo > 0,8) el 2 de diciembre del 2020.

A las 4:00 del día 19 de enero se despertó con taquicardia de hasta 136 lpm y extrasístoles. Posteriormente, apareció dolor en el lugar de la punción, cansancio, escalofríos, febrícula, mialgias, artralgias, cefalea e hipersensibilidad cutánea generalizada. Toda esta sintomatología desapareció tras 36 h, salvo la extrasistolia sintomática que ha sido valorada por el Servicio de Cardiología, pautándose tratamiento farmacológico y seguimiento. Las extrasístoles no han remitido a pesar de haber transcurrido más de 1 semana desde la administración de la primera dosis de la vacuna.

Se da la circunstancia de que 2 de los 3 casos tenían como antecedente enfermedad tiroidea que, por sí misma, podría ser causa de taquicardia, pero esta asociación se descartó ya que en ambas los controles tiroideos han permanecido estables en los últimos años.

Consideramos que es preciso contrastar la aparición de esta reacción adversa tras la recepción de la vacuna en sujetos con historia de infección previa por SARS-CoV-2 y en caso de confirmarse deberían tomarse las medidas necesarias en sujetos con cardiopatía previa.

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## Therapeutic drug monitoring of colistin in plasma and cerebrospinal fluid in meningoventriculitis caused by a carbapenem-resistant *Enterobacter cloacae*

## *Monitorización terapéutica de niveles de colistina en plasma y líquido cefalorraquídeo en meningoventriculitis causada por* Enterobacter cloacae *resistente a meropenem*

### Clinical case

A 35-year-old 80 kg man was admitted in the Resuscitation Unit after a craniotomy and the placement of a double external ventricular drainage for a malignant midline glioma with obstructive hydrocephalus. After three weeks, when the patient presented septic symptoms (C-reactive protein of 23 mg/dL, 4220 leukocytes/mm$^3$) the drainages were replaced. The cerebrospinal fluid (CSF) biochemistry was compatible with a bacterial central nervous system (CNS) infection (glucose < 2 mg/dL and proteins 550 mg/dL). Broad spectrum antibiotic therapy was started with intravenous (IV) linezolid 600 mg q12h and meropenem 2000 mg q8h in a 4h extended infusion.

Five days later, a Class B carbapenemase (metallo-β-carbapenemase)-producing *Enterobacter cloacae* with intermediate susceptibility to meropenem with minimum inhibitory concentration (MIC) of 8 mg/L and susceptible to colistin (MIC = 0.20 mg/L) was isolated in both CSF and blood cultures (drainages were not cultured). In addition, a Class A carbapenemase (KPC)-producing *Klebsiella pneumoniae* (colistin MIC ≤ 2 mg/L) and an extensively drug-resistant *Pseudomonas aeruginosa* (colistin MIC ≤ 0.5 mg/L; meropenem MIC = 8 mg/L) were isolated in blood cultures. These nosocomial microorganisms were not isolated in any other culture and they could be a consequence of an incorrect drainage manipulation in a COVID pandemic situation, with a higher prevalence of multi-drug resistant bacteria. Linezolid was stopped and intravenous colistimethate sodium (CMS) at a dose of 6 MIU q12h was added to meropenem due to the synergic effects of both antibiotics.[1] In addition, intraventricular colistin (10 mg q4h administered through each CSF drainage) was added to try to ensure therapeutic concentrations into the CSF, as described in exceptional cases.[2,3]

On day 7 of CMS treatment, total colistin sulphate levels in plasma, determined by high performance liquid chromatography, were infratherapeutic ($C_{ss}$ < 2 mg/L). Due to severity of the infection,

**Table 1**
Colistin levels in plasma and CSF.

| Day of CMS treatment | Extraction time | Extraction site | Colistin concentration (mg/L) |
|---|---|---|---|
| 7 | Trough or pre IV dose | Plasma | 1.0 |
| 7 | Trough or pre IT dose | Right CSF drain | 2.5 |
| 7 | Peak (3 h after IT administration) | Right CSF drain | 5.6 |
| 7 | Trough or pre IT dose | Left CSF drain | 2.5 |
| 7 | Peak (3 h after IT administration) | Left CSF drain | 4.4 |
| 15 | Trough or pre IV dose | Plasma | 1.0 |

CSF levels of colistin were also determined and ranged between 2.5 and 5.6 mg/L, a value 10 times higher than the colistin MIC. Both IV and intraventricular CMS doses were maintained. Eight days later plasma colistin concentration were still low (see Table 1). The intraventricular and IV CMS treatments were stopped after 15 and 30 days, respectively. Finally, after 63 days in the Resuscitation Unit, the patient could be discharged to a conventional hospital ward without any signs and symptoms of an active CNS infection.

Colistin-associated nephrotoxicity[4] was not observed during CMS treatment being the estimated glomerular filtration rate greater than 120 ml/min/1.73 $m^2$ during treatment. Neurotoxicity, a side effect caused by colistin,[5] could not be assessed because patient's impaired status of consciousness caused by a diencephalic irritation during the previous surgery.

Meningoventriculitis caused by *Enterobacter* spp. is a rare infectious complication in neurosurgical patients but associated with a high morbidity and mortality.[6] The treatment is often complex due to the isolation of bacterial strains resistant to multiple antibiotics, such as third-generation cephalosporins and even, as in the present case, to carbapenems. In these cases, colistin becomes one of the last available therapeutic options.

The achievement of adequate antibiotic concentrations at the infection site is essential in these difficult-to-treat infections. Although CNS penetration in patients with meningoventriculitis might be increased by 60% for some antimicrobials, in other cases intraventricular administration may be necessary to reach therapeutic levels.[7]

Colistin is an antimicrobial with a very complex pharmacokinetics. Therapeutic plasma colistin concentrations are difficult to achieve, even after the administration of very high CMS doses, especially in patients with conserved renal function.[8] This is due to the fact that CMS is rapidly renally excreted before it can be hydrolyzed to colistin, the active compound.[7] In addition, colistin penetration into the CSF after its IV administration has been reported to be very low and variable, ranging between 5% and 7% in some experiences and[7] up to 25% in others.[9]

Our patient, with preserved renal function, presented suboptimal colistin plasma levels, even after the administration of a high CMS IV dose.[8] The local intraventricular administration allowed to achieve optimal colistin levels in CSF (10 times above the MIC).[7]

In conclusion, when using colistin for the treatment of a CNS infection, local intraventricular administration could be necessary to reach optimal levels at the infection site, especially in the case of young patients with preserved renal function and infections caused by multi-drug-resistant Gram-negative bacteria.

In addition, therapeutic drug monitoring of colistin may be a useful strategy for optimizing the treatment of these complicated infections that can help to ensure an optimal exposure while reducing the risk of nephrotoxicity.

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## *Pantoea stewartii:* ¿un nuevo patógeno causante de bacteriemia?

### Pantoea stewartii*: A new pathogen as a cause of bacteriemia?*

El género *Pantoea* está actualmente formado por 31 especies y 2 subespecies de bacilos gramnegativos *(List of Prokaryotic Names with Standing in Nomenclature*; http://lpsn.dsmz.de). Son microorganismos raramente considerados como patógenos cuya especie más relevante en seres humanos es *Pantoea agglomerans (P. agglomerans)*, anteriormente denominada *Enterobacter agglomerans*[1,2]. En 1993, *Pantoea stewartii (P. stewartii)* fue transferida desde el género *Erwinia*, formando una nueva especie dentro del género *Pantoea*[3]. Según nuestro conocimiento, se describe por primera vez una bacteriemia causada por *P. stewartii* en una paciente con un ictus cerebral.

Mujer de 57 años, con hipertensión arterial y aneurisma de localización basilar, que es ingresada en la Unidad de Cuidados Intensivos tras realización de una arteriografía, la colocación de un *stent* y la embolización del aneurisma. Al finalizar dicho procedimiento, manifiesta náuseas, diplopía y disminución del nivel de consciencia, realizándose una nueva arteriografía, observándose trombosis completa del *stent* implantado, procediéndose a colocar uno nuevo. En una tomografía axial computarizada craneal se observaron múltiples infartos en el territorio posterior con afectación bulbar. Clínicamente, la paciente se encontraba tetrapléjica con respuesta motora patológica extensora. Tras 48 días de ingreso, la paciente presentó dolor abdominal y fiebre