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

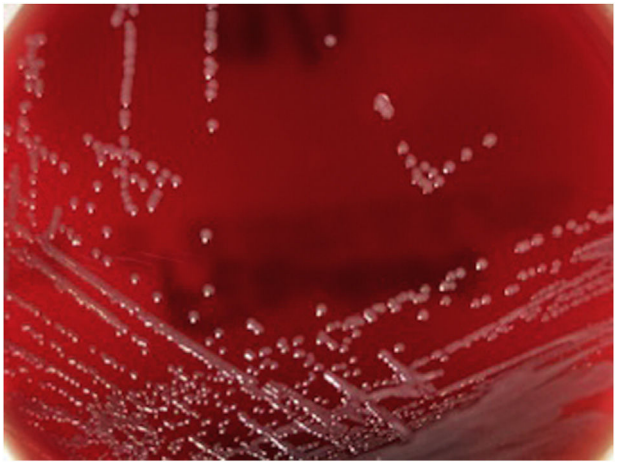

Figura 1. Se observan colonias blanco-grisáceas, redondeadas y brillantes en agar sangre, finalmente identificadas como *Pantoea stewartii* (crecimiento a las 18 h).

Figura 2. Se observan colonias azuladas de *Pantoea stewartii* en UriSelect™ 4 Medium (crecimiento a las 48 h).

(38,5 °C). Antes del inicio de antibioterapia, se extrajeron 2 tomas de hemocultivos y una muestra de orina para cultivo (que resultó negativa). Además, se inició tratamiento empírico con levofloxacino (500 mg/12 h/IV). Los hemocultivos se incubaron en el sistema de monitorización BACTEC FX (Becton Dickinson, Frankin Lakes, NY, EE. UU.). Tras 11 h de incubación, las 2 tomas resultaron positivas, realizándose subcultivo en agar, incubándose a 37 °C. En la tinción de Gram, se observaron bacilos gramnegativos y, a las 18 h de incubación, se observó crecimiento de abundantes colonias circulares, grisáceas y brillantes en cultivo puro en agar sangre (fig. 1). Hubo también crecimiento de colonias con pigmentación azulada en UriSelect™ 4 Medium (Bio-Rad, Francia) (fig. 2). Se realizó identificación mediante MALDI-TOF MS versión 9 (8.468 msp) (Bruker Biotyper, Billerica, MA, EE. UU.), identificándose como *Pantoea septica* (score 2,30), con un rango de identificación medianamente concordante (hasta rango 5). No obstante, la cepa se envió al Centro de Genómica e Investigación Oncológica (GENYO, Granada, España) para análisis del gen 16S ARNr mediante secuenciación[4]. Se amplificó un fragmento de 1,212 pares de bases, obteniéndose una similitud del 99,69% con *P. stewartii*, cepa 08BF 11 TN (número de acceso KX 146472.1). La sensibilidad a antimicrobianos se realizó utilizando el sistema MicroScan WalkAway System (Beckman Coulter, Inc, CA, EE. UU.), panel NC82 para enterobacterias, siendo sensible a todos los antibióticos testados, excepto a ampicilina (CMI > 8 μg/ml). La interpretación se realizó siguiendo los criterios establecidos por el EUCAST[5]. Se sustituyó el tratamiento antibiótico por ciprofloxacino (400 mg/12 h/IV) manteniéndose durante 10 días. Tras el cuarto día de tratamiento, la fiebre desapareció y, desde el punto de vista neurológico, la paciente evolucionó favorablemente con recuperación de parte de la movilidad. Tras 4 meses de ingreso fue dada de alta.

Pantoea spp. son microorganismos gramnegativos, no encapsulados y no formadores de esporas, que se pueden aislar de plantas, semillas, muestras ambientales y de heces humanas[1,2]. La especie más frecuentemente patógena en humanos es *P. agglomerans*[6], que puede producir infección en diversas localizaciones, incluso brotes a nivel hospitalario[7,8]. En general, existen pocos casos descritos de infección por este género, aunque se ha descrito bacteriemia por *Pantoea dispersa*[9].

En general, se consideran microorganismos de baja patogenicidad y la mayoría de los casos de infección se producen en pacientes inmunodeprimidos. También pueden producir infecciones en inmunocompetentes, sobre todo colecistitis, y en los últimos años se han descrito como productores de sepsis neonatal con una frecuencia creciente[10]. Es de destacar que los casos descritos han respondido de forma favorable al tratamiento antibiótico. Suelen ser muy sensibles a antimicrobianos, pero la mayoría de cepas de *P. agglomerans* son resistentes a fosfomicina. La introducción de MALDI-TOF MS en la rutina diagnóstica puede conducir a la identificación de nuevas especies de patógenos poco frecuentes. Sin embargo, en determinadas circunstancias, como un bajo *score* de identificación, diagnóstico poco consistente o la presencia de microorganismos poco habituales, la identificación definitiva debería realizarse mediante técnicas moleculares, como la secuenciación del 16S ARNr. Cuando se utiliza MALDI-TOF MS para la identificación, alguna especie de *Enterobacterales*, como *Klebsiella ozaenae*, puede confundirse de forma errónea con microorganismos pertenecientes al género *Pantoea*[9]. De entre todas las características bioquímicas de *P. stewartii* destaca, junto a *Pantoea ananatis*, la positividad de la prueba del indol (solo la subespecie *indologenes*) y la hidrólisis de gelatina que podría ayudar a distinguirla de otras especies. Sin embargo, debido a la heterogeidad genética, este género es difícil de identificar mediante pruebas bioquímicas.

En conclusión, según nuestro conocimiento, este es el primer caso de bacteriemia producida por *P. stewartii* en cultivo puro. Este caso enfatiza la necesidad de confirmar los resultados en las circunstancias anteriormente reseñadas.

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HIV infection in the setting of PrEP: Development of antiretroviral resistance and breakthrough infection. Report of two cases in real-life

Infección por el VIH en el contexto de la PrEP: desarrollo de resistencia a los fármacos antirretrovirales e infección de brecha. Descripción de 2 casos en la vida real

Dear Editor:

Pre-exposure prophylaxis (PrEP) is a biomedical intervention aimed at preventing the transmission of the human immunodeficiency virus (HIV) in people at high risk of infection. Currently, the most frequent route of HIV transmission in Spain is sexual intercourse. It accounted for 83.1% of new HIV diagnoses in 2018, representing gay, bisexual and other men who have sex with men (MSM), the 56.4% of new diagnoses.[1]

The currently approved regimen by the European Medicines Agency (EMA) and suggested by the European AIDS Clinical Society (EACS) consists of co-formulated TDF/FTC[3] 1 tablet per day. The implementation of PrEP has shown a significant decrease in new HIV infections among vulnerable population.[2]

Although PrEP was approved by EMA several years ago, it became available in Spain in November 2019.[3] The initial experience with our PrEP implementation has been recently published.[4] PrEP is highly effective when adherence is high; however, rare cases of seroconversion may occur, mostly when adherence is poor. Resistance to antiretroviral therapy (ART), mostly to 3TC can occur, being most frequent when PrEP is initiated in extremely early cases where Ag/Ab test have been negative, or when the patient acquire infection between the screening period and PrEP initiation.[5] We report two cases of HIV infection in PrEP users who developed resistance to ART.

The first case is a 23-year-old male sex worker, who practiced chemsex and had been using PrEP for 6 months at another institution who was transferred to our center to continue PrEP In the baseline visit, positivity for HIV Ag/Ab was detected. Genotyping revealed mutations for M184V and K103N, suggesting exposure to a resistant strain. The patient reported use of condoms in more than 90% of cases but irregular adherence to PrEP. Fig. 1A shows the temporal evolution of the case.

The second case is a 35-year-old male, who started the PrEP program with a first negative screen Ag/Ab test for HIV. At 15 days, a new determination for HIV (Ag/Ab rapid test) was performed prior to PrEP initiation. At one month PrEP visit, rapid Ag/Ab test was positive. Viral load revealed 24,600 copies/mL, and the resistance genotyping test showed M184V and M184I substitution in a significant proportion (>90% of sequences for both substitutions together). Probably, the patient could have been infected within a few days before the time of the screening or between the time of screening and PrEP initiation. Fig. 1B shows the temporal evolution of the case.

The implementation of the PrEP in Spain represents a major progress in HIV prevention. However, many centers are still developing PrEP programs and real-life experience may be useful to prevent cases of seroconversion and development of resistances to ART that may limit treatment options.[6] The two cases described emphasize the importance of baseline determinations prior to PrEP initiation, as well as the need for regular periodic controls as recommended in most PrEP protocols and guidelines.[2,3] There are several scenarios for acquiring HIV infection and developing resistance in PrEP users. Exposure to a resistance strain seems to be the mechanism for the case 1 (although his adherence was also poor), while initiation of PrEP in an extremely early infection seems to be the mechanism for the second.

The period between initial screening in the program and PrEP initiation is critical and may drive to rapid development of resistance is HIV infection is unnoticed, as described by our second case. A molecular test (such as a PCR) could be considered for screening, but its cost limits this approach. In addition, the recommendations of condom use should be stressed in this period. As PrEP users seroconverting have frequently lower viral load compared to non-PrEP users, primary HIV infection is asymptomatic and, sometimes, seroconversion is delayed complicating diagnosis of infection.[5] This more difficult diagnosis has been also described in the PrEP trials with cabotegravir long-acting[7] and should

[3] Tenofovir disoproxilo/Emtricitabine.