later; pain at the puncture site; and, eight hours later, tiredness, chills, fever, muscle pain, joint pain and runny nose.

Case 3

The third case was a 51-year-old woman with no personal history of note.

She presented acute disease on 6 March 2020, with tiredness, muscle pain, joint pain, headache, fever, skin hypersensitivity, dry cough and diarrhoea.

She had a positive PCR test on 19 March and a negative one on 2 April 2020.

The result of her latest serology (ELISA) was IgG 1 U (positive >0.8) on 2 December 2020.

At 4:00 AM on 19 January, she woke up with tachycardia of up to 136 bpm and extrasystoles. Subsequently, she developed pain at the puncture site, tiredness, chills, fever, muscle pain, joint pain, headache and generalised skin sensitivity. All these symptoms resolved after 36 h, except her symptomatic extrasystoles, for which she was assessed by the cardiology department and prescribed drug treatment with follow-up. Her extrasystoles have not remitted even though more than one week has elapsed since the administration of the first dose of the vaccine.

It so happens that two out of the three cases had a history of thyroid disease, which in itself might be a cause of tachycardia; however, this association was ruled out since both cases showed stable thyroid laboratory test results in recent years.

We find it necessary to confirm the onset of this adverse reaction after vaccine administration in subjects with a history of prior SARS-CoV-2 infection and, if it is confirmed, take the required measures in subjects with prior heart disease.

References

1. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. N Engl J Med. 2020;27:2603–15.
2. Informe sobre la situación de COVID-19 en personal sanitario en España a 21 de mayo de 2020. Equipo COVID-19. RENAVE. CNE. CNM (ISCIII), [Accessed 25 January 2021]. Available from: https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documents/INFORMES/Informes%20COVID-19/COVID-19%20en%20Espa%C3%B1a.%20Situaci%C3%B3n%20en%20Sanitarios%20a%2021%20de%20mayo%20de%202020.pdf.
3. Ficha Técnica Comirnaty concentrado para dispersión inyectable, [Accessed 22 January 2021]. Available from: https://cima.aemps.es/cima/dochtml/ft/1201528001/FT_1201528001.html.
4. 1.ª Informe de Farmacovigilancia sobre vacunas COVID-19 (25-01-2021). Agencia Española de Medicamentos y Productos Sanitarios, [Accessed 26 January 2021]. Available from: https://www.aemps.gob.es/la-aemps/ultima-informacion-de-la-aemps-acerca-del-covid%E2%80%9119/vacunas-contra-la-covid%E2%80%9119/1o-informe-de-farmacovigilancia-sobre-vacunas-covid-19-25-01-2021/.
5. Nota Informativa vacuna en individuos que ya han pasado la enfermedad. Sociedad Española de Inmunología, [Accessed 22 January 2021]. Available from: https://www.inmunologia.org.

M. Teresa Marco García [a,*], Álvaro Torres Lana [b], M. Berta Anta Agudo [a], M. de la Trinidad Rufino Delgado [a]

[a] *Gerencia de Atención Primaria de Tenerife, Servicio Canario de Salud, Santa Cruz de Tenerife, Spain*
[b] *Dirección General de Salud Pública, Servicio Canario de Salud, Santa Cruz de Tenerife, Spain*

* Corresponding author.
E-mail address: mmargart@gobiernodecanarias.org (M.T. Marco García).

https://doi.org/10.1016/j.eimce.2022.03.002

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]

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

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, 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.

References

1. Branka B, Car H, Slačanac D, Sviben M, Čačić M, Lukić-Grlić A, et al. In vitro synergy and postantibiotic effect of colistin combinations with meropenem and vancomycin against Enterobacteriaceae with multiple carbapenem resistance mechanisms. J Infect Chemother. 2018;24:1016–9.
2. Karaiskos I, Galani L, Baziaka F, Giamarellou H. Intraventricular and intrathecal colistin as the last therapeutic resort for the treatment of multidrug-resistant and extensively drug-resistant acinetobacter baumannii ventriculitis and meningitis: a literature review. Int J Antimicrob Agents. 2013;41:499–508.
3. Ziaka M, Markantonis SL, Fousteri M, Zygoulis P, Panidis D, Karvouniaris M, et al. Combined intravenous and intraventricular administration of colistin methanesulfonate in critically ill patients with central nervous system infection. Antimicrobials Agents Chemother. 2013;57:1938–40.
4. Javan AO, Shokouhi S, Sahraei Z. A review on colistin nephrotoxicity. Eur J Clin Pharmacol. 2015;71:801–10.
5. Dai C, Xiao X, Li J, Ciccotosto GD, Cappai R, Tang S, et al. Molecular mechanisms of neurotoxicity induced by polymyxins and chemo-prevention. ACS Chem Neurosci. 2019;10:120–31.
6. Foster DR, Rhoney DH. Enterobacter meningitis: organism susceptibilities, antimicrobial therapy and related outcomes. Surg Neurol. 2005;63:533–7.
7. Nau R, Blei C, Eiffert H. Intrathecal antibacterial and antifungal therapies. Clin Microbiol Rev. 2020;33:190–219.
8. Garonzik SM, Li J, Thamlikitkul V, Paterson DL, Shoham S, Jacob J, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrobials Agents Chemother. 2011;55:3284–94.
9. Jimenez-Mejias ME, Pichardo-Guerrero C, Márquez-Rivas FJ, Martín-Lozano D, Prados T, Pachón J, et al. Cerebrospinal fluid penetration and pharmacokinetic/pharmacodynamic parameters of intravenously administered colistin in a case of multidrug-resistant acinetobacter baumannii meningitis. Eur J Clin Microbiol Infect Dis. 2002;21:212–4.

Pablo Acín[a], Sonia Luque[a,b,c,*], Luisa Sorli[b,c,d,e], Santiago Grau[a,b,c,f]

[a] *Pharmacy Department, Hospital del Mar, Parc de Salut Mar, Barcelona, Spain*
[b] *Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain*
[c] *Infectious Pathology and Antimicrobials Research Group (IPAR), Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain*
[d] *Infectious Diseases Department, Hospital del Mar, Parc de Salut Mar, Barcelona, Spain*
[e] *Universitat Pompeu Fabra, Barcelona, Spain*
[f] *Universitat Autònoma de Barcelona, Barcelona, Spain*

* Corresponding author.
E-mail address: sluque@parcdesalutmar.cat (S. Luque).

https://doi.org/10.1016/j.eimc.2021.02.011

Pantoea stewartii: A new pathogen as a cause of bacteremia?☆

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

The genus *Pantoea* currently comprises 31 species and two subspecies of Gram-negative bacilli (List of Prokaryotic names with Standing in Nomenclature; http://lpsn.dsmz.de). These microorganisms are rarely considered pathogenic; the most significant species in humans is *Pantoea agglomerans (P. agglomerans)*, previously called *Enterobacter agglomerans*[1,2]. In 1993, *Pantoea stewartii (P. stewartii)* was transferred from the genus *Erwinia*, thus forming a new species within the genus *Pantoea*[3]. To our knowledge, this is the first report of bacteraemia caused by *P. stewartii* in a patient with a stroke.

A 57-year-old woman with hypertension and a basilar aneurysm was admitted to the intensive care unit after an arteriogram, placement of a stent and embolisation of the aneurysm. Upon completion of this procedure, she presented nausea, diplopia and a decreased level of consciousness. Another arteriogram showed complete

☆ Please cite this article as: Cobo F, González A, Pérez-Carrasco V, García-Salcedo JA. *Pantoea stewartii*: ¿un nuevo patógeno causante de bacteriemia? Enferm Infecc Microbiol Clin. 2022;40:278–280.