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.

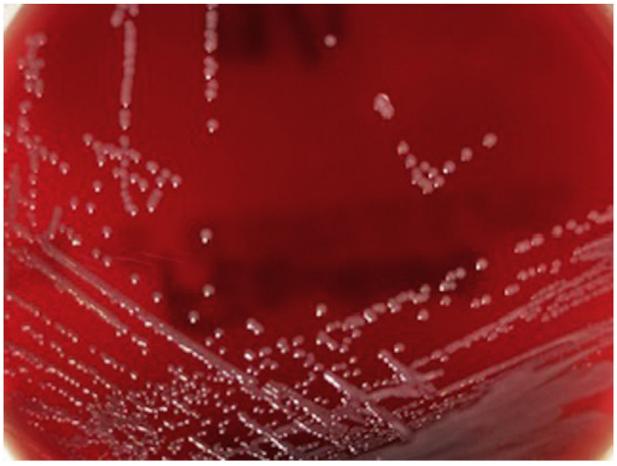

Fig. 1. Greyish-white, round, shiny colonies were observed on blood agar and ultimately identified as *Pantoea stewartii* (growth after 18 h).

Fig. 2. Bluish colonies of *Pantoea stewartii* were seen on UriSelect™ 4 Medium (growth after 48 h).

thrombosis of the implanted stent, whereupon a new stent was placed. A computed tomography scan of the head showed multiple infarctions in the posterior region with bulbar involvement. Clinically, the patient was tetraplegic with pathological extensor motor response. Following 48 days of admission, the patient presented abdominal pain and fever (38.5 °C). Before antibiotic therapy was started, two blood samples and one urine sample were collected for culture (which was negative). In addition, empirical treatment was started with intravenous levofloxacin (500 mg/12 h). The blood cultures were incubated in the BACTEC FX monitoring system (Becton Dickinson, Frankin Lakes, NY, United States). After 11 h of incubation, the two samples tested positive, and subculture was performed on agar, with incubation at 37 °C. Gram staining revealed Gram-negative bacilli and, after 18 h of incubation, growth of abundant circular, greyish, shiny colonies was observed in pure culture on blood agar (Fig. 1). There was also growth of colonies with bluish pigmentation on UriSelect™ 4 Medium (Bio-Rad Laboratories Inc., Marnes-la-Coquette, France) (Fig. 2). Matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry (MS) version 9 (8.468 msp) (Bruker Biotyper, Billerica, MA, United States) was used to identify *Pantoea septica* (score 2.30), with a moderately consistent range of identification (up to range 5). However, the strain was sent to the Centro de Genómica e Investigación Oncológica [Centre for Genomics and Oncology Research] (GENYO) in Granada, Spain, for analysis of the 16S rRNA gene by means of sequencing[4]. A fragment of 1,212 base pairs was amplified, yielding 99.69% similarity to *P. stewartii*, strain 08BF 11 TN (access number KX 146472.1). The MicroScan WalkAway system (Beckman Coulter, Inc., CA, United States), panel NC82 for enterobacteria, was used to determine sensitivity to antimicrobial agents, revealing sensitivity to all antibiotics tested, except for ampicillin (minimum inhibitory concentration [MIC] >8 μg/ml). The interpretation was performed according to the criteria established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST)[5]. The antibiotic therapy was replaced with ciprofloxacin (400 mg/12 h/IV) and maintained for 10 days. After the fourth day of treatment, the patient's fever disappeared and, from a neurological point of view, she followed a favourable course with partial recovery of mobility. She was discharged after four months of admission.

Pantoea spp. are Gram-negative, non-encapsulated, non–spore-forming micro-organisms that can be isolated from plants, seeds, environmental samples and human faeces[1,2]. The most commonly pathogenic species in humans is *P. agglomerans*[6], which can cause infection in various locations, including hospital outbreaks[7,8]. In general, there are few reported cases of infection with this genus, although bacteraemia due to *Pantoea dispersa* has been reported[9].

These micro-organisms are generally considered to be of low pathogenicity and most cases of infection occur in immunosuppressed patients. They can also cause infections in immunocompetent individuals, especially cholecystitis, and in recent years they have been reported to cause neonatal sepsis with a growing frequency[10]. It should be noted that the cases reported responded favourably to antibiotic therapy. They tend to be highly sensitive to antimicrobial agents, but most *P. agglomerans* strains are resistant to fosfomycin. The introduction of MALDI-TOF MS into the diagnostic routine may lead to the identification of uncommon new pathogenic species. However, under certain circumstances, such as a low identification score, an inconsistent diagnosis or the presence of unusual micro-organisms, definitive identification should be performed using molecular techniques, such as 16S rRNA sequencing. When MALDI-TOF MS is used for identification, some species of *Enterobacterales*, such as *Klebsiella ozaenae*, may be mistaken for micro-organisms belonging to the genus *Pantoea*[9]. Notable among all the biochemical characteristics of *P. stewartii*, along with *Pantoea ananatis*, are a positive indole test result (only the *indologenes* subspecies) and gelatin hydrolysis which could help to distinguish it from other species. However, due to genetic heterogeneity, this genus is difficult to identify by means of biochemical tests.

In conclusion, to our knowledge, this is the first case of bacteraemia caused by *P. stewartii* in pure culture. This case emphasises the need to confirm results under the above-mentioned circumstances.

Funding

No funding was received for this study.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Gavini F, Mergaert J, Beji A, Mielcarek C, Izard D, Kersters K, et al. Transfer of *Enterobacter agglomerans* (Beijerink 1888) Ewing and Fife 1972 to *Pantoea* gen. nov. as *Pantoea agglomerans* comb. nov. and description of *Pantoea dispersa* sp. nov. Int J Syst Bacteriol. 1989;39:337–45.
2. Walterson AM, Stavrinides J. *Pantoea*: insights into a highly versatile and diverse genus within the *Enterobacteriaceae*. FEMS Microbiol Rev. 2015;39:968–84.
3. Mergaert J, Verdonck L, Kersters K. Transfer of *Erwinia ananas* (*Erwinia uredovora*) and *Erwinia stewartii* to the genus *Pantoea* emend as *Pantoea ananas* (Serrano 1928) comb. nov. and *Pantoea stewartii* (Smith 1898) comb. nov.,

respectively, and description of *Pantoea stewartii* subsp. *indologenes* subsp. nov. Int J Syst Bacteriol. 1993;43:399.
4. Klindworth A, Pruesse E, Schweer T, Peplies J, Quast C, Horn M, et al. Evaluation of general 16S ribosomal RNA gene PCR primers for classical and next-generation sequencing-based diversity studies. Nucleic Acids Res. 2013;41(1), e1–e1.
5. European Committee on antimicrobial susceptibility testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 11.0; 2021. Fecha de consulta: 7 de enero de 2021. Disponible en: http://eucast.org
6. Cruz AT, Cazacu AC, Allen CH. *Pantoea agglomerans*, a plant pathogen causing human disease. J Clin Microbiol. 2007;45:1989–92.
7. Borrego García E, Ruiz Sancho AL, Plaza Lara E, Díaz Gómez L, Delgado Ureña A. Bacteremia outbreak due to *Pantoea agglomerans* in hemodialysis, an infection by an unexpected guest. Nefrología. 2020;40:573–5.
8. Yablon BR, Dantes R, Tsai V, Lim R, Moulton-Meissner H, Arduino M, et al. Outbreak of *Pantoea agglomerans* bloodstream infections at an oncology clinic-Illinois, 2012-2013. Infect Control Hosp Epidemiol. 2017;38:314–9.
9. Asai N, Koizumi Y, Yamada A, Sakanashi D, Watanabe H, Kato H, et al. *Pantoea dispersa* bacteremia in an immunocompetent patient: a case report and review of the literature. J Med Case Rep. 2019;13:33.
10. Mani S, Nair J. *Pantoea* infections in the neonatal intensive care unit. Cureus. 2021;13:e13103.

Fernando Cobo[a,*], Adrián González[a], Virginia Pérez-Carrasco[b], José A. García-Salcedo[a,b]

[a] *Servicio de Microbiología e Instituto de Investigación Biosanitaria ibs. GRANADA, Hospital Universitario Virgen de las Nieves, Granada, Spain*
[b] *GENYO, Centro de Investigación Genómica y oncológica Pfizer/Universidad de Granada/Gobierno Regional de Andalucía, Granada, Spain*

* Corresponding author.
E-mail address: fernando.cobo.sspa@juntadeandalucia.es (F. Cobo).

Received 10 February 2021
Accepted 16 March 2021

https://doi.org/10.1016/j.eimce.2021.03.005

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 always be considered when suspecting HIV infection in a PrEP user.

Overall, inconsistent adherence to PrEP often increases the likelihood of acquiring HIV infection in PrEP users.[5] Therefore, it is extremely important to establish strategies to reinforce adherence to PrEP, based on patient's empowerment: complete information

[3] Tenofovir disoproxilo/Emtricitabine.