

bacterial pneumonia, ventilator-associated pneumonia, and health-care-associated pneumonia is also underway.

Huttner also states that “unfortunately, neither baseline resistance nor emergence of resistance to cefiderocol was reported”. However, baseline resistance to cefiderocol was provided in the appendix. Additionally, we assessed resistance throughout the study and observed no development of resistance to cefiderocol among cases where microbiological failure was present.

Although this study was termed a phase 2 study (first use in human infection), it was also a pivotal study with robust inferential testing, as required for US regulatory review. Our study was adequately powered for non-inferiority, and the finding of superiority over high-dose imipenem clearly shows efficacy in this population of patients with complicated urinary tract infections, many of which were multidrug resistant.

Huttner also mentioned the new US Food and Drug Administration complicated urinary tract infections guidelines,⁵ stating that “any trial launched more than 4 months ago (including an ongoing phase 3 cefiderocol trial, NCT02714595)³ will now be adhering to outdated standards and requirements.” However, the new guidelines are not relevant to our ongoing phase 3 trial, because the trial involves carbapenem-resistant infections and is not limited to complicated urinary tract infections. Additionally, applying the endpoints of the new guidelines to our pivotal complicated urinary tract infections study would not have altered the conclusion of superior efficacy observed. Finally, although the catechol moiety of cefiderocol leading to siderophore activity was mentioned, one of the key and additionally unique features of this cephalosporin is its structural stability against all known classes of

carbapenemases. It is this combination of unique cell entry and β -lactamase stability that makes cefiderocol so promising.

SP is employed by Shionogi Inc. RE reports consultancy fees from Shionogi Inc and Shionogi & Co Ltd. TDN is employed by Shionogi & Co Ltd.

*Simon Portsmouth, Roger Echols, Tsutae Den Nagata

simon.portsmouth@shionogi.com

Shionogi Inc, Florham Park, NJ, USA (SM); ID3C, Easton, CT, USA (RE); and Shionogi & Co Ltd, Osaka, Japan (TDN)

- Huttner A. Cefiderocol in context. *Lancet Infect Dis* 2018; **18**: 1290–91.
- Portsmouth S, van Veenhuizen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. *Lancet Infect Dis* 2018; **18**: 1319–28.
- Study of S-649266 or best available therapy for the treatment of severe infections caused by carbapenem-resistant Gram-negative pathogens (CREDIBLE - CR). 2018. <https://clinicaltrials.gov/ct2/show/NCT02714595?term=cefiderocol&rank=2> (accessed Nov 1, 2018).
- Clinical study of S-649266 for the treatment of nosocomial pneumonia caused by Gram-negative pathogens (APEKS-NP). 2018. <https://clinicaltrials.gov/ct2/show/NCT0303280?term=cefiderocol&rank=3> (accessed Nov 1, 2018).
- US Food and Drug Administration. Complicated urinary tract infections: developing drugs for treatment guidance for industry. 2018. <https://www.fda.gov/downloads/Drugs/Guidances/ucm070981.pdf> (accessed Nov 1, 2018).

Author's reply

The enormous efforts of investigators and trial participants in the pre-market development of cefiderocol should be neither disregarded nor underestimated: thanks to their work,¹ this drug might soon be accessible to patients who might benefit from it. Nonetheless, a drug tested on only a few hundred people and for a few narrow indications will always require additional, postmarket development. As I have stated,² because we, the public, have demanded an accelerated path to approval, novel antibiotics are now entering the market on the basis of very thin clinical experience. This is not specific to cefiderocol; the new aminoglycoside plazomicin won FDA approval in 2018, on the strength of

a single phase 3 trial with a 15% non-inferiority margin that allowed for a small sample size.³ If allocation is even in the two ongoing cefiderocol trials mentioned by Simon Portsmouth and colleagues, they will together include a total of 225 patients receiving cefiderocol.

Although baseline resistance to other antibiotics was reported in detail in the study by Portsmouth and colleagues,¹ it was not reported for cefiderocol. For cefiderocol, only a range of minimal inhibitory concentrations (MICs) was provided in the appendix, with no report of the total number of isolates tested, as was carefully done for other antibiotics. Was the reported MIC range representative of all isolates, or only of a selected subset? Why was no denominator provided for cefiderocol, when it was provided for all other antibiotics tested? Because of these gaps in reporting, no conclusions can be drawn. Regarding the development of resistance after therapy, it is reassuring to read Portsmouth and colleagues' statement that none was observed, but the question was not addressed in the Article, where no data pertaining to cefiderocol resistance development are reported.

The merits of the US Food and Drug Administration endpoints in place at the time that the study launched were long subject to debate. The efficacy of cefiderocol, as defined by these endpoints, was certainly demonstrated; yet the value of temporarily reducing a bacterium's count from 10⁵ CFU/mL to 10⁴ CFU/mL in a follow-up urine culture, when repeat cultures have no place in the clinic, remains questionable. Again, this is a broader regulatory issue that is not specific to cefiderocol, the developers of which are working within the framework they've been given. And there is no simple solution to the problem of defining efficacy in complicated urinary tract infection studies. Outcomes that are meaningful to patients are notoriously

subjective, so it is understandable that bacterial counts continue to have a role in endpoint definitions. Hopefully, the new endpoints⁴ will provide a somewhat more representative picture of a novel drug's true efficacy, although it is already clear that this new picture will stay limited to early effects (the primary timepoint remains 5 days after treatment cessation) and will not capture resistance outcomes.

We urgently need new antibiotics with activity against multiresistant Gram-negative organisms, and cefiderocol holds enormous promise. I too am rooting for this cleverly designed drug and will be thrilled when promise is replaced by even more proof.

I declare no competing interests.

Angela Huttner

angela.huttner@hcuge.ch

Division of Infectious Diseases, Geneva University Hospitals, 1205 Geneva, Switzerland

- 1 Portsmouth S, van Veenhuyzen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. *Lancet Infect Dis* 2018; **18**: 1319–28.
- 2 Huttner A. Cefiderocol in context. *Lancet Infect Dis* 2018; **18**: 1290–91.
- 3 Theuretzbacher U, Paul M. Developing a new antibiotic for extensively drug-resistant pathogens: the case of plazomicin. *Clin Microbiol Infect* 2018; published online Aug 1. DOI:10.1016/j.cmi.2018.07.020.
- 4 US Food and Drug Administration. Complicated urinary tract infections: developing drugs for treatment guidance for industry. 2018. <https://www.fda.gov/downloads/Drugs/Guidances/ucm070981.pdf> (accessed Nov 18, 2018).

A case of sepsis in a 17th century man from Porto Ercole

We read with interest the Correspondence by Michel Drancourt and colleagues¹ concerning the identification of a case of *Staphylococcus aureus* sepsis in the skeletal remains of an early 17th century man exhumed at Porto Ercole (Italy). These remains have been confidently attributed

by Drancourt and colleagues to Michelangelo Merisi, also known as Caravaggio. We wish to point out several inconsistencies in Caravaggio's identification, place of death, and cause of his death.

Caravaggio did not father children, nor did his brother, Giovanni Battista, who was a Catholic priest.² Therefore, no contemporary pre-sumed patrilineal descendants of Caravaggio were available for direct Y chromosome comparison.^{1,3} No detailed accompanying data were provided, such as DNA typing methods or biostatistics, which might have supported the identification of Caravaggio through the combination of genetic analysis and surname information, including the actual Merisi–Merisio Y-STR haplotype matching that was obtained from skeletal remains.^{1,3}

The presence of high levels of lead in the bones of the 17th century skeleton from Porto Ercole does not support the attribution of the remains to Caravaggio either. From antiquity to the Renaissance, exposure to heavy metals (ie, lead, mercury, or arsenic) through dietary intake and medicinal uses has contributed to absorption of these toxins in bones. Exposure to heavy metals also occurred with the use of pewter and other lead-bearing cooking utensils, tableware, and pottery. Similarly, the use of lead water pipes and ingestion of foods and beverages adulterated with lead-based additives contributed to chronic lead poisoning.⁴

Lastly, historical sources indicate that Caravaggio was assaulted and severely disfigured in Naples in late September, 1609, 10 months before his demise.^{2,5} After having recovered, he went back to work and, between Oct 20–24, 1609, and July 18, 1610, he painted several masterpieces, including *David and Goliath* (1610).¹ The hypothesis of a secondary sepsis due to superinfection of healed facial wounds appears, therefore, to be unfounded. Finally, both the place of death (Porto Ercole) and the

authenticity of the death register^{1,3} are still a matter of debate among art historians.²

We agree with Drancourt and colleagues that the presence of *S aureus* and the osteomyelitis lesions in the male skeleton exhumed at Porto Ercole might indicate that this man died of sepsis. However, more focused historical and biological research is needed before these remains are unequivocally attributed to Caravaggio.

We declare no competing interests.

Antonio Perciaccante, Carlo Robino, Donatella Lippi, Otto Appenzeller, Tomaso Montanari, *Raffaella Bianucci
r.bianucci@warwick.ac.uk

Department of Medicine, San Giovanni di Dio Hospital, Gorizia, Italy (AP); Legal Medicine Section, Department of Public Health and Paediatric Sciences, University of Turin, Turin, Italy (CR, RB); Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy (DL); New Mexico Health Enhancement and Marathon Clinics Research Foundation and New Mexico Museum of Natural History and Science, Albuquerque, NM, USA (OA); Dipartimento di Studi umanistici, Università degli Studi di Napoli Federico II, Naples, Italy (TM); Warwick Medical School, Microbiology and Infection Unit, University of Warwick, CV4 7AL Coventry, UK (RB); and UMR 7268, Laboratoire d'Anthropologie bio-culturelle, Droit, Etique & Santé (Adés), Faculté de Médecine de Marseille, Marseille, France (RB)

- 1 Drancourt M, Barbieri R, Cilli E, et al. Did Caravaggio die of *Staphylococcus aureus* sepsis? *Lancet Infect Dis* 2018; **18**: 1178.
- 2 Castaldo G, Silvestri N. Perché quelle ossa non sono di Caravaggio. In: Pacelli V, Forgiogione G, eds. Caravaggio tra arte e scienza. Naples: Paparo edizioni, 2012: 350–54.
- 3 Vinceti S, Gruppioni G. L'enigma Caravaggio—Ipotesi scientifiche sulla morte del pittore. Rome: Armando Editore, 2010: 107–10.
- 4 Lanzirotti A, Bianucci R, LeGeros R, et al. Assessing heavy metal exposure in Renaissance Europe using synchrotron microbeam techniques. *J Archaeol Sci* 2014; **52**: 204–17.
- 5 Cantore GM. Il foglietto volante di Porto Ercole: da atto di morte del Merisi a falso moderno. In: Pacelli V, Forgiogione G, eds. Caravaggio tra arte e scienza. Naples: Paparo edizioni, 2012: 354–55.

Author's reply

I thank Antonio Perciaccante and colleagues for their comments on our Correspondence¹ reporting on the remains of a man who died from *Staphylococcus aureus* sepsis, who