Proficiency Testing for Meropenem and Piperacillin Therapeutic Drug Monitoring: Preliminary Results From the Belgian Society on Infectiology and Clinical Microbiology Pharmacokinetic–Pharmacodynamic Working Group

To the Editor:

Infection is a well-recognized but persisting problem in critically ill patients with high mortality and morbidity.[1] Timely and appropriate antibiotic therapy after source control is considered to be the mainstay of treatment. Achieving adequate antibiotic exposure may also be important, as shown by a recent point prevalence study, suggesting a correlation between plasma concentrations of the antibiotics and outcome.[2] β-lactam antibiotics are most commonly used because of their favorable safety profile and broad spectrum of activity.[3] Optimizing antibiotic exposure is proving to be a great challenge with recent data showing that the antibiotic concentrations in critically ill patients are highly variable, unpredictable, and commonly suboptimal,[2,4–6] not only between patients but also within the same patient.[7]

Although there is currently no evidence that therapeutic drug monitoring (TDM) leads to improved clinical outcomes, it is gaining popularity as a means to individualize antibiotic dosing in difficult patient populations such as the critically ill.[8–11] TDM of β-lactam antibiotics has also been recommended in a recently published guideline by a multidisciplinary expert panel as a strategy to improve antibiotic therapy in intensive care units.[12] Therefore, several laboratories developed β-lactam assays. These methods undergo an in-house validation, covering accuracy, precision, selectivity, matrix effect, and stability. Although these validations are properly performed and based on international guidelines, the lack of a commercially available control or calibration material remains a major hurdle.[13] To test the concordance of these laboratory-developed tests, we performed an interlaboratory proficiency testing program for the measurement of meropenem and piperacillin. In this report, we describe the results of this round robin test.

In 2015, we sent 2 sets of 8 meropenem and 2 sets of 8 piperacillin samples on dry ice to the 9 participating laboratories in Belgium. Each set contained 3 spiked samples (bovine serum spiked with a low, medium, and high concentration) and 5 patient pool samples (low, medium, and high) from patients treated with the antibiotic. These sets included identical samples to be able to calculate a consensus mean and to calculate intralaboratory variability. The concentrations of the samples were in the range of concentrations expected in patients treated with these antibiotics. All participating laboratories were provided feedback on their results. The accuracy of a result was acceptable if the reported concentration was within the 80%–120% limits of the consensus mean. This 80%–120% threshold is based on guidelines for method validation where a fixed criterion for inaccuracy of 20% at the lowest level of quantification is commonly used.[14,15] The details on the preparation of the quality control, the patient samples, and the calculation of the consensus mean are provided in the **Supplemental Digital Content 1** (http://links.lww.com/TDM/A218) and **Supplemental Digital Content 2 and 3** (see **Supplementary Tables 1 and 2**, http://links.lww.com/TDM/A215, http://links.lww.com/TDM/A216, respectively).

All 9 participating laboratories analyzed the meropenem samples. Three of the 9 participating centers only perform this analysis for study purposes. One center is still in the validation phase and 5 centers perform it on a routine basis. More details on the laboratories performing this analysis as part of the routine are summarized in Table 1.

Two laboratories did not have an assay for piperacillin available and 1 laboratory failed to send in their results for piperacillin. Therefore, the results of only 6 laboratories on the samples containing piperacillin are reported. Most participants (n = 6/9 for meropenem and n = 4/6 for piperacillin) used liquid chromatography with an ultraviolet detector. The other centers used liquid chromatography with mass spectrometry detection to determine the concentrations. Details on the methods used can be found in the **Supplemental Digital Content 4**, (see **Supplementary Table 3**, http://links.lww.com/TDM/A217).

A quantitative result was obtained for 93% (n = 134/144) of the samples for meropenem (technical accident for 8 samples, 2 samples with a concentration < lower limit of quantification). For meropenem, the results of 2 laboratories were excluded from the calculation of the consensus mean because the mean reported concentration of 2/3 spiked samples deviated >50% from the weighed-in concentration. The results are shown in Figures 1A, B. Only 57% of the results for meropenem were within the predefined accuracy limits (77/134). For piperacillin, a quantitative result was obtained for 86/96 samples (9 samples < lower limit of quantification), and only 72% of the results were within accuracy limits (63/87).

The percentage of accurate results per laboratory ranged between 0% and 94% for meropenem (median 63%) and between 6% and 100% (median 72%) for piperacillin. Five of the 9 laboratories determining meropenem had ≤2 samples within the 80%–120% limits of the consensus mean. One center reported all meropenem samples inaccurately and another center reported all

The authors declare no conflict of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.drug-monitoring.com).

TABLE 1. Participating Laboratories

Laboratory	No. of Runs per Week	No. of Samples per Year	Indication for TDM	Preanalytical Instructions
1	1 (analysis the next day if urgent)	120	Special cases*	Rapid transportation of the blood sample to the laboratory. Storage of plasma at −20°C until analysis
2	3	100	Special cases*	Transport of the blood sample at 4° C. Storage of plasma at −20°C until analysis
3	On request	50	Special cases*	Transport of the blood sample in a container with ice. Storage of plasma at −80°C
4	2	50	Special cases*	Transport of the blood sample in a container with ice. Storage of plasma at −20°C
5	5	1400	All patients in the intensive care unit + special cases*	Transport of the blood sample in a container with ice. Storage of plasma at −80°C

*Special cases such as clinical failure, augmented renal clearance, treatment of a resistant isolate infection, and extracorporeal circuits.

but 1 sample inaccurately. These results are summarized in **Supplemental Digital Content 3 and 4**, (see **Supplementary Tables 2 and 3**, http://links.lww.com/TDM/A216, http://links.lww.com/TDM/A217, respectively).

This small study shows that 43% of the meropenem and 28% of the piperacillin samples were measured inaccurately. It is unclear what factors caused the observed variability. Usage of in-house prepared calibration material from different sources may be an important factor, but the limited stability of these antibiotics might also add to the observed variability. Our findings are in line with data from similar quality control programs, such as Asqualab (Assurance qualité des laboratories de biologie médicale), a French association of clinical chemists that organizes quality control programs. The results of this quality control program on specialized antibiotics (which also includes piperacillin) also showed a very wide variability among laboratories (results of EEQ 1865A received by our laboratory). These findings are clinically relevant because inaccurate results may result in incorrect dose adjustments in TDM and

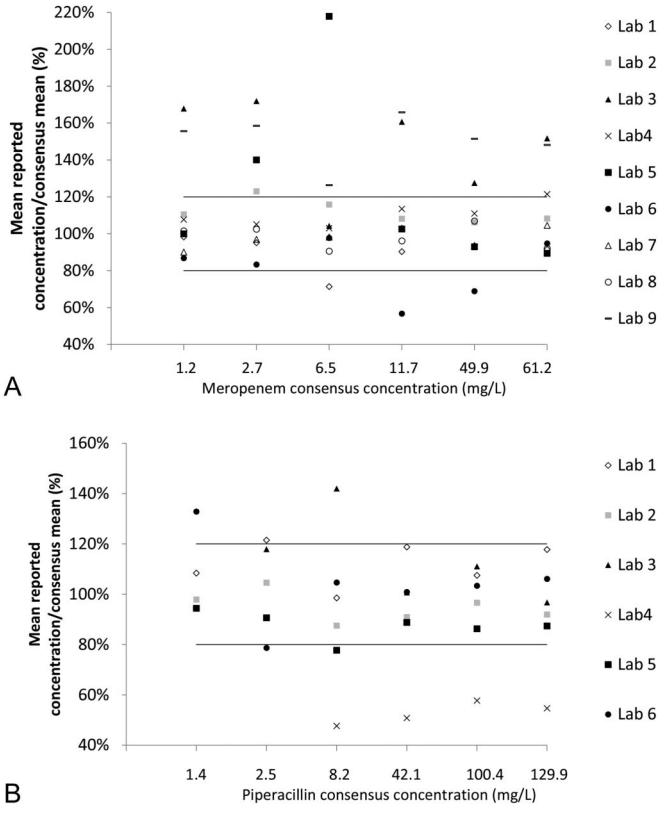

FIGURE 1. A, Mean meropenem concentration per laboratory. B, Mean piperacillin concentration per laboratory.

potentially lead to treatment failure or unnecessary toxicity.

The results of the first round of this interlaboratory proficiency testing program therefore demonstrates the need for an ongoing proficiency testing program to improve these assays.

Mieke Carlier, PharmD, PhD*
Alexandre Athanasopoulos, PharmD, PhD†
Daniëlle Borrey, PharmD, PhD‡
Pieter Colin, PharmD, PhD§
Frédéric Cotton, PharmD, PhD‖
Raphael Denooz, PharmD, PhD¶
Hugo Neels, PharmD, PhD#
Isabel Spriet, PharmD, PhD
Timothy Ghys, PharmD††
Alain G. Verstraete, MD, PhD*‡‡
Veronique Stove, PharmD, PhD*‡‡
*Department of Laboratory Medicine, Ghent University Hospital, Ghent
†Department of Clinical Chemistry, University Hospital of Charleroi, Charleroi
‡Department of Clinical Chemistry, AZ Sint Jan Brugge, Bruges
§Unit of Medical Biochemistry and Clinical Analysis, Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Ghent
‖Department of Clinical Chemistry, Erasme Hospital, Brussels
¶Department of Clinical Chemistry, University Hospital Liège, Liège
#Department of Clinical Chemistry, Ziekenhuisnetwerk Antwerpen, Antwerp
**Clinical Pharmacology and Pharmacotherapy, University Hospital Leuven, Leuven
††Department of Clinical Chemistry, AZ Sint Lucas Gent, Ghent
‡‡Department of Clinical Chemistry, Microbiology and Immunology, Ghent University, Ghent, Belgium

REFERENCES

1. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *J Am Med Assoc.* 2009;302:2323–2329.
2. Roberts J, Paul S, Akova M, et al. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients. *Clin Infect Dis.* 2014;58:1072–1083.
3. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis.* 1998;26:1–10.
4. Roberts DM, Roberts JA, Roberts MS, et al. Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: a multicentre pharmacokinetic study. *Crit Care Med.* 2012;40:1523–1528.
5. Udy AA, Varghese JM, Altukroni M, et al. Subtherapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. *Chest*. 2012;142:30–39.
6. Carlier M, Carrette S, Roberts J, et al. Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? *Crit Care.* 2013;17:R84.
7. Carlier M, Carrette S, Stove V, et al. Does consistent piperacillin dosing result in consistent therapeutic concentrations in critically ill patients? a longitudinal study over an entire antibiotic course. *Int J Antimicrob Agents.* 2014;43:470–473.
8. De Waele JJ, Carrette S, Carlier M, et al. Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: a randomised controlled trial. *Intens Care Med.* 2014;40:380–387.
9. Fournier A, Eggimann P, Pagani JL, et al. Impact of the introduction of real-time therapeutic drug monitoring on empirical doses of carbapenems in critically ill burn patients. *Burns*. 2015;41:956–968.
10. Hayashi Y, Lipman J, Udy AA, et al. β-Lactam therapeutic drug monitoring in the critically ill: optimising drug exposure in patients with fluctuating renal function and hypoalbuminaemia. *Int J Antimicrob Agents.* 2013;41:162–166.
11. Lonsdale DO, Udy AA, Roberts JA, et al. Antibacterial therapeutic drug monitoring in cerebrospinal fluid: difficulty in achieving adequate drug concentrations. *J Neurosurg.* 2013;118:297–301.
12. Bretonniere C, Leone M, Milesi C, et al. Strategies to reduce curative antibiotic therapy in intensive care units (adult and paediatric). *Intensive Care Med.* 2015;41:1181–1196.
13. Carlier M, Stove V, Wallis SC, et al. Assays for therapeutic drug monitoring of β-lactam antibiotics: a structured review. *Int J Antimicrob Agents.* 2015;46:367–375.
14. *Guidance for Industry Bioanalytical Method Validation*. Silver Spring, MD. U.S. Department of Health and Human Services Food and Drug Administration; 2001.
15. *Guideline on Bioanalytical Method Validation*. United Kingdom. European Medicine Agency; 2011.