this equation has been validated (even if with other drugs) showing a reliable estimation of the AUC [4].

So, even if we agree that we provided not many data, that they need further confirmation, and that we used a not completely accurate equation to calculate AUC, in the present era of increasing antibiotic resistance that requires administration of drugs poorly known in terms of pharmacokinetics/pharmacodynamics, especially in children, we believe that our results can represent a useful starting point.

**Note**

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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**Dose Suggestions for Intravenous Colistin in Pediatric Patients: Caution Required**

To the Editor—Mesini et al reported plasma concentrations of colistin in 7 pediatric patients (aged 46 days to 13 years) who were receiving intravenously the inactive prodrug colistimethate; across all patients, plasma colistin concentrations were measured on 13 occasions [1]. That report has been the subject of critical appraisal by Magréault et al [2], who expressed substantial concerns about the magnitude of the plasma colistin concentrations reported and the pharmacokinetic analysis conducted by Mesini and coworkers. I agree with Magréault et al and amplify their comments. I have very substantial concerns about the dosing recommendations implicitly presented in the report of Mesini and coworkers.

In the study of Mesini et al plasma concentrations of colistin (the active and nephrotoxic entity formed from colistimethate) were determined at the end of a 1-hour infusion of the prodrug (the authors referred to this colistin concentration as C_{max}) and just before the next infusion (so-called C_{min}) [1]. The reported median plasma colistin C_{max} and C_{min} values across the 13 occasions were 9.4 mg/L (range, 4.3–18.9 mg/L) and 1.7 mg/L (range, 0.4–3.0 mg/L), respectively. It is unfortunate and worrying that Mesini et al did not compare their measured concentrations with those reported for pediatric patients by other authors [3, 4]. Antachopoulos et al reported serum concentrations of colistin immediately before and 30 minutes after a 20-minute infusion of colistimethate on 5 occasions in 3 patients (age, 1.5 months to 14 years) [3]. When the concentrations reported by Antachopoulos and coworkers are normalized to the maintenance dose employed by Mesini et al (150 000 U/kg/day), the median plasma colistin concentrations just after and before a colistimethate short-term infusion were 1.20 mg/L (range, 0.73–1.68 mg/L) and 0.60 mg/L (range, 0.48–1.53 mg/L), respectively. It is immediately evident that, especially at early times in a dose interval, the colistin concentrations reported by Mesini et al are substantially higher than those reported by Antachopoulos and coworkers. From the pharmacokinetic analysis arising from a single-dose study in 7 critically ill patients <1 month old, Nakwan et al predicted that a maintenance colistimethate dose of 150 000 U/kg/day would result in an average steady-state plasma colistin concentration of 1.1 ± 0.43 mg/L [4], again appearing to be much lower than concentrations that may be inferred from Mesini et al.

The higher concentrations reported by Mesini et al [1], especially at the end of the infusion, are very likely artefactual. It is well established that plasma colistimethate concentrations early in a dose interval are substantially higher than those of colistin, in both adult [5–7] and pediatric [3] patients. It is also known that colistimethate will undergo spontaneous conversion to colistin after samples have been collected, unless samples are collected, processed, transported, stored, and analyzed under conditions that minimize such potential ongoing in vitro conversion [8–10]. Mesini et al quantified colistin using a method [11] involving steps (in particular subjecting extracts of samples to 50°C for 1.5 hour) likely to favor the ongoing conversion of colistimethate to colistin. While the report of the analytical method described quite extensive validation of colistin-spiked plasma samples, there is no evidence that colistimethate-spiked samples were used to investigate the stability of the prodrug during the multiple steps involved in the assay [11].

In view of the magnitude of the plasma colistin concentrations they measured, Mesini et al proposed that 150 000 U/kg/day is “a good way to obtain plasma concentrations with the highest probability of effectiveness.” Based on their own pharmacokinetic data, Antachopoulos et al and Nakwan et al suggested that colistimethate doses >150 000 U/kg/day may be required in pediatric...
patients [3, 4]; this may be expected to be most applicable to patients without renal impairment. Daily doses higher than this level appear to be generally well tolerated, even when administered for a prolonged treatment course [3, 12].

Because of the likely overestimation of plasma colistin concentrations in the study of Mesini et al [1]. very substantial caution is required in any consideration given to applying the reported findings to dosing of pediatric patients. Underdosing may decrease the probability of achieving efficacious concentrations and increase the likelihood of emergence of resistance.

Note
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References

Incorporating Insights into Early Syphilis Management

In the epidemic of early syphilis in MSM, the potential for increased infectiousness and transmission may not be well understood. A recent study by Mermin et al [4] found that MSM with early syphilis have a higher risk of acquiring HIV than those without early syphilis. However, the exact nature of this association is not well understood.

The authors of the study noted that MSM with early syphilis are more likely to present with latent-phase disease than patients with an earlier stage of syphilis. This finding is consistent with previous studies that have shown a higher risk of progression to late-stage syphilis in MSM [5–7].

Increased in Asymptomatic Early Syphilis May Reflect Increases in Repeated Episodes of Syphilis and Not Enhanced Screening

To the Editor—In their analysis of men who have sex with men (MSM) attending a national sentinel network of 46 sexual health clinics in Australia between 2007 and 2014, Chow et al [1] found a decline in the proportion of syphilis cases that were secondary syphilis and a corresponding increase in early latent syphilis. These changes occurred during a period of increased coverage and frequency of syphilis testing in MSM. The authors interpret this association as representing an “interruption of syphilis progression” and thereby a reduction in the infectiousness of syphilis.

Here I advance an alternative hypothesis to explain these findings. The current outbreak of syphilis in MSM in multiple countries is characterized by an increasing proportion of cases caused by repeated episodes of syphilis (Figure 1) [2, 3]. Magnuson et al [4] showed via inoculation experiments in the 1950s that persons with previous episodes of syphilis had an attenuated clinical and immunological response to intradermal challenge with Treponema pallidum. Others and I have found that patients with repeated episodes of syphilis have an attenuated immune response and are more likely to present with latent-stage disease than patients with an initial episode of syphilis [5–7]. Chow et al did not provide a breakdown of repeated versus initial episodes of syphilis. However, if the proportion of syphilis in MSM due to repeated episodes is increasing in Australia, as surveillance data suggest it is [3], then this increase may be responsible for the increase in the proportion of syphilis cases classified as latent in MSM.

Figure 1. Cases of initial and repeated episodes of syphilis by year of diagnosis at the Institute of Tropical Medicine, Antwerp, 1995 to 2012 (adapted from Kenyon et al [2], with permission).

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