Colistin, the most widely used polymyxin antibiotic, was originally introduced in the late 1950s before the establishment of the present-day drug approval process. Originally shelved due to toxicity concerns, colistin, in the form of its inactive prodrug colistin methanesulfonate, has undergone a renaissance in the past 15 years. Unfortunately, this is not because of an improved adverse-effect profile but because colistin is among the only remaining antibiotics with activity against multidrug-resistant gram-negative bacilli. Pharmacokinetic and pharmacodynamic data are limited to guide the appropriate use of colistin; however, important advances have occurred over the past 5 years. Since its reintroduction, published reports regarding colistin have produced discordant results in terms of both efficacy and safety. Because the efficacy and toxicity of colistin are dose dependent, the impact of discordant dosing recommendations cannot be understated. This review highlights the issues leading to differing and often conflicting dosing recommendations, reviews the recent pharmacokinetic advances, and provides recommendations for the optimal use of colistin.

**Key Words** colistin, colistimethate, polymyxins, pharmacokinetics, pharmacodynamics.

for Colomycin and colistin base activity (CBA) for Coly-Mycin M) and in different dosing units (millions of international units (MU) of CMS, milligrams of CMS, or milligrams of CBA).1, 2 The conversions among these units are as follows: 1 MU CMS = 80 mg CMS = 30 mg CBA.3 This gets further complicated because the two package insert dosing recommendations are inconsistent with one another (Table 1). In a 70-kg patient, the recommended daily dosage of Colomycin is 90–180 mg CBA (3–6 MU CMS),1 which is roughly 50% lower than the recommended daily dosage of Coly-Mycin M Parenteral (175–350 mg CBA or 5.8–11.7 MU CMS),2 despite the contents of the vials having the same product. Because the efficacy and toxicity of colistin are dose dependent, the impact of these discordant dosing recommendations cannot be understated.

**Pharmacokinetic Issues and Misunderstandings**

Many of the PK issues and misunderstandings stem from the fact that colistin is given in the form of its inactive prodrug, CMS, rather than the active moiety colistin.6 CMS is an unstable compound that converts to colistin both in vivo and in aqueous and biologic fluids ex vivo.7, 8 Historically, this conversion significantly limited researchers’ abilities to obtain accurate PK/PD data because CMS, if not promptly and properly stored, continues to hydrolyze after blood samples are obtained, leading to falsely elevated levels of colistin. The second obstacle that limited progress in this area was the fact that, until recently, plasma concentrations of CMS and formed colistin were not differentiated in the literature. In the early 2000s, high-performance liquid chromatographic methods became available, allowing for quantitative assessment of both compounds individually.9, 10 Before this, it was understood that CMS was the prodrug of colistin, but it was unknown how much each component contributed to overall bacterial killing. These sampling and analyses issues are the primary reasons why the package insert–based dosing is inaccurate and why data prior to 2003 regarding the pharmacokinetics of “colistin” in humans are invalid.

### Modern Pharmacokinetic Data

As previously mentioned, the dosing recommendations in the original package insert for CMS was established when the drug first came to market and were largely derived from both faulty and insufficient PK evidence to support the recommendations. To help resolve these dosing discrepancies, newer studies have undertaken the task of providing accurate PK information to help guide CMS/colistin dosing recommendations. A population PK model4 presented data from 18 patients who received 3 MU of CMS (90 mg CBA) every 8 hours and represents the first significant breakthrough in our modern-day understanding of colistin PK. Three extremely important advances came from these data. First, the authors showed that predicted maximum serum concentrations, even with this dosage, which was above the upper limit of the European package insert dosage range recommendation,
would be 0.6 μg/ml with the first dose and 2.3 μg/ml at steady state. When protein binding of ~60% is taken into account, these numbers for the first time brought into serious question the appropriateness of the current susceptibility breakpoint for colistin 2 μg/ml. Second, the half-life of colistin was determined to be 14.4 hours showing that without a loading dose it would take ~60 hours for colistin to reach steady state. Finally, and perhaps most concerning, the authors showed that hydrolysis of CMS to active colistin in critically ill patients was slow, with maximum concentrations occurring ~7 hours after the dose.

In 2011, one report significantly enhanced our PK understanding for critically ill patients by using data from 105 patients across a wide range of renal function. Pivotal findings from this study included both important advances of our understanding of the PK of CMS and colistin (described later), as well as confirmations of the data from the study cited earlier regarding the appropriateness of the current susceptibility breakpoint for colistin 2 μg/ml. It is imperative for the clinician to understand that, based on neutropenic mouse thigh infection models in both Pseudomonas aeruginosa and Acinetobacter baumannii, this exposure would only reliably be associated with a 2-log10 kill in bacterial burden for organisms with a minimum inhibitory concentration (MIC) of up to 0.5 μg/ml and that for organisms with an MIC of 1 mg/l, a 1-log10 kill is more likely. For organisms with an MIC of 2 mg/l (the current susceptibility breakpoint) or above, minimal kill would be expected, highlighting the controversy around the current breakpoint. It is important to note that the Sanford Guide recommends a target concentration of 3.5 μg/ml, which would equate to an AUC0–24 of 34 mg.hour/ml. Given the high rates of nephrotoxicity discussed earlier when trough concentrations were significantly lower than this, coupled with the knowledge that toxicity is dose dependent, we would not recommend this higher target concentration because the safety of the doses required to reach that concentration has not been sufficiently studied. In addition, true bactericidal activity (3-log10 kill) remains unlikely even with that exposure. Therefore, we question if there is any bang for your buck, so to speak, in going higher with the target concentration.

In addition, these data suggest that in spite of U.S. package insert recommendations, the following equation for determining the maintenance dose with creatinine clearance (Clcr) normalized to body surface area:

\[
\text{Maintenance dose (mg of CBA)} = \text{colistin } C_{ss,avg} \text{ target } \times \left( (1.50 \times \text{Cl}_{cr}) + 30 \right)^5
\]

To first implement this equation, the clinician needs to determine the target colistin steady-state concentration (\(C_{ss, avg}\)). The authors suggest an average target concentration of 2.5 μg/ml, which would equate to a free concentration of ~1.0 μg/ml. This target was suggested as a compromise between efficacy and toxicity because the mean total colistin concentration observed in patients in this PK analysis was 2.36 μg/ml, which was associated with 48% patients having a greater than 50% increase in serum creatinine concentration. These toxicity rates are in concordance with a recent report that showed rates of nephrotoxicity of 65–85% with trough concentrations greater than 2.2 μg/ml. With a free colistin concentration target of 1.0 μg/ml, the free area under the unbound colistin concentration-versus-time curve over 24 hours (AUC0–24) would be 24 μg.hour/ml given the “flat” plasma concentration versus time profiles of formed colistin.

Understanding and Using the Recently Developed Dosing Equation

After giving the patient a onetime loading dose of 5 mg/kg CBA based on actual or ideal body weight, whichever is lower (maximum dose 300 mg CBA), the authors proposed the

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  - **Maintenance dose (mg of CBA)**
  - **Colistin Css,avg target**
  - **[(1.50 × Clcr) + 30]⁵**

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maintenance dose of CMS should not be based on weight because the equation only includes target colistin concentrations and Cl\text{cr}. We believe it is crucial to point out two important caveats. First, the median (range) weight in this study was 59.1 (30.0–106.4) kg. Therefore, applying these algorithms to the obese population requires further clinical PK/PD studies. In addition, if you use this equation for your patients, it is important to highlight that Cl\text{cr} in this study was calculated by using actual body weight corrected to body surface area in Cl\text{cr} equations. On average, in obese patients, using actual body weight normalized to body surface area leads to a significantly larger Cl\text{cr} than when using ideal body weight in Cl\text{cr} equations and therefore significantly larger doses (Table 2).

Finally, the authors suggest dividing the daily dose into three doses in patients with normal renal function. This dosing schema was based on a rat model comparing regimens equivalent to once/day and twice/day dosing in humans, which resulted in development of more severe and diverse renal lesions among the group that received the equivalent of once/day colistin administration\textsuperscript{18} and on an in vitro PK/PD model study suggesting that dividing the daily dose into an every-8-hour regimen decreases the emergence of colistin resistance\textsuperscript{19}. Although limitations to these data exist, we feel at the current time that this strategy is reasonable.

What Are the Important Lessons Learned from These Newer Pharmacokinetic Data?

If we accept the reasonable conclusion that the target colistin concentration should be 2.5 \mu g/mL, it becomes immediately apparent that this is likely to be unachievable in certain patient populations, specifically in patients with normal to good renal function or obesity. The authors explicitly state that when Cl\text{cr} is greater than 70 ml/minute, the equation gives doses for which the safety is unknown (e.g., the daily maintenance dose for a target concentration of 2.5 \mu g/mL and a Cl\text{cr} of 70 ml/minute is 338 mg CBA). Although in our clinical practice we occasionally go above this daily dose, multiple publications have suggested there is a significant increase in toxicity with a daily dose above 5 mg/kg of ideal body weight\textsuperscript{20, 21} whereas there are no data equating this to improved efficacy. As we previously stated, to use this equation in obese patients, actual body weight normalized to body surface area must be used in Cl\text{cr} determinations. This will often give a Cl\text{cr} more than 70 ml/minute, even in the setting of moderate renal insufficiency, which leads to the same problem (i.e., requirement of high doses with unknown safety) stated earlier above in nonobese patients without renal dysfunction.

In addition, the clinician must remember that a target colistin concentration of 2.5 \mu g/mL equates to an area under the curve (AUC\textsubscript{0–24}) of 60 \mu g\textperiodcentered hour/mL (IAUC\textsubscript{0–24} of ~24 \mu g\textperiodcentered hour/mL) and is only associated with, at best, a static effect for MIC values of 0.5–2.0 \mu g/mL.

<table>
<thead>
<tr>
<th>Weight used</th>
<th>Resultant Cockcroft-Gault equation</th>
<th>Calculated creatinine clearance (ml/min)</th>
<th>Colistin maintenance dose recommendation (mg/day CBA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use ideal body weight</td>
<td>(\frac{(140 - \text{age}) \times \text{IBW}}{72 \times \text{Scr}})</td>
<td>53</td>
<td>273</td>
</tr>
<tr>
<td>Use actual body weight corrected for BSA</td>
<td>(\frac{(140 - \text{age}) \times \text{TBW}}{72 \times \text{Scr}} \times \frac{1.73}{\text{BSA}})</td>
<td>70</td>
<td>338</td>
</tr>
</tbody>
</table>

BSA = body surface area; CBA = colistin base activity; IBW = ideal body weight; Scr = serum creatinine concentration; TBW = total body weight.

\textsuperscript{a}Patient characteristics were as follows: 54-year-old male; height = 67 inches; weight = 128 kg; IBW = 66.1 kg; Scr = 1.5 mg/dl; BSA = 2.45 m\textsuperscript{2}; colistin minimum inhibitory concentration for organism = 1 \mu g/mL; target colistin concentration 2.5 \mu g/mL.
How Should I Dose and Use the Drug in My Patients?

Ultimately, the question remains: Which of these many dosing options available should be used? Unfortunately, the clinical impact of higher or more aggressive dosing on efficacy still remains unclear, and PK/PD targets as a function of infection type warrant further exploration. Two studies that appeared to show a dose-efficacy response with “higher dosing” both used 9 MU/day of CMS (270 mg CBA),22, 23 which is lower than doses commonly used in the United States (300 mg/day of CBA in a 60-kg patient), and they did not evaluate efficacy relative to the colistin MIC for the pathogen. Alternatively, another analysis showed poor outcomes even when using up to 10 mg/kg/day (maximum 600 mg) of CBA.25 If we choose to dose based on the U.S. package insert, the question of what dosing weight to use in obesity remains, and, as previously discussed, data5 suggest that weight (in the form of an increased Clcr) will increase the required CMS dose. Of importance, however, this needs to be balanced against the finding that using dosing weights other than ideal body weight with the U.S. dosing schemes will increase both the CMS dose and the risk of toxicity.20, 21

When determining what to do, in the end, we need to come back to the important finding that even with the most aggressive of these dosing regimens, our likely obtainable colistin concentrations are relatively low and likely to result in bacteriostatic effects. When these relatively low exposures are combined with the known heteroresistance to colistin in multidrug-resistant gram-negative bacilli25–27 and the impressive synergy seen in vitro, the role of combination therapy with other active or synergistic agents becomes increasingly important. Because the data with imipenem show synergy even with subtherapeutic (0.5 × MIC) concentrations of colistin,27 we promote a more conservative approach to dosing the drug, regardless of dosing strategy used, to maximize efficacy and minimize nephrotoxicity. After the patient receives a loading dose, this conservative approach includes maintenance dosing strategies such as capping the dose in the equation presented earlier5 at roughly 340 mg/day as the authors suggest, dosing on ideal body weight with the U.S. package insert, or administering a fixed dose of 9 MU CMS as currently done by many Europeans in patients with normal renal function, with subsequent dosage reductions in patients with renal insufficiency. Although this will undoubtedly lead to subtherapeutic concentrations in some types of infection scenarios, we question whether “therapeutic” colistin concentrations are even possible in some situations and therefore stress combination therapy and safety. Of importance, despite the theoretical advantages of combination therapy, the efficacy data in patients comparing colistin monotherapy versus combination therapy have been inconclusive to this point, with no evident consistent advantage. Two ongoing randomized controlled trials (one of which is blinded) comparing colistin versus a colistin-meropenem combination should help shed light on this important question. Although combination therapy makes sense, it is important in this era of increasing drug resistance that we ensure combination therapy equates to improved outcomes and that there are no detrimental ecological impacts of increased exposure to the synergistic (or active) second agents, most notably, the carbapenems.

References