Colistin in Ventilator-Associated Pneumonia

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(See the Major Article by Florescu et al, on pages 670–80.)

It is interesting to observe how advances in research, as well as unmet medical needs, change attitudes and decisions in clinical practice. The expansion of use of intravenous colistin for the treatment of patients with multidrug-resistant (MDR) gram-negative bacterial infections is certainly such an example.

Even a few years ago there were many opponents to the use of colistin. The medication was not considered adequately effective. More so, most considered its use to be probably dangerous because of safety issues. Others questioned the scientific validity of the various studies that emerged on the clinical effectiveness and safety of colistin. However, the necessity to treat infections due to MDR gram-negative bacteria led to the revival of colistin in clinical practice at the dawn of the 21st century [1].

In this issue of Clinical Infectious Diseases, Florescu et al [2] specifically evaluate the published clinical evidence on the use of colistin for ventilator-associated pneumonia (VAP). They conclude that the effectiveness and safety of colistin are not statistically different from those of frontline antibiotics for the treatment of VAP. Indeed, their meta–regression analysis shows no significant change in clinical response after controlling for concomitant antibiotic treatment. Their analysis reinforces that colistin is indeed an effective and acceptably safe choice in the treatment of VAP in the era of “bad bugs—no drugs.”

The conclusion of this study is significant as it conveys the current standing of the therapeutic role of colistin in VAP. It is of particular importance because there have been concerns in the past regarding the pharmacokinetics and pharmacodynamics of colistin, especially whether the drug could achieve appropriate levels in the lung. This hesitation by physicians to use colistin in its intravenous and nebulized forms is interesting because colistin has been used uninterruptedly during the last decades in patients with cystic fibrosis for severe Pseudomonas aeruginosa respiratory tract infections. Gradually, the use of colistin has entered successfully clinical practice mainly in the intensive care unit (ICU) setting in most parts of the world, including now the United States [3]. More so, various patient populations have received colistin (intravenously and/or nebulized) including neonates, children [4], and patients with cancer [3].

To address the effectiveness of colistin in the treatment of VAP is far from an easy task. It is important that one be aware of the differences in the groups compared. It is almost predictable that colistin is administered in patients in whom there is no other therapeutic choice. In contrast, in the comparator group, there are always more classes of antibiotics that could be used. This difference may be an important confounding factor when comparing outcomes. Also, the attributable mortality associated with MDR bacteria, including Acinetobacter baumannii, cannot be questioned nowadays, because inappropriate empirical antibiotic treatment is associated with increased mortality [5]. Hence, physicians use colistin mostly when there is resistance to all other available antibiotics (including carbapenems) or when clinical failure ensues after using other antibiotics or even empirically in the ICU setting when MDR, extensively drug-resistant (XDR), or pandrug-resistant (PDR) [6] gram-negative bacteria constitute a significant proportion of isolated bacteria. Obviously, one would not consider treating carbapenem-resistant bacteria with carbapenem monotherapy nor carbapenem-susceptible bacteria with colistin monotherapy as this would be not considered medically acceptable. However, one must take this very point into consideration, namely, that colistin was used in the published studies in a potentially different patient population against that of other comparators. Although the APACHE score may help us in the...
evaluation of patient status, different risk factors may lead to the evolution of these, potentially different regarding their virulence, bacteria. There are no definitive data to confirm or refute whether bacteria susceptible only to colistin are more virulent than MDR bacteria. Some will argue that when bacteria acquire resistance to more antibiotic classes (ie, MDR bacteria evolving to XDR bacteria), they may lose biological fitness. Nevertheless, analogous patients with infection due to extended-spectrum β-lactamase (ESBL) producers fare worse than if infections are due to non-ESBL bacteria [7]. Furthermore, carbapenem-resistant bacteria have led to nationwide strategies to confront them [8] as they are associated with increased mortality if inappropriate antibiotics are given empirically [5, 9].

It would be scientifically correct to treat the same infectious disease (ie, VAP) due to the same bacterium (ie, Pseudomonas aeruginosa) with the same resistance pattern (ie, XDR) with the comparable medications to deduce if any effectiveness differences exist. Such studies are not available. This fact has led to a real-life scenario of the authors’ paper, in which there are a relatively small number of heterogeneous studies with 2 arms and a majority of the studies with only 1 arm. Some would argue that most of the included studies are small in size and that they have the inherent problems of retrospective studies. However, to deprive critically ill patients of their right to receive an effective and safe medication when this is absolutely needed, in view of waiting for the perfect study to be published, may be unjustified. From this perspective, we think that the study design of the authors is the optimal design that one could achieve on the basis of the current evidence.

One could potentially expect a more beneficial effect of colistin regarding reduction of the mortality attributed to VAP, on the basis of the trend of better microbiological outcome in patients who received colistin. There are inherent difficulties to reach statistical significance when evaluating cohort studies in VAP, as these are often underpowered to detect differences [10]. This difficulty to reach statistical significance may also apply to the potentially therapeutically additive effect of nebulized colistin to the intravenously administered colistin. Thus it remains unresolved and is debated whether to administer nebulized colistin as adjunctive to the intravenous formulation [11]. In addition, various studies of higher methodological design regarding the use of other therapeutic interventions in VAP have not been able to show a statistically significant difference when it comes to mortality evaluation [12, 13].

Beyond the therapeutic effectiveness of colistin, the systematic review and meta-regression emphasizes the comparable nephrotoxicity of colistin and its comparators in the six 2-arm studies. Nephrotoxicity associated with polymyxins has been the main concern for physicians treating infections due to MDR bacteria. However, previously published literature regarding extreme nephrotoxicity has not been verified in the current era [14]. To minimize the possibility of nephrotoxicity, one must calculate colistin dosage accurately, using the manufacturers’ data regarding maximum daily dose, and adjust the dose (decrease) if impairment of renal function is present. Furthermore, avoidance of other potential nephrotoxic agents (especially aminoglycosides) should be followed to minimize adverse events [14].

Steadily, over the last decade, colistin has established its reputation. However, due to the extensive use of the medication, it is not surprising that resistance to colistin has emerged [15]. Hence, the medication should be used when so dictated by the clinical setting. If used empirically, then discontinuation of colistin must be considered, if in vitro susceptibility results permit other therapeutic options. Detailed pharmacokinetic and pharmacodynamic data regarding the colistin were lacking in the previous century. However, there is an accumulation of such information in the last decade. In vitro pharmacodynamic studies do not support using colistin as a single therapeutic option [16]. Clinical data from the largest cohort of patients who received intravenous colistin for microbiologically documented MDR gram-negative bacterial infections point to the fact that combination with carbapenem may lead to the best clinical results [17]. Furthermore, as pharmacokinetic data have accumulated over the last decade, interim suggestions for modified doses are emerging [18]. One must be careful, however, to see that these data are verified in studies with larger number of patients and ideally in randomized controlled studies.

Probably, because we potentially will not have sufficient alternative antibiotic choices for MDR gram-negative bacteria during the following years, it is essential to understand that colistin is of paramount importance and should neither be recklessly administered nor stubbornly denied to those critically ill patients in most need. Colistin is a valuable antibiotic [19] for the management of infections due to MDR, XDR, and PDR gram-negative bacteria in the beginning of the 21st century.

Note

Potential conflicts of interest. M. E. F. has participated in advisory boards of Astellas, Bayer and Pfizer and has received lecture honoraria from Astellas, AstraZeneca, Cipla, Glenmark, Merck, Novartis and Pfizer.

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References


