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EDITORIAL COMMENTARY

Colistin and a New Paradigm in Drug Development

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(See the Major Article by Nation et al on pages 552–8.)

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In this issue of *Clinical Infectious Diseases*, Nation and colleagues (from a consortium of academic institutions in Australia, the United States, Thailand, and Greece) present a critical analysis of the United States (Food and Drug Administration [FDA]) and European (European Medicines Agency [EMA]) dosing recommendations for the intravenous administration of colistin in relation with pharmacokinetic/pharmacodynamic target attainment rates [1]. Together with the large number of recent publications from members of this consortium and other academic institutions, this analysis and the efforts of both regulatory agencies come at an appropriate time and also illustrate a new paradigm in drug development. Colistin is indeed a quite old antibiotic (isolated in Japan in 1949 from *Bacillus polymyxa* var *colistinus*). It was only sparingly used in human clinical practice for parenteral administration until the emergence of multi- and panresistant gram-negative organisms in the beginning of this century [2]—that is, at a time when it was no longer under patent protection. In parallel, colistin has been and is still used in large amounts in animals both for curative treatments and for prevention of disease [3]. As a result, there was no or little interest for the pharmaceutical industry to meet the expectations of clinicians when requesting information and hard data about optimal human dosages. Likewise, no effort was made at re-registering colistin for treatment of infections caused by resistant organisms. This may be understandable in a context of drug development made essentially by profit-making industries, which has been and is still largely the system in which most industrial countries have been able to obtain modern medicines. There was also a fear from industry that regulatory agencies would never approve colistin for the indications required by clinicians given the many uncertainties about its true pharmacokinetics (complicated by the fact that colistin is used in humans as prodrug [colistimethate], which hydrolyzes to liberate active colistin rather slowly), its ability to control infections alone (thus requiring combination therapies), and the potential for nephro- and neurotoxic reactions.

Thus, colistin may be unique so far in having known a development for human use following modern approaches to pharmacokinetics and pharmacodynamics that is essentially the result of academic efforts (including by Nation et al) with the support of public authorities (eg, the AIDA project, undertaken within the Seventh European Union Framework Program [FP7] project and involving since 2011 the collaboration between 14 partners from 11 different countries [http://www.aida-project.eu/], and the numerous grants awarded by the National Institutes of Health [NIH] for studies on colistin [see https://clinicaltrials.gov/show/NCT01597973, and the general description of NIH efforts at http://www.niaid.nih.gov/topics/antimicrobialResistance/Pages/colistin.aspx]).

It is also unusual for regulatory authorities to address issues about dosing of a drug that has no industrial applicant (although this may become more frequent with the increase in numbers of generics of molecules for which the original marketing authorization holder has lost interest because of patent expiration). So, both agencies are to be commended for their efforts at providing the anti-infective community with guidelines that could help clinicians to use colistin, if needed, more optimally. It is, however, regrettable that these guidelines are not made more coherent on both sides of the Atlantic, and that each agency comes with specific but distinct recommendations, with divergences that affect mainly patients with low body weight and those with low creatinine clearance, for whom the FDA-approved guidelines seem to provide attainment rates for plasma colistin exposure that are substantially lower than those that may be achieved with EMA-approved dosing suggestions. This is unfortunate because colistin is now increasingly used in Southeast Asia where patients with low body weight are more frequent than in the United States. The authors are cautious in not raising undue controversies between these somewhat conflicting recommendations, but their analysis nevertheless shows clearly which direction the clinicians should follow. Hopefully, more in-depth discussions and information exchange between regulatory agencies and academic groups

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involved in clinical research about colistin will help in decreasing these divergences.

Second, the authors state that their results will assist in current deliberations on clinical breakpoints for colistin. This is also essential and there is good hope that some consensus may be reached in the future. At the present time, indeed, we live with different clinical breakpoints as set by the European Committee on Antimicrobial Susceptibility Testing on one side and the FDA (and/or the Clinical and Laboratory Standards Institute) on the other. Although setting clinical breakpoints is a difficult task and sometimes closer to an art than to a fully objective scientific exercise, it is urgent for these organizations to come to a consensus. There is indeed no reason why such breakpoints should be different, unless the conditions of administration of colistin would vary to a commensurate extent between the United States and Europe, which is not the case. Other countries, such those in Southeast Asia, may not easily understand the reasons for this situation and could, justifiably, decide to define their own breakpoints, which would only add to the confusion.

Last, the authors point to an extremely narrow therapeutic window for this drug, which should encourage systematic therapeutic monitoring. This would require the development of rapid and easy-to-use methods for specifically measuring the free concentration of the active molecule. This remains a challenge in many clinical settings today.

Note

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