ACS Infectious Diseases

In This Issue

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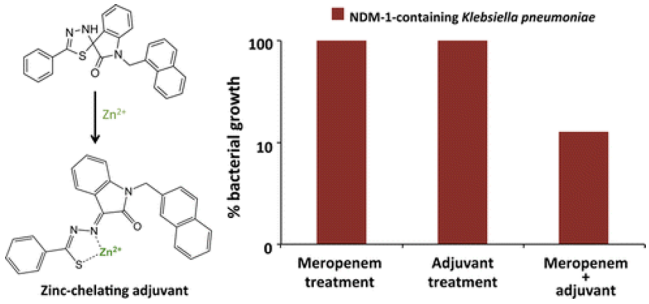
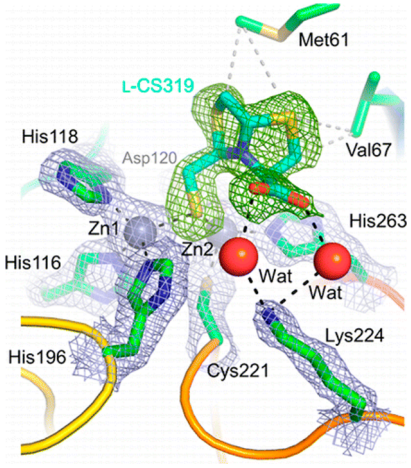
GETTING TO THE ZINC



Carbapenems are β-lactam antibiotics that exhibit enhanced stability against most β-lactamases, which render earlier generations of β-lactams ineffective. Recently, however, the rapid spread of Enterobacteriaceae and other Gram-negative bacteria harboring metallo-β-lactamase genes has threatened the utility of carbapenems as a viable therapeutic option. As metallo-β-lactamases present a catalytic mechanism requiring zinc that is distinct from other β-lactmases, traditional β-lactamase inhibitors are ineffective in suppressing their activity. To rescue carbapenems from the effects of metallo-β-lactamases, β-lactamase inhibitors with zinc-chelating activity have been proposed.

In this special issue on Gram-negative resistance, Falconer et al. (DOI: 10.1021/acsinfecdis.5b00033) use a previously described agent demonstrated to have iron-chelating properties as chemical scaffold for developing a series of compounds with the ability to potentiate carbapenem activity against a bacterial strain possessing metallo-β-lactamase activity. The authors demonstrate that a zinc-chelating derivative of the agent is capable of restoring susceptibility to the carbapenem, meropenem, both in vitro and in an in vivo mouse model of infection.

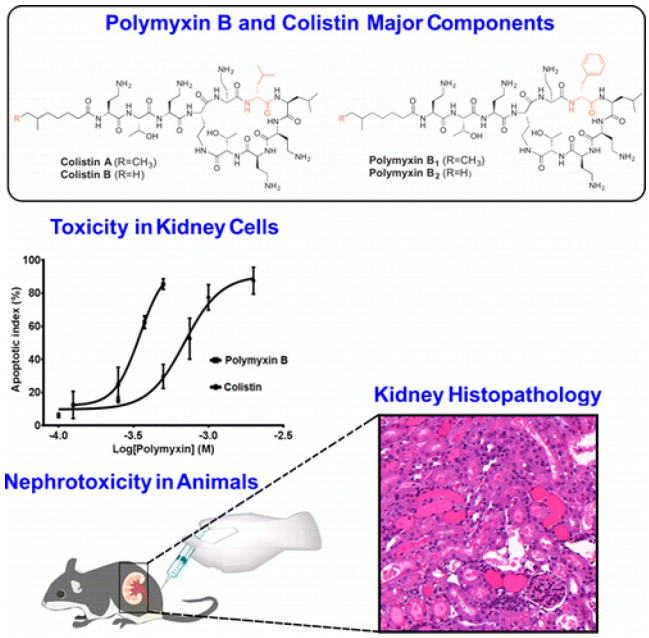
MAKING NDM-1 INHIBITION CRYSTAL CLEAR



NDM-1 is a metallo-β-lactamase capable of hydrolyzing carbapemen antibiotics including imipenem. NDM-1 is transferred as part of a mobile genetic element and is the most widespread clinically relevant metallo-β-lactamase.

In this issue, González et al. (DOI: 10.1021/acsinfecdis.5b00046) use a bisthiazolidine scaffold to develop four compounds with NDM-1 inhibitory activity. The authors demonstrate the compounds are capable of inhibiting hydrolysis of imipenem in NDM-1-producing bacteria. Finally, the authors obtain the crystal structure of NDM-1 in complex with the most potent of the NDM-1 inhibitors.

NOT ALL POLYMYXINS ARE CREATED EQUAL



Polymyxins, which include polymyxin B and colistin, are a class of antibotics with exceptional activity against Gram-negative infections. Nonetheless, their use for most infections had fallen out of favor due to associated nephrotoxicities. Polymyxins are generally thought of as a treatment of last resort for infections caused by multidrug-resistant Gram-negative bacteria. With the rapid increase in multidrug resistance to other antibiotics, use of polymyxins is once again becoming common practice. Commercial formulations of polymyxins contain a mixture of many closely related structures, and the exact composition may vary by manufacturer.

Here, Roberts et al. (DOI: 10.1021/acsinfecdis.5b00085) investigate the respective antimicrobial activities and toxicities of the major components of polymyxin B and colisitin. The authors compare activities and toxicities of the individual components of polymyxin B and colisitin to the commercial multicomponent mixtures both in vitro and in vivo. A better understanding of the composition of polymyxin formulations may provide insight into a mechanism to reduce toxicity associated with polymyxins.

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