



New Antibiotics against Multi-resistant Gram-negative Bacteria

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Because of emerging resistance in gram-negative bacteria to many and in some cases all currently available antimicrobial agents, there is a strong medical need for additional agents active against these resistant pathogens. Much recent drug development has focused on new agents to address the parallel problem of multidrug resistance in gram-positive pathogens, but there are fewer agents in the pipeline to address current resistance in gram-negative pathogens. Although smaller in number overall, broad-spectrum agents with coverage of resistant gram-negative bacteria under clinical development do exist in several drug classes, including β -lactams, tetracyclines, and quinolones, and one older agent has been resurrected because of the urgency of need.

For some multidrug resistant strains of *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, colistin (polymyxin E, colistimethate) is the only currently available systemic agent active *in vitro*. Newly resurrected despite prior limitations of nephrotoxicity and neurotoxicity, intravenous colistin has been shown to be equivalent to imipenem when *A. baumannii* strains are susceptible to the treating agent in patients with ventilator-associated pneumonia. In pneumonia and bacteremia caused by strains of *P. aeruginosa* or *A. baumannii* susceptible only to colistin response rates have been ~75%. There have also been case reports of successfully treated patients with sepsis due to *Klebsiella pneumoniae*, but strains of *Proteus*, *Serratia*, and *Burkholderia* tend to be resistant *in vitro*.

Carbapenems as a class have generally had the broadest spectrum of antimicrobial activity against gram-negative bacteria. Two new carbapenems are in clinical development, doripenem and CS-023. Doripenem (S-4661), a 1- β -methyl carbapenem, is more potent than imipenem but similar in potency to meropenem against enteric bacteria. Although also similar to meropenem in its activity against *A. baumannii* strains, doripenem is notably two-to fourfold more active than meropenem and imipenem against *P. aeruginosa*. In *P. aeruginosa*, however, the activity of doripenem like that of imipenem is reduced in OprD-mutants and in strains carrying metallo- β -lactamases. Being stable to renal dehydropeptidase, doripenem is being developed without combination with a dehydropeptidase inhibitor. CS-023 (R-115685) is also a 1- β -methyl carbapenem that is stable to renal dehydropeptidase, and it too has somewhat increased activity against *P. aeruginosa* relative to meropenem and is four-to eightfold more potent than meropenem in a small number of meropenem-resistant strains. CS-023, however, is less active than meropenem and imipenem against *A. baumannii*. Clinical trials are ongoing for both doripenem and CS-023. Other carbapenem structures (J-111,347) have also been shown to have greater potency *in vitro* than meropenem against both *A. baumannii* and *P. aeruginosa*, and another compound (J-111,225) has shown increased stability to several metallo- β -lactamases.

BAL9141 (Ro 63-9141), a novel pyrrolidinone-3-ylidenemethyl cephalosporin under clinical development, exhibits broad spectrum activity. Potency against enteric bacteria and *P. aeruginosa* is similar to that of cefepime, and activity against *A. baumannii* is two- to fourfold greater than that of cefepime. BAL9141 is a poor substrate for AmpC β -lactamases, but a number of ESBLs inactivate it, and cef-tazidime-resistant strains of *P. aeruginosa* are cross-resistant. BAL9141, like cefepime, has poor activity against *Stenotrophomonas maltophilia*.

Acquired resistance to tetracyclines is widespread in gram-negative bacteria. The related glycyliclins were developed to circumvent the established mechanisms of resistance due to Tet efflux pumps and ribosomal protection. Tigecycline, a glycyliclin, is undergoing clinical development as a broad spectrum agent against both gram-positive and gram-negative bacteria. Activity *in vitro* includes many but not all enterics and some strains of *Acinetobacter* and *Stenotrophomonas*. It lacks activity against *P. aeruginosa* and its activity against *Proteus* and *Morganella* is less than other enterics due in all three cases to the activity of native multidrug efflux pumps that include tigecycline as a substrate. Other semisynthetic tetracycline derivatives are also being investigated but are not yet in clinical development.

Quinolones in clinical development include sitafloxacin and garenoxacin. Sitafloxacin (DU6859a) has activity against gram-negative bacteria similar to or greater than that of ciprofloxacin, including fourfold to 16-fold greater activity against *Acinetobacter*, 16-fold greater activity against *S. maltophilia*, twofold greater activity against *P. aeruginosa*, and eightfold greater activity against ofloxacin-resistant strains of *P. aeruginosa*. Sitafloxacin-resistant strains of *P. aeruginosa* and *A. baumannii* of diverse lineages already exist in European hospitals, however. For *K. pneumoniae* and *Enterobacter cloacae* with established *gyrA* or *parC* resistance mutations, sitafloxacin in some cases maintains activity by clinical laboratory criteria. Published clinical trials provide only limited data on efficacy in patients with systemic gram-negative bacillary infections. Garenoxacin (BMS-284756), a 6-desfluoro-quinolone, also has broad spectrum activity, including potency against many enteric bacteria, although usually less than that of ciprofloxacin. Although eightfold less potent than ciprofloxacin against *P. aeruginosa*, it is twofold more potent against *Acinetobacter*.

Although not yet in clinical development, inhibitors of specific resistance mechanisms are being pursued. β -lactamase inhibitors continue to be explored, and those that include AmpC as well as other enzymes remain a goal. In addition, inhibitors of Tet efflux pumps in *E. coli* and broad-range inhibitors of endogenous efflux pumps in *P. aeruginosa* have been identified. In the latter case, one compound (MC 207,110) was shown as a proof of principle to be effective in inhibiting all four multidrug resistance efflux pumps of *P. aeruginosa* and in increasing the activity of fluoroquinolones against both wildtype strains and strains with the commonly acquired resistance due to efflux pump overexpression.

Although a number of new compounds with enhanced activity against gram-negative bacteria have reached the stage of clinical development and may provide future therapeutic options against multidrug resistant gram-negative pathogens, none is free from issues related to established resistance mechanisms. Thus, the need for control of existing resistance and the need for further exploration for new compounds must both be emphasized.