Azithromycin Phenotypic versus Clinical Resistance

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Jia and colleagues report that the azithromycin MICs for 25 environmental isolates of *Legionella pneumophila* were about 2-fold greater than the EUCAST epidemiologic cutoff value of 1 mg/liter for this species, based on the presence of the *lpeAB* efflux pump (1). This phenotypic resistance should not be conflated with clinical resistance. The ECOFF indicates a value greater than the wild-type azithromycin MIC population distribution but cannot be accurately used to determine the azithromycin clinical breakpoint. One good example of this is the benzylpenicillin EUCAST ECOFF value for *Streptococcus pneumoniae* of 0.064 mg/liter, which is far below the CLSI clinical breakpoint of ≤ 2 for susceptibility and ≥ 8 mg/liter for resistance to nonmeningeal isolates. Azithromycin concentrations inside cells, the only site of *L. pneumophila* growth, are very high and persist for weeks. Humans without pneumonia given a single 500-mg oral dose of azithromycin achieved an azithromycin alveolar macrophage area under the concentration-time curve from 0 to 48 h (AUC_{0-48}) to an AUC_{0-72} of 5,804 mg · h/liter, with a maximum concentration (C_{max}) in macrophages of 194 mg/liter (2). In another study of azithromycin pharmacokinetics in healthy people given daily intravenous azithromycin for 5 days, alveolar macrophage azithromycin concentrations 24 h after the last drug infusion were 734 mg/liter (3). After 5 days of oral administration of 500 mg of azithromycin to healthy people, alveolar macrophage concentrations were 464, 304, 112, 110, and 82 mg/liter on the last day of administration and 2, 5, 9, and 16 days after drug cessation, respectively (4). Azithromycin concentrations in alveolar macrophage, lung, and bronchoalveolar lavage were significantly greater in *L. pneumophila*-infected guinea pigs and their macrophages than in uninfected animals (5), concordant with the delivery of azithromycin to infected tissues by phagocytic cells (6). Finally, azithromycin was reported to have high efficacy for the treatment of pneumococcal pneumonia when the bacterial isolates were azithromycin resistant (7). The extremely high azithromycin macrophage exposures make a 2-fold increase in azithromycin MICs extraordinarily unlikely to result in azithromycin treatment failure of Legionnaires' disease. I therefore caution journal readers not to conflate non-wild-type azithromycin MICs with clinical resistance.

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