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Best in class: a good principle for antibiotic usage to limit resistance development?

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The causes of antibiotic resistance are often complex and it is difficult to identify strategies to prevent or delay its emergence. One strategy has been to use less active members of a drug class, so that when resistance develops the more active members will still prevail. This stratagem may often fail because this resistance may form the basis of resistance to the whole class. Often, less active drugs are the first to be discovered and more active versions follow, so we have had no choice; however, increasingly less active drugs are available to deal with specific infections and this may have a detrimental effect on the class as a whole.

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In the 1990s, the WHO recommended the use of the quinolone nalidixic acid for the treatment of infections caused by *Shigella* spp. in southern Asia; however, nalidixic acid has relatively low activity. Its use has been shown to select a mutation in codon 83 of the *gyrA* gene,[1] giving high-level resistance. However, this is also the first mutation required for resistance to the much more active fluoroquinolone, ciprofloxacin.[1] Therefore the use of this drug appears implicated in the preliminary stage on the progression to ciprofloxacin resistance. The WHO rationale was that the use of the less active compound would preserve the more active drugs when resistance developed. The tactic appears flawed as nalidixic acid resistance *and* a concomitant decrease in ciprofloxacin susceptibility emerged in *Shigella* spp. at the end of the 20th century compromising future use of the fluoroquinolones.[2]

The stratagem of using less active drugs first has long been part of microbiology folklore. However, it ignores the fact that resistance to one member of a drug class often brings resistance to the whole class and that less active class members are often more adept at selecting resistance than their more active counterparts. The use of the earlier, poorly penetrating fluoroquinolones, such as pefloxacin in France, for the treatment of infections caused by *Acinetobacter baumannii* has been associated with rapid increases in resistance not only to pefloxacin but also to ciprofloxacin.[3,4] The same principle could be seen with the introduction of the anti-Gram-positive fluoroquinolones for the treatment of *Streptococcus pneumoniae*. These drugs were being compromised by the concurrent usage of fluoroquinolones that were designed primarily for anti-Gram-negative use but were less effective against Gram-positive bacteria.[5,6]

The use of less active drugs has also been associated with the emergence of the TEM-derived extended-spectrum β-lactamases (ESBLs). Cefotaxime is a fast penetrating cephalosporin in Enterobacteriaceae, whereas ceftazidime penetrates more slowly. However, ceftazidime was used extensively against *Klebsiella* infections and the initial ESBL mutations arose rapidly. Once formed, the subsequent mutations that broadened the spectrum of ESBL activity could be selected more readily.[7] The impact of the ESBLs is now well known and has largely stopped all cephalosporin development for Gram-negative infections. The last major cephalosporins to be launched against Gram-negative bacilli were cefepime and cefpirome, which are fast penetrating cephalosporins in the Enterobacteriaceae. Had these drugs been used at the beginning, then it is likely that the development of resistance would have, at least, been delayed. Instead, the use of poorer-penetrating cephalosporins selected resistance that even the superior qualities of cefepime and cefpirome may not be able to overcome.[8]

The major drug class of last resort for Gram-negative bacteria is the carbapenems. Imipenem and meropenem are very active against most Gram-negative bacteria, though there are β-lactamases (carbapenemases) capable of conferring resistance.

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However, resistance has been quite slow to develop and is virtually non-existent in some species. This has encouraged the development of less active carbapenems, such as ertapenem, aimed mainly at Enterobacteriaceae causing community-acquired infections. However, its usage has been advocated more widely,[9] but only in areas where there is no risk of infection by non-fermenters, which is difficult to guarantee in hospitals. As ertapenem is believed to have no activity against non-fermenting organisms, such as *Pseudomonas aeruginosa* and *A. baumannii*, its use would not preferentially select variants of these bacteria resistant to the more active carbapenems. It has been suggested that this concept is flawed and likely to select resistance in non-fermenting pathogens.[10] This can be demonstrated *in vitro* if a mixture of two *A. baumannii* strains, one harbouring the carbapenemase OXA-65 and the other lacking it, are challenged with ertapenem in the ratio of 1:99. In the absence of antibiotics, the ratio of the strains remains constant with the carbapenemase-negative strain dominating the culture. However, on challenge with ertapenem, the carbapenemase-containing strain soon takes over the population; so this carbapenem is selecting a carbapenemase that encodes resistance to all carbapenems (personal observation).

With increasing knowledge of pharmacodynamics and the molecular mechanisms of antibiotic resistance, antibiotic dosages can be more intelligently selected based on the desired antibiotic exposure at the site of infection. The use of more active bactericidal agents that provide increased free drug activity (without increased toxicity) is likely to provide a lethal antibiotic exposure to the pathogen. In many instances, we now have knowledge of the drug exposure required to kill organisms that may already have developed single-step mutations, leading to only modest increases in the organism's MIC. If a less active antibiotic is used, selection of the single-step mutants is facilitated, which then allows for the development of further mutations, thereby rendering the pathogen resistant to all agents in the class. Development of resistant pathogens impacts both the patient and other patients in the hospital unit. Antibiotic-resistant pathogens are more likely to cause subsequent infections in that patient, as well as spread to other patients if infection control techniques are not stringently followed. Prevention of the development of resistant organisms by using the appropriate antibiotic at the appropriate dosage not only protects the patients in the institution, but it prolongs the useful life of the class of agents and prevents the need for the use of other, potentially more toxic agents. Using more active agents in one class of antibiotics may decrease the need for novel agents targeting multidrug-resistant organisms.[11]

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