Antimicrobial Stewardship and Antimicrobial Resistance

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KEYWORDS

• Antimicrobial resistance • Antimicrobial stewardship • Interventions
• Antimicrobial restriction • Antimicrobial cycling • Decision support

KEY POINTS

- Antimicrobial stewardship programs over the years have had several goals, including reducing costs, optimizing therapeutic outcomes, and reducing antimicrobial resistance. Reductions of antimicrobial resistance have been the most elusive.
- The relationship between antimicrobial usage and resistance is also not always direct, especially with molecular mechanisms that confer resistance to multiple classes of antibiotics or through transferable plasmids and transposons that contain multiple resistance genes.
- The understanding of which techniques are most effective is limited by the fact that many studies are descriptive or quasiexperimental.
- More recently, several meta-analyses or systematic reviews of stewardship programs have been published, offering encouragement that some interventions, especially those that involve prospective auditing and feedback, have the effect of reducing overall antimicrobial selective pressure, and are associated with infection control interventions, can have an important impact on resistance rates in individual institutions.

INTRODUCTION

Since the concept of antimicrobial stewardship was introduced by McGowan and Finland[1] and others in the 1970s, stewardship programs have evolved from cost-containment exercises to efforts to optimize the treatment of infections (primarily in hospitals) and more recently to decrease the antimicrobial selective pressure that promotes the emergence and spread of antimicrobial resistance. Stewardship programs' track records of decreasing antimicrobial costs have been generally positive, using in many cases preapproval programs that promote the use of less expensive antimicrobial alternatives.[2] Strategies designed to optimize the treatment of infections have

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generally used computer programs that offer advice on appropriate dosing of infections relative to the patient,[3] such as programs that recommend appropriate adjustments of antimicrobial doses in patients with renal failure, in pediatric patients, or in patients with larger than normal body masses. Such programs may also recommend optimal dosing based on commonly accepted pharmacodynamic principles, such as the killing parameters for a given antibiotic class (concentration-dependent killing, time-dependent killing, or area under the curve calculations). Examples of the beneficial effects of these types of pharmacodynamic analyses include the use of aminoglycosides in a single daily dose (optimizing killing and minimizing toxicity)[4] or the development of daptomycin as a single daily dose antibiotic.[5] Other recommendations based on pharmacodynamic data, such as the use of β–lactam agents as a continuous infusion, have not been widely demonstrated to result in improved outcomes in the clinical setting, but may be useful for critically ill patient with sepsis with respiratory infections.[6]

Comprehensive programs designed to minimize overall antimicrobial resistance are recent and take their cues in some cases from previous examples of outbreaks of resistant bacteria that have been successfully controlled by limiting the use of a particular class of agents. We discuss several examples of such strategies later in this article, but it is first important to delineate some general definitions and principles relevant to the relationship between antimicrobial use and resistance. **Table 1** lists six principles that should be kept in mind when evaluating any stewardship strategies.

HISTORICAL BASES FOR BELIEF THAT STEWARDSHIP CAN CONTROL ANTIMICROBIAL RESISTANCE

Although it is sometimes said that there would not be antimicrobial resistance without the use of antibiotics, this sentiment is not strictly true. It is known, for example, that gram-negative bacilli are intrinsically resistant to vancomycin, presumably because the large vancomycin molecule cannot traverse the porins of the gram-negative outer membrane. Similarly, anaerobic bacteria are resistant to aminoglycosides because the movement of aminoglycosides across the cytoplasmic membrane is an oxygen-dependent process. We do not formally consider these resistance phenotypes to be problems because they are considered the natural spectrum of the antibiotic in question. Resistance is considered a problem when it occurs in bacteria normally within an antibiotic's spectrum of activity, such as *Escherichia coli* resistance to ampicillin, *Pseudomonas aeruginosa* resistance to imipenem, *Staphylococcus aureus* resistance to oxacillin, or *Enterococcus faecium* resistance to vancomycin. In such instances, increasing levels of resistance are virtually always associated with use of one or more classes of antibiotics.

The association between use and resistance is sometimes interpreted as causation, and with good reason. Most antibiotics have broad spectra of activity. Use of these antibiotics invariably alters the flora of the person who is taking them, creating a circumstance where resistant bacteria have a selective advantage for growth. The emergence and spread of resistant bacteria logically occurs in settings where this selective advantage is present. It is also sometimes claimed that resistant bacteria are at a selective disadvantage because expressing resistance has some metabolic cost, either because of the energy required to replicate a resistance plasmid or activate an efflux pump, or because of the compromised function of a target protein that has mutated to resistance, or metabolic disadvantages that result from the loss of normal functions of porins or efflux pumps. In some cases, selective disadvantages are demonstrated in growth experiments comparing mutated with wild-type strains.

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