19.4.1 Antibiotic–Antibiotic Combinations

Antibiotic combination therapy involving the use of two, three, or even four different antibiotics – multiple antibiotic regimens – is routinely used and often is the only available treatment option for infections caused by MDR organisms. This combination therapy can be divided into (i) antibiotic that targets in different pathways, (ii) antibiotics with different targets in the same pathway, and (iii) antibiotics that target the same pathway in different ways.

19.4.1.1 Targets in Different Pathways

One example of this strategy is the combination therapy used for the treatment of MTb infections, which is a combination of four drugs, namely, isoniazid, ethambutol, and pyrazinamide, which target the cell wall biosynthesis, and rifampicin which target mRNA synthesis.

Other examples of combination therapy that inhibits targets in different pathways are those therapies used to treat MDR Gram-negative infections such as MDR *Acinetobacter* spp., which is often combination of colistin (a cationic polypeptide antibiotic) with aminoglycoside, ampicillin/sulbactam, a carbapenem, or rifampin. Colistin/tigecycline and an aminoglycoside, a carbapenem, colistin, fosfomycin, rifampin, or tigecycline have been successful against carbapenemase-producing *Enterobacteriaceae*. A combination therapy of a broad-spectrum β-lactam and an aminoglycoside or a fluoroquinolone has been used for suspected Gram-negative sepsis and severe infections caused by *Pseudomonas* spp.

19.4.1.2 Different Targets in the Same Pathway

A well-known example of combination therapy that inhibits different targets in the same pathway is the combination of sulfamethoxazole and trimethoprim, which inhibit successive steps in the folic acid biosynthetic pathway. Another example is the targeting of teichoic acid synthesis in Gram-positive bacteria by tunicamycin (drug produced by *Streptomyces lysosuperificus*), which exhibits synergism with β-lactam against *S. aureus*. Tunicamycin inhibits *N*-acetylglucosamine-1-phosphate transferase (TarO), the first enzyme in the pathway of wall teichoic acid biosynthesis. The antiplatelet drug ticlopidine (Ticlid), a nonantibiotic that is a TarO inhibitor, has the ability to potentiate the activity of the cefuroxime against MRSA strains.

19.4.1.3 Same Target in Different Ways

A very interesting example of combination antibiotic therapy that inhibits the same target in different ways is the use of streptogramins, natural cyclic peptides produced by a number of *Streptomyces* species. These peptides represent a unique class of antibacterial that has two structurally distinct macrocyclic components: group A streptogramins (macrolactones), such as virginiamycin