limit the development of resistance *in vitro* in comparison with drug monotherapy. The overall expected clinical outcome for this strategy is to have lower patient mortality rates. However, combination therapy is not limited to antibiotic agents but includes therapeutic interventions that may use anti-virulence agents or helper molecules, also known as adjuvants with no or poor antibacterial activity capable of enhancing the efficacy of a primary antibiotic. In fact, it has been argued that the antibiotic–adjuvant combination approach offers a more attractive option in the treatment of drug-resistant bacterial infection than using multiple antibiotics (Wright 2016).

18.4 Antibiotic–Antibiotic Combination Approach

The use of two or more antibiotic agents that have different targets is an attractive strategy to overcome drug resistance. The hypotheses of the antibiotic–antibiotic combination approach are (i) to achieve drug synergism between each drug component in a way that enhances treatment efficacy and (ii) to simultaneously impact multiple targets in pathogens, resulting in the suppression of antibiotic resistance development and complete eradication of bacterial strains with intermediate susceptibility or resistance to one of two antibiotics (Williams 2014). The assumption is that the bacterial cell will have difficulty surviving with multiple "hits" at the same time. Clinicians sometimes employ this strategy during empirical treatment of infection, and such an approach might indeed prolong the clinical utility of antibiotics. For instance, the combination of trimethoprim and sulfamethoxazole has been in use since 1968 for the treatment of bacterial infections caused by the *Enterobacteriaceae* family and non-fermentative opportunistic pathogens (Huovinen 2001; Masters et al. 2003). Both antibiotics work together to inhibit sequential steps in bacterial folic acid synthesis, which is detrimental as most bacteria are obligate folate synthesizers while humans acquire folate through diet. The sulfonamide, sulfamethoxazole, inhibits dihydropteroate synthase that converts para-aminobenzoic acid to dihydrofolate, and trimethoprim inhibits dihydrofolate reductase that converts dihydrofolate to tetrahydrofolate (Masters et al. 2003). Trimethoprim–sulfamethoxazole is an efficacious antibiotic used to treat urinary tract and select gastrointestinal bacterial infections (Libecco and Powell 2004; McIsaac et al. 2008). Sulfamethoxazole may be replaced with the sulfonamide, sulfametrole, in some European Union countries, although both, when combined with trimethoprim, exhibit the same clinical efficacy (Livermore et al. 2014). However, the success of the trimethoprim-sulfamethoxazole combination has been affected by the dissemination of resistance mechanisms that prevent both antibiotics from eliciting their biological functions. Overexpression of multidrug efflux pumps able to expel both trimethoprim and sulfamethoxazole out of the cell and membrane modifications that limit their intracellular