

not work for ciprofloxacin or erythromycin, suggesting that ClpXP inhibition only improves the efficacy of antibiotics that target the cell wall or cell membrane. They also found that F2 increased the antimicrobial activity of human whole blood, possibly demonstrating AMP sensitization under physiological conditions (McGillivray et al. 2012). It has been long known that thioridazine (TDZ), an old neuroleptic, can sensitize MRSA to β -lactam antibiotics, but there is no clear mechanism why. The hypothesis has been that TDZ works as an EPI. Recently, Thorsing et al., presented evidence against this hypothesis by showing that TDZ interferes with cell wall synthesis in MRSA (Thorsing et al. 2013). Bacteria treated with TDZ exhibited a thickened and irregular cell wall with decreased intracellular concentrations of amino acids. The authors suggest that TDZ interferes with the formation of pentaglycine branches in the peptidoglycan that sensitize MRSA to antibiotics targeting the cell wall, exemplified in the study by a synergistic effect between TDZ and dicloxacillin (Thorsing et al. 2013). TDZ, being an old neuroleptic, might be associated with similar problems as the antipsychotic drugs mentioned above, with problematic side effects.

Nonetheless, the use of cell wall-interacting sensitizers feels like a smart approach since many important and safe antibiotics use related mechanisms. Sensitizers affecting cell wall integrity could also lead to treatment advantages associated with effect on membrane proteins (such as transporters) and increased permeability, which could increase concentrations of intracellular antibiotics.

17.3.3 Biofilms and Quorum Sensing

Biofilms are complex microbial communities encased in a self-produced matrix of extracellular substances, in which the bacteria have an altered phenotype compared with planktonically growing bacteria (Donlan and Costerton 2002; Lewis 2008). One of these phenotypes is an up to thousand times increased resistance to antimicrobial factors, including antibiotics, which in this context refers to an increased tolerance rather than an inherent resistance due to mutations or acquisition of resistance genes through horizontal transfer (Donlan and Costerton 2002; Yankaskas et al. 2004; Slinger et al. 2006). Additionally, biofilms are extremely common, and recent estimates say that they are present in 80% of bacterial infections (Lewis 2007; Wolcott and Ehrlich 2008). This makes interfering with biofilm formation or structure a promising approach to increase antibiotic resistance. As this topic will be discussed in detail in Chapter 9 in this book, we will only present the general aspects of the strategies being pursued in this chapter.

Biofilm tolerance is probably due to a combination of factors including the protective matrix and the layers of bacteria that are difficult for antimicrobial compounds to penetrate. Additionally, evidence is mounting that biofilm