9.3.1 Antibiotics (Bacteriocins) Natural and Synthetic Molecules: Phages

Some antibiotics are able to counteract biofilm development, such as aztreonam, by blocking quorum sensing and increasing sensitivity to hydrogen peroxide and the complement system. Aztreonam can also inhibit alginate production and polymerization of *P. aeruginosa* alginate by its incomplete precipitation and high levels of readily dialyzable uronic acids (Hoffmann et al. 2007). The development of antibiotic adjuvants, such as meridianin D, that increase the effectiveness of currently available antibiotics is a promising alternative approach (Huggins et al. 2018). Topical, inhaled, combined, and sequential antibiotic treatments have been tested in various situations, with variable results according to the study (Ciofu et al. 2017). In particular, Gallo et al. (2017) tested meropenem on *Acinetobacter calcoaceticus–Acinetobacter baumannii* persisters and claimed that the meropenem concentration did not influence persistent fractions, even when far above the MIC. Pamp et al. (2008) observed that biofilm *P. aeruginosa* cells exhibit low metabolic activity and are effectively killed by colistin. New technologies, such as the use of nanoparticles (Qayyum and Khan 2016; Kulshrestha et al. 2017; Zaidi et al. 2017) or quantum dots (QDs) (Li et al. 2016b), allow better penetration of antibiotics within the biofilm (Ficai et al. 2018). QDs are colloidal semiconductor nanocrystals that emit photoluminescence in proportion to the dot size. Their association with biofilm components can be utilized to determine the impact of surface chemistry on QD mobility and distribution in bacterial biofilms, which can be evaluated by epifluorescent or confocal microscopy (Morrow et al. 2010).

Bacteriocins are a family of peptides or proteins naturally synthesized by certain bacteria; they are not antibiotics but have antibiotic properties, causing the formation of pores in the bacterial membrane. Bacteriocins play an important role in the competition between bacterial strains, and their production is stimulated by quorum sensing. Oliveira et al. (2015) showed that antibiotics can act as stress inducers in a bacterial biofilm environment. At high density, cells can better control the environment with secreted products that favor their genotype over others, such as *P. aeruginosa* secreting pyocin, which acts as a narrow-spectrum antibiotic but may also stimulate biofilm formation by increasing cell attachment. Many bacteriocins have been described after the first discovery of colicin and nisin (Mathur et al. 2018; Yi et al. 2018), including derivatives (Seal et al. 2018).

Many natural or synthetic molecules have been tested, alone or in combination with antibiotics, for their anti-biofilm properties, such as skyllamycins (Navarro et al. 2014). Laser scanning confocal microscopy has revealed that aloe-emodin treatment inhibits extracellular protein production in *S. aureus*, and the Congo red assay showed that it also reduces the accumulation of polysaccharide intercellular adhesin on the cell surface (Xiang et al. 2017). Many