18.2 Anti-Virulence Strategy

The development of agents that are not bactericidal but indirectly inhibit the molecular pathway responsible for bacterial communication is a viable strategy to address the problem of antibiotic resistance (Williams 2014; Brannon and Hadjifrangiskou 2016; Dickey et al. 2017). Compounds of this type are perceived to exert reduced evolutionary selective pressure and lower rates of resistance development (Rampioni et al. 2014). One such example involves the blocking of bacterial quorum sensing (QS). QS is characterized by bacterial production release and group-wide detection of autoinducer molecules as a mode of bacterial communication with their neighbors (Asfahl and Schuster 2017). This network of communication is triggered by environmental factors within the microbial community, such as differences in bacterial density or the presence of environmental challenges (Lee and Zhang 2015; Grandclement et al. 2016). Once these signaling molecules are detected, cascades of physiological and metabolic changes occur by orchestrated alterations in bacterial gene expression, resulting to the secretion of biomolecules needed for biofilm formation and virulence (Papenfort and Bassler 2016). Therefore, hindering QS may result in the pathogen not being able to cause harm to the host. Several agents that block QS are in preclinical development. For example, the synthetic agent meta-bromo-thiolactone (mBTL) has been reported to curb the production of the virulence factor pyocyanin and biofilm formation in *P. aeruginosa* by affecting the regulation of Las and Rhl quorum-sensing systems (O'Loughlin et al. 2013). Moreover, *in vitro* protection of human lung epithelial cells and *in vivo* protection of *Caenorhabditis elegans* by mBTL against *P. aeruginosa* have been described (O'Loughlin et al. 2013). A follow-up report detailed the optimization of mBTL for enhanced stability as the thiolactone ring is susceptible to chemical and enzymatic hydrolysis (Miller et al. 2015). Other anti-quorum-sensing agents at the preclinical stage have also been reported (Oh et al. 2010; Alasil et al. 2015; Lidor et al. 2015; Simonetti et al. 2016). Nevertheless, this strategy remains controversial (Kalia et al. 2014; Scutera et al. 2014) especially in the light that certain clinical isolates are resistant to established anti-quorum-sensing agents (Garcia-Contreras et al. 2013).

18.3 Antibiotic Combination Strategy

Combination therapy, the concomitant use of two or more antibacterial agents, has been around for more than three decades (Hilf et al. 1989). Clinicians often prescribe two or more antibiotics concomitantly, during empirical treatment to ensure coverage of all possible bacterial pathogens and resistance profiles. Moreover, the use of multiple antibiotic agents in a therapeutic cocktail may