tetracycline, or β-lactams with other antibiotics that preferentially kill biofilm cells with low metabolic activity, such as colistin, provides a rational option to establishment combination therapy (Pamp et al. 2008; Ciofu et al. 2017).

In this perspective, studies have demonstrated efficient combinations for the treatment of infections caused by pathogenic biofilms. For example, at *in vitro* assays using pharmacokinetic/pharmacodynamic models of mature (susceptible and methicillin-resistant) *S. aureus* biofilms, Ruiz and co-workers (2010) demonstrated that the combination of the antibiotics daptomycin or moxifloxacin with clarithromycin was significantly effective against mature biofilms, whereas in isolation, those same antibiotics tested in high concentrations were not able to demonstrate a bactericidal activity against staphylococcal biofilms (Parra-Ruiz et al. 2010). Similarly, from an *in vitro* pharmacokinetic/pharmacodynamic model, the combination of linezolid antibiotics with daptomycin was superior to each agent alone, suggesting another therapeutic option for staphylococcal biofilms (Parra-Ruiz et al. 2012). In another study, the *in vitro* anti-biofilm activity of the antibiotics clarithromycin, cefazolin, and vancomycin isolated and combined against *S. aureus* biofilms formed on titanium devices was evaluated (Fujimura et al. 2008). As a result, individual antibiotics were not able to eradicate *S. aureus* biofilm; in contrast, the combination of clarithromycin with cefazolin or vancomycin was clearly efficient (Fujimura et al. 2008). Therefore, combined therapy seems to be the most efficient way to achieve the pathogenic biofilm eradication (Jacqueline and Caillon 2014).

Regarding other biofilm configurations, it has been found that antibiotic combinations may represent an ideal anti-biofilm strategy for use in patients with cystic fibrosis (Heijerman et al. 2009). In this sense, the combination of the antibiotics tobramycin and colistin proved to be more efficient than the respective antibiotics individually tested to *in vitro* kill *P. aeruginosa* biofilm cells. Moreover, the combination significantly reduced the cell counts of *P. aeruginosa* in a lung infection model in rats and in patients with cystic fibrosis (Herrmann et al. 2010). Likewise, the unique combination of broad-spectrum antibiotics fosfomycin and tobramycin in inhalation has been shown to be effective against *P. aeruginosa*, demonstrating that it is also a therapeutic potential for patients with cystic fibrosis (Trapnell et al. 2012).

Furthermore, based on the concept of combining antibiotics targeting different metabolic states of the biofilm cell subpopulations, the combination of ciprofloxacin with colistin produced promising results for *in vitro* biofilm eradication of *P. aeruginosa*, since biofilm cells exhibiting low metabolic activity were killed by colistin and ciprofloxacin was able to specifically kill the subpopulation of metabolically active biofilm cells (Pamp et al. 2008).

Different studies suggest that concurrent combination therapy may be more effective than antibiotic monotherapy to combat pathogenic biofilms.