2002; Petersen et al. 2002), *Legionella pneumophila* (Edelstein et al. 2003), *Stenotrophomonas maltophilia* (Betriu et al. 2002), and a number of other clinical isolates including multidrug-resistant ones (Abbanat et al. 2003; Milatovic et al. 2003; Fritsche et al. 2004; Bouchillon et al. 2005; Sader et al. 2005; Borbone et al. 2008; Nørskov-Lauritsen et al. 2009; Dowzicky and Chmelařová 2011; Balode et al. 2013; Morfin-Otero et al. 2015; Marco and Dowzicky 2016; Tärnberg et al. 2016; Stefani and Dowzicky 2016; Giammanco et al. 2017). The antibiotic displayed outstanding therapeutic response in animal infection models as well as in clinical trials aimed at treating intra-abdominal and skin and soft tissue infections (Hawkey and Finch 2007).

23.9 Resistance to Third-Generation Tetracyclines

While clinical efficiency of tigecycline remains satisfactory including infections resistant to the first- and second-generation tetracyclines (Bertrand and Dowzicky 2012; Hawser et al. 2012; Mayne and Dowzicky 2012; Giammanco et al. 2017), our efforts should be directed toward preserving its efficiency and lifespan by elaborating strategies to prevent the emergence of the corresponding resistance. The presently known mechanisms of resistance in clinical isolates are mainly associated with a nonspecific efflux of the drug from the cell such as mediated via resistance-nodulation-division (RND) family of efflux pumps. In *Pseudomonas aeruginosa*, for example, the removal of tigecycline from the cell is driven by the RND family of efflux pumps, in particular the MexXY-OprM complex (Dean et al. 2003). In the absence of MexXY-OprM, however, two other efflux pumps, MexAB-OprM and MexCD-OprJ, are involved in the drug efflux. In *Proteus mirabilis*, the efflux of tigecycline is mediated by another representative of the RND family of efflux pumps, encoded by the *acrAB* homologue of *Escherichia coli*, the AcrAB-TolC system (Visalli et al. 2003; Ruzin et al. 2005). Reduced susceptibility of clinical isolates of *A. baumannii* toward tigecycline is also due to the elevated expression of the RND family of efflux pumps such as AdeABC and AdeIJK (Peleg et al. 2007; Damier-Piolle et al. 2008). Overexpression of another RND pump, AdeFGH, in *A. baumannii* confers resistance to multiple drugs, including tigecycline (Coyne et al. 2010). Reduced tigecycline susceptibility in clinical isolates of *Enterobacter cloacae* and *E. coli* is also due to the elevated expression of another efflux pump in the RND family, AcrAB (Keeney et al. 2007, 2008). In clinical *Klebsiella pneumoniae* strains, mutations in the regulatory *ramR* gene may also lead to the overexpression of RamA, which is a positive regulator of the AcrAB efflux system, thus resulting in the concomitant resistance to multiple antibiotics, including tigecycline (Hentschke et al. 2010). The similar mechanisms of tigecycline resistance may emerge because of therapy by other antibiotics. Ciprofloxacin therapy of *E. cloacae* infection, for example, may