2.6 *Stenotrophomonas maltophilia* and Its Uncommon Mechanisms of Resistance to Quinolones

As above stated, the selection of mutations in genes encoding the bacterial topoisomerases still remains as the main mechanism of resistance to quinolones. Nevertheless the Gram-negative opportunistic pathogen *S. maltophilia* is an exception to such rule. Studies with *in vitro* obtained quinolone-resistant mutants as well as with clinical isolates have shown that quinolone resistance is not associated with mutations in bacterial topoisomerases (Garcia-Leon et al. 2014a; Ribera et al. 2002; Valdezate et al. 2002). Some recent works have described the presence of amino acid changes in the topoisomerases of clinical *S. maltophilia* isolates, but the observed changes are outside the QRDRs and seem to be likely allelic forms of these genes more than mutations involved in quinolone resistance (Cha et al. 2016; Jia et al. 2015).

The analysis of quinolone-resistant mutants and clinical isolates of *S. maltophilia* has shown that the MDR efflux pump SmeDEF is a major contributor to the intrinsic resistance to quinolones of this microorganism when expressed at its basal wild-type level (Zhang et al. 2001). Overexpression of this efflux pump increase MIC levels of quinolones above the breakpoints defining resistance in this microorganism (Alonso and Martinez 2000; Sanchez et al. 2002; Sanchez and Moreno 2005), and mutants overexpressing SmeDEF are frequently found among clinical *S. maltophilia* isolates (Alonso and Martinez 2001; Cho et al. 2012; Gould and Avison 2006; Liaw et al. 2010; Sanchez et al. 2004). While overexpression of this efflux pump produces a fitness cost (Alonso et al. 2004), it might be possible that this cost might be lower than those associated with mutations in genes encoding the bacterial topoisomerases. This differential fitness might be the reason for the lack of topoisomerase mutants among the quinolone-resistant mutants of this bacterial species. Notably, even when the SmeDEF efflux pump is removed, mutations in topoisomerases are not selected in presence of quinolones. The main mechanism of resistance in this case becomes to be the overexpression of another efflux pump, SmeVWX (Garcia-Leon et al. 2014a). Overexpression of this efflux pump has been reported for clinical *S. maltophilia* isolates, indicating that these types of mutants are selected *in vivo* (Garcia-Leon 2015).

In addition to efflux pumps capable of efficiently extruding quinolones, *S. maltophilia* presents in its genome (Sanchez et al. 2008; Shimizu et al. 2008) a *qnr* determinant (Sm*qnr*) that contributes to intrinsic resistance to these antimicrobials (García-León et al. 2012; Sanchez and Martinez 2010; Sanchez and Martinez 2015b). Nevertheless, Sm*qnr* mutants have not been described neither upon *in vitro* selection by quinolones nor in clinical isolates, which cast doubts on the role of this determinant in acquired resistance to quinolones of *S. maltophilia*. More recently, a novel mechanism of resistance based on the increased expression of the heat shock response upon the inactivation of