MYCOBACTERIUM ULCERANS

M. ulcerans is susceptible *in vitro* to rifampicin (Portaels *et al.*, 1998; Ji *et al.*, 2006). Combination therapy with rifampicin plus aminoglycosides amikacin (Dega *et al.*, 2000; Dega *et al.*, 2002; Marsollier *et al.*, 2003a; Lefrançois *et al.*, 2007) or streptomycin (Lefrancois *et al.*, 2007), and rifampicin plus oral agents clarithromycin, linezolid, or moxifloxacin (Ji *et al.*, 2006; Ji *et al.*, 2007; Ji *et al.*, 2008), is bactericidal and able to cure established *M. ulcerans* infection in mice. The combination of rifampicin and sitafloxacin exhibited *in vitro* synergy against *M. ulcerans* (Dhople and Namba, 2002). The combination of rifampicin and clofazamine demonstrated superior sterilizing activity compared to rifampicin and clarithromycin in a mouse model (Converse *et al.*, 2015).

OTHER NON-TUBERCULOUS MYCOBACTERIA

Rifampicin is active against many nontuberculous mycobacteria, and CLSI recommends 1 μg/ml as a critical concentration for rifampicin for nontuberculous mycobacteria (CLSI, 2011). Other mycobacterial species usually susceptible *in vitro* and/or in animal models to rifampicin include *M. asiaticum* (Blacklock *et al.*, 1983), *M. bohemicum* (van Ingen *et al.*, 2010), *M. genavense* (Böttger, 1994), *M. gordonae* (Rodríguez *et al.*, 2004), *M. marinum* (Aubry *et al.*, 2000), *M. szulgai* (Tortoli *et al.*, 1998) and *M. xenopi* (Tortoli and Simonetti, 1995). *M. haemophilum* isolates were almost all susceptible in previous reports (Bernard *et al.* 1993; Lindeboom *et al.*. 2011), but van Ingen *et al.* (2010) reported 96% of isolates were resistant.

Mycobacterial species usually resistant *in vitro* to rifampicin include *M. celatum* (Piersimoni *et al.*, 2003), *M. conspicuum* (Springer *et al.*, 1995), *M. lentiflavum* (Safdar and Han, 2005), *M. mucogenicum*, *M. shimoidei* (Mayall *et al.*, 1999), and *M. smegmatis* (Wallace *et al.*, 1988), *M. simiae* (Al-Abdely *et al.*, 2000), and *M. terrae* (Smith *et al.*, 2000). Rapidly growing mycobacteria *M. fortuitum* and *M. chelonae-abscessus* complex are naturally resistant to the rifamycins, including rifampicin (Woodley *et al.*, 1972; Thornsberry *et al.*, 1983; Heifets, 1988). *M. malmoense* isolates were almost all resistant in previous reports (Hoffner *et al.*, 1993), but van Ingen *et al.* (2010) reported only 32% of isolates were resistant.

For *in vitro* drug susceptibilities of clinical non-tuberculous mycobacterial isolates (n = 2275, 49 species) see van Ingen *et al.* (2010), and also Tortoli (2014) for newly described *Mycobacterium* species.

GRAM-POSITIVE COCCI

Rifampicin is highly active against *Stapylococcus aureus* and coagulase-negative staphylococci, such as *S. epidermidis*, *S. saprophyticus*, *S. haemolyticus*, *S. hominis*, *S. lugdunensis*, *S. schleiferi*, and *S. warneri* (Turnidge *et al.*, 1996; Speller *et al.*, 1997; Morgan *et al.*, 1999; Andrews *et al.*, 2000; Diekema *et al.*, 2001; Samra *et al.*, 2001; Hoban *et al.*, 2003; Nimmo *et al.*, 2003; Hanberger *et al.*, 2004; Zinn *et al.*, 2004; Udo *et al.*, 2006; Cuevas *et al.*, 2007; Health Protection Agency, 2007). Both methicillin-susceptible and methicillin-resistant strains of these bacteria, including isolates of community-associated methicillin-resistant *S. aureus* (MRSA) (Gosbell *et al.*, 2001; Yamamoto *et al.*, 2006; Gubbay *et al.*, 2008), are usually rifampicin-sensitive. Although rifampicin resistance is described, largely among methicillin-resistant staphylococci (see section 2b, Emerging resistance and cross-resistance), rifampicin has retained its high level of anti-staphylococcal activity in studies reported between 2008 and 2015, with rates of resistance of 5% or less from both hospital and community settings and from a range of regions and countries (Ho *et al.*, 2008; Wackett *et al.*, 2012; Coombs *et al.*, 2013; Kali *et al.*, 2013; Hanaki *et al.*, 2014; Cuny *et al.*, 2015; Decousser *et al.*, 2015; Souli *et al.*, 2016). Resistant mutants readily emerge *in vitro* and *in vivo* in the presence of rifampicin as a single drug, so rifampicin is always combined with other antibiotics such as fusidic acid (see Chapter 80, Fusidate sodium), ciprofloxacin (see Chapter 101, Ciprofloxacin), antistaphylococcal penicillins (see Chapter 7, Isoxazolyl penicillins: oxacillin, cloxacillin, dicloxacillin, and flucloxacillin, and Chapter 8, Nafcillin), or vancomycin (see Chapter 43, Vancomycin) to treat established staphylococcal infections. Numerous *in vitro* and animal studies have investigated the activity of rifampicin in combination with other antistaphylococcal agents, particularly newer ones. Although they differ greatly in technical and other aspects and their findings are not entirely consistent (even those of the same agent), most studies indicate a synergistic or additive effect when rifampicin is added to one of these agents. Agents that have been studied in combination with rifampicin are quinupristin–dalfopristin (Sambatakou *et al.*, 1998; Hamel *et al.*, 2008; see Chapter 77, Quinupristin–dalfopristin), linezolid (Dailey *et al.*, 2003; Jacqueline *et al.*, 2003; Murillo *et al.*, 2008; Baldoni *et al.*, 2009; Tang *et al.*, 2012; Tang *et al.*, 2013; see Chapter 73, Linezolid), daptomycin (Baltch *et al.*, 2007; John *et al.*, 2009; LaPlante and Woodmansee, 2009; Cirioni *et al.*, 2010; Garrigos *et al.*, 2010; Lefebvre *et al.*, 2010; Saleh-Mghir *et al.*, 2011; Rose *et al.*, 2013; Mihailescu *et al.*, 2014; Hall Snyder *et al.*, 2015; see Chapter 45, Daptomycin), tigecycline (Garrigos *et al.*, 2011; Tang *et al.*, 2013; see Chapter 70, Tigecycline), fosfomycin (see Chapter 79, Fosfomycin) (Tang *et al.*, 2013; Mihailescu *et al.*, 2014), dalbavancin (Baldoni *et al.*, 2013; see Chapter 47, Dalbavancin), minocycline (Tang *et al.*, 2012; Wu *et al.*, 2013; see Chapter 69, Minocycline) and ceftaroline (Barber *et al.*, 2015; see Chapter 32, Ceftaroline and ceftaroline–avibactam). Synergy has also been demonstrated between rifampicin and New Zealand Manuka honey, which is applied topically to wounds and has antistaphylococcal activity (Muller *et al.*, 2013).

S. pneumoniae is rifampicin sensitive, including penicillin nonsusceptible and resistant strains; rates of resistance have been less than 1% in four successive nationwide surveys in the USA by Doern and co-workers (Doern *et al.*, 1996; Doern *et al.*, 1999; Doern *et al.*, 2001; Doern *et al.*, 2005) and Thornsberry *et al.* (1999) and in studies from the UK (Johnson *et al.*, 1996), China (Wang *et al.*, 1998), Europe (Fluit *et al.*, 1999), Australia (Gosbell and Neville, 2000; Gosbell *et al.*, 2006), South Africa (Huebner *et al.*, 2000), Italy (Marchese *et*