shown to enhance activity of daptomycin against methicillin-resistant *S. aureus* (MRSA) (see Chapters 8, Nafcillin; Chapter 32, Ceftaroline and ceftaroline–avibactam; and Chapter 45, Daptomycin). Case series have described clearance of refractory MRSA when these agents were added to daptomycin (Dhand *et al*., 2011; Sakoulas *et al*., 2014). The mechanism is likely the same as with ticarcillin–clavulanate.

Anaerobic Gram-positive bacteria, such as anaerobic streptococci, *Peptococcus, Peptostreptococcus, Clostridium, Lactobacillus, Actinomyces*, and *Propionibacteria*, are usually susceptible to ticarcillin–clavulanate (Denys *et al*., 1983; Smith *et al*., 1996b), and this agent is a useful therapeutic choice for mixed infections when coverage of these organisms and Gram-negative organisms is required.

GRAM-NEGATIVE ORGANISMS

Ticarcillin–clavulanate has efficacy across a broad range of Gram-negative bacteria. The addition of clavulanic acid was reported to reduce the minimal inhibitory concentration (MIC) for ticarcillin by more than eight times for 92% of Enterobacteriaceae tested in large studies during the 1980s (Barry *et al*., 1984; Fuchs *et al*., 1984). In a survey of isolates in the USA between 1998 and 2001, ticarcillin–clavulanate retained activity against 74–83% of Enterobacteriaceae, 70–80% of *Acinetobacter baumannii* strains, and 70–80% of *Pseudomonas aeruginosa* strains (Karlowsky *et al*., 2003a; Karlowsky *et al*., 2003b).

It is the type of beta-lactamase and the amount present that largely determine susceptibility to ticarcillin–clavulanate for Gram-negative bacilli. Class A (e.g. TEM, SHV) and to a slightly lesser extent class D beta-lactamases are generally inhibited by clavulanate, whereas class B (e.g. the metallo-beta-lactamase s) and class C (e.g. AmpC) are not (Thomson *et al*., 1990). The class A beta-lactamases are common in Enterobacteriaceae and the addition of clavulanic acid is therefore useful for many of these commonly encountered Gram-negative organisms (Jacobs *et al*., 1986a; Jacobs *et al*., 1986b; Kempers and MacLaren, 1990).

Gram-negative bacteria with plasmid-mediated class A beta-lactamases (such as TEM), which include strains of *Haemophilus influenzae, Neisseria gonorrhoeae, Moraxella catarrhalis*, and *Escherichia coli,* are usually susceptible to ticarcillin–clavulanate. Bacteria with chromosomally mediated class A beta-lactamases such as *Klebsiella pneumoniae, Proteus mirabilis*, and *Bacteroides fragilis* are also usually susceptible to ticarcillin–clavulanate. The inducible chromosomally mediated beta-lactamases that confer resistance to third-generation cephalosporins (e.g. AmpC) found in *Morganella morganii, Providencia rettgeri, Serratia marcescens*, and *Enterobacter cloacae* are generally resistant to ticarcillin–clavulanate (Pulverer *et al*., 1986; Verbist and Verhaegen, 1986).

Clavulanic acid cannot always be relied on to overcome ticarcillin resistance, if present, in *Pseudomonas* spp., as the usual mechanism of resistance in *Pseudomonas* is via altered permeability rather than production of beta-lactamases. In some cases, however, ticarcillin resistance in *Pseudomonas* is mediated by a beta-lactamase that can be overcome using ticarcillin–clavulanate (Philippon *et al*., 1997). As a general rule, piperacillin is more active than ticarcillin against *Pseudomonas* species (Clarke and Zemcov, 1984; Greenberg *et al*., 1986; Smith and Henry, 1988).

Ticarcillin–clavulanate has activity *in vitro* against *Burkholderia pseudomallei*, but *in vitro* data must be interpreted with caution with this pathogen. It may be useful as a second-line agent (Sookpranee *et al*., 1991). Most *Burkholderia cepacia* is resistant to ticarcillin-clavulanate. Modeling studies have suggested possible high-dose regimens that may be effective for patients with cystic fibrosis and colonization with this pathogen , but clinical data are lacking (Lupo *et al.,* 2015; Zobell *et al.,* 2014; Zobell *et al.*, 2011).

Ticarcillin–clavulanate has some activity against *Stenotrophomonas maltophilia*, In most cases, however, the MIC is still too high to consider this drug effective enough alone. It has, however, been used in combination with other agents. Checkerboard testing studies have suggested additive or synergistic effects when ticarcillin–clavulanate is combined with either trimethoprim–sulfamethoxazole or ciprofloxacin, but the clinical relevance of these *in vitro* results for this pathogen is uncertain (Poulos *et al*., 1995; San Gabriel *et al*., 2004). More recent work has also suggested possible *in vitro* synergy of ticarcillin-clavulanate with aztreonam, colistin and levofloxacin for *Stenotrophomonas* (Milne and Gould, 2012; Chung *et al.,* 2013; Church *et al.,* 2013). In the USA, ticarcillin–clavulanate has been described as the second most active agent behind co-trimoxazole for this pathogen (Sattler *et al*., 2000). It has the advantage over some therapeutic alternatives for this pathogen of being bactericidal (Watanakunakorn, 1984; Vartivarian *et al*., 1994). In Spain, 50% of *Stenotrophomonas* isolates were reported to be susceptible to ticarcillin–clavulanate in one study (Valdezate *et al*., 2001), In the USA, 45% were reported to be susceptible (Tsiodras *et al*., 2000), while a more recent study suggested 49.2% (Garazi *et al.,* 2012). Susceptibility rates of 85% have been reported in Canada (Naidu and Smith, 2012). Two separate studies published in 2004 reported susceptibility rates to ticarcillin–clavulanate of 94.8% and 59.1% in Brazil (Nicodemo *et al*., 2004; Travassos *et al*., 2004). High rates of resistance to ticarcillin–clavulanate has been reported from China, where 36% were reportedly susceptible (Hu *et al.,* 2014), and Korea, where 40% of *Stenotrophomonas* isolates were susceptible (Cho *et al.,* 2015). The regional variations in susceptibility have been summarized (Chang *et al.,* 2015). In general, increasing rates of resistance to ticarcillin–clavulanate among *Stenotrophomonas* isolates have been reported over time (Barbier-Frebour *et al*., 2000).

Ticarcillin–clavulanic acid has high efficacy against Gram-negative anaerobes such as *Bacteroides, Prevotella*, and *Fusobacterium* (Roy *et al*., 1977; Bansal and Thadepalli, 1983; Barry *et al*., 1986; Appelbaum *et al*., 1990; Bourgault *et al*., 1992; Chen *et al*., 1992; Appelbaum, 1993; Johnson, 1993; Citron *et al*., 1995; Dubreuil *et al*., 2003; Brook, 2007;