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β-Lactams and β-Lactamase Inhibitors: An Overview

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β-Lactams are the most widely used class of antibiotics. Since the discovery of benzylpenicillin in the 1920s, thousands of new penicillin derivatives and related β-lactam classes of cephalosporins, cephamycins, monobactams, and carbapenems have been discovered. Each new class of β-lactam has been developed either to increase the spectrum of activity to include additional bacterial species or to address specific resistance mechanisms that have arisen in the targeted bacterial population. Resistance to β-lactams is primarily because of bacterially produced β-lactamase enzymes that hydrolyze the β-lactam ring, thereby inactivating the drug. The newest effort to circumvent resistance is the development of novel broad-spectrum β-lactamase inhibitors that work against many problematic β-lactamases, including cephalosporinases and serine-based carbapenemases, which severely limit therapeutic options. This work provides a comprehensive overview of β-lactam antibiotics that are currently in use, as well as a look ahead to several new compounds that are in the development pipeline.

When Alexander Fleming was searching for an antistaphylococcal bacteriophage in his laboratory in the 1920s, he deliberately left plates out on the bench to capture airborne agents that might also serve to kill staphylococci (Fleming 1929). His success was greater than he must have hoped for. His initial publication on benzylpenicillin described a substance that was unstable in aqueous solution but that might serve as an antiseptic or as a selective agent for isolation of Gram-negative bacteria that were present in mixed cultures of staphylococci and streptococci. As the potential utility of penicillin G as a parenteral therapeutic agent became more obvious, Fleming, Abraham, Florey, and a consortium of scientists from England and the United States were able to optimize the isolation and identification of benzylpenicillin to assist in the treatment of Allied soldiers in World War II (Macfarlane 1979). These activities set the stage for the launch of the most successful class of antibiotics in history.

β-Lactam antibiotics are currently the most used class of antibacterial agents in the infectious disease armamentarium. As shown in Figure 1, β-lactams account for 65% of all prescriptions for injectable antibiotics in the United States. Of the β-lactams, cephalosporins comprise nearly half of the prescriptions (Table 1). The β-lactams are well tolerated, efficacious,

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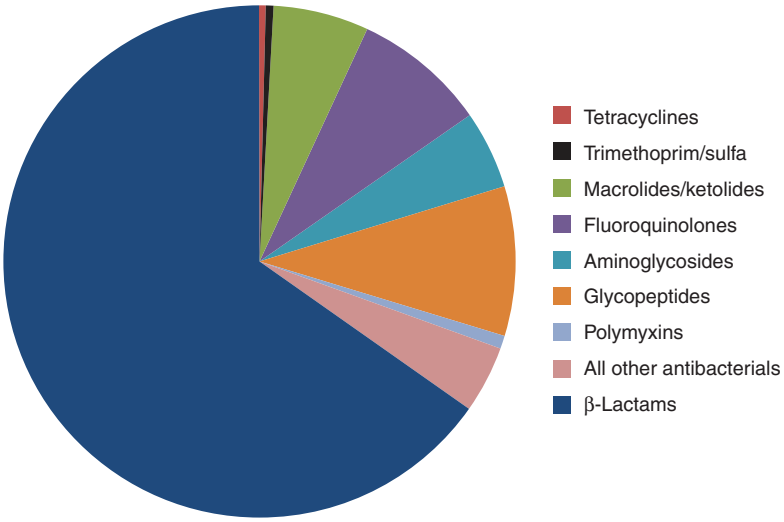

Figure 1. Proportion of prescriptions in the United States for injectable antibiotics by class for years 2004–2014. The percentage of standard units for each injectable antibiotic prescribed in the United States from 2004 to 2014 is shown as follows: β-lactams, 65.24%; glycopeptides, 9%; fluoroquinolones, 8%; macrolides/ketolides, 6%; aminoglycosides, 5%; polymyxins, 1%; trimethoprim/sulfamethoxazole, 0.5%; tetracyclines (excluding tigecycline), 0.4%; all other antibiotics (including daptomycin, linezolid, and tigecycline), 4.21%. (Data from the IMS MDART Quarterly Database on file at AstraZeneca.)

and widely prescribed. Their major toxicity is related to an allergic response in a small percentage of patients who react to related side chain determinants; notably, these reactions are most common with penicillins and cephalosporins with minimal reactivity caused by monobactams (Saxon et al. 1984; Moss et al. 1991). The bactericidal mechanism of killing by β-lactams is perceived to be a major advantage in the treatment of serious infections. When these agents were threatened by the rapid emergence of β-lactamases, β-lactamase-stable agents were developed, as well as potent β-lactamase inhibitors (BLIs). In this introductory description of the β-lactams, the most commonly available β-lactams and BLIs will be presented, with a brief summary of their general characteristics. Occasional agents have been included for their historical or scientific importance. Note that resistance mechanisms will be discussed in detail in other articles in this collection.

Table 1. Usage of parenteral β-lactams by class from 2004–2104 in the United States

Class of β-lactam	Percentage of prescriptions[a]
Narrow spectrum penicillins	3.12
Broad spectrum penicillins[b]	36.54
Cephalosporins	47.49
Monobactams	1.66
Carbapenems	11.20

[a]The percentage for each injectable antibiotic class prescribed in the United States from 2004 to 2014. (Data from the IMS MDART Quarterly Database on file at AstraZeneca.)

[b]Broad-spectrum penicillins include the β-lactam/β-lactam-inhibitor combinations piperacillin-tazobactam, ticarcillin-clavulanate, and ampicillin-sulbactam.

MECHANISM OF ACTION

β-Lactam antibiotics are bactericidal agents that interrupt bacterial cell-wall formation as a result of covalent binding to essential penicillin-binding proteins (PBPs), enzymes that are involved in the terminal steps of peptidoglycan cross-linking in both Gram-negative and Gram-positive bacteria. Every bacterial species has its own distinctive set of PBPs that can range from

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three to eight enzymes per species (Georgopapadakou and Liu 1980). The inhibition of bacterial peptidoglycan transpeptidation by penicillin was described mechanistically in a classical paper by Tipper and Strominger (1965), who noted a structural similarity of penicillin G to the terminal D-Ala-D-Ala dipeptide of the nascent peptidoglycan in the dividing bacterial cell. This mechanism is now known to involve binding of penicillin, or another β-lactam, to an active site serine found in all functional PBPs (Georgopapadakou et al. 1977). The resulting inactive acyl enzyme may then slowly hydrolyze the antibiotic to form a microbiologically inactive entity (Frère and Joris 1985). In addition to these functionalities, recent work has shown the binding of selected β-lactams, such as ceftaroline, to an allosteric site in PBP2a from *Staphylococcus aureus*, resulting in an increased sensitization of the organism to the antibiotic (Otero et al. 2013; Gonzales et al. 2015).

PBPs may be divided into classes according to molecular mass (Goffin and Ghuysen 1998; Massova and Mobashery 1998), with low-molecular-mass PBPs serving mainly as monofunctional D-Ala-D-Ala carboxypeptidases. High-molecular-mass PBPs have been divided into two subclasses, one of which (class A) includes bifunctional enzymes with both a transpeptidase and a transglycosylase domain, and the second of which (class B) encompasses D-Ala-D-Ala-dependent transpeptidases. At least one PBP is deemed to be essential in each species, with a unique specificity for β-lactam binding that varies among each species and each β-lactam class (Curtis et al. 1979; Georgopapadakou and Liu 1980). In Gram-negative bacteria, essential PBPs include the high-molecular-weight PBPs 1a and 1b that are involved in cell lysis, PBP2, the inhibition of which results in a cessation of cell division and the formation of spherical cells, and PBP3 for which inhibition arrests cell division, resulting in filamentation. Cell death may occur as a result of inhibiting one or more of these PBPs (Spratt 1977, 1983). The roles of PBPs in Gram-positive bacteria and *Mycobacterium tuberculosis* are discussed in detail in Fisher and Mobashery (2016).

PENICILLINS

Penicillin G (benzylpenicillin) was the first β-lactam to be used clinically, most frequently to treat streptococcal infections for which it had high potency (Rammelkamp and Keefer 1943; Hirsh and Dowling 1946). Another naturally occurring penicillin, penicillin V (phenoxymethylpenicillin), in an oral formulation is still used therapeutically and prophylactically for mild to moderate infections caused by susceptible *Streptococcus* spp., including use in pediatric patients (Pottegard et al. 2015). However, the selection of penicillin-resistant penicillinase-producing staphylococci in patients treated with penicillin G led to decreased use of this agent, and prompted the search for more penicillins with greater stability to the staphylococcal β-lactamases (Kirby 1944, 1945; Medeiros 1984). A list of historically important and clinically useful penicillins is provided in Table 2. Among the penicillinase-stable penicillins of clinical significance are methicillin, oxacillin, cloxacillin, and nafcillin, with the latter suggested as the β-lactam of choice for skin infections, catheter infections, and bacteremia caused by methicillin-susceptible *S. aureus* (Bamberger and Boyd 2005). All were used primarily for staphylococcal infections until the emergence of methicillin-resistant *S. aureus* (MRSA) in 1979–1980 (Hemmer et al. 1979; Saroglou et al. 1980).

Penicillins with improved activity against Gram-negative pathogens included the orally bioavailable ampicillin and amoxicillin, both of which were introduced in the 1970s. These agents were initially used for the treatment of infections caused by Enterobacteriaceae and did not effectively inhibit the growth of *Pseudomonas aeruginosa*, which became more of a concern during the late 1970s. Carbenicillin was the first antipseudomonal penicillin to be introduced, but lacked stability to β-lactamase hydrolysis and was less potent than piperacillin or ticarcillin, later antipseudomonal penicillins. These latter drugs were considered to be potent broad-spectrum penicillins that included penicillin-susceptible staphylococci, enteric bacteria, anaerobes, and *P. aeruginosa* in their

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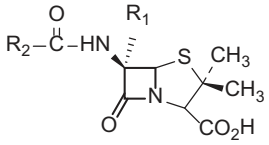
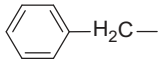
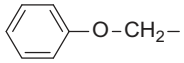
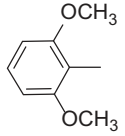
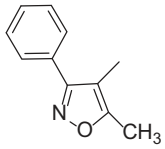
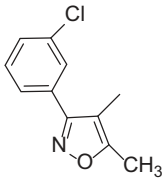
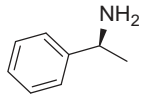
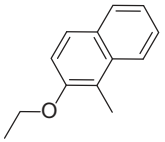
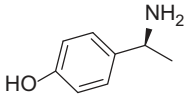
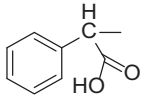
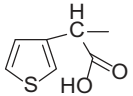
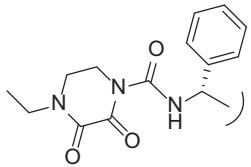
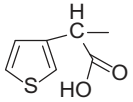
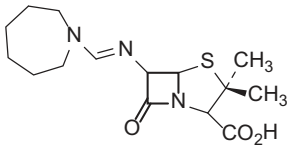
Table 2. Penicillins of current and historical utility



Name	R_1	R_2	Route of administration	Approval date[b,c]	Status
Benzylpenicillin (penicillin G)	—H		IM or IV	1946	Approved worldwide
Phenoxymethylpenicillin (penicillin V)	—H		Oral	1968	Approved worldwide
Methicillin	—H		IV	1960	No longer available; of historical interest
Oxacillin	—H		Oral, IV	1962	Widely available, but not in the United Kingdom
Cloxacillin	—H		Oral, IV	1974	Widely available, but not in the United Kingdom
Ampicillin	—H		Oral, IV	1963	Widely available

Continued

Table 2. *Continued*

Name	R_1	R_2	Route of administration	Approval date[b,c]	Status
Nafcillin	—H		IV	1970	Limited availability
Amoxicillin	—H		Oral, IV	1972	Widely available
Carbenicillin	—H		Oral	1972	Discontinued
Ticarcillin	—H		IV	1976	Limited availability
Piperacillin	—H		IV	1981	Widely available, primarily in combination with tazobactam
Temocillin	—OCH_3		IV	1985 in Europe (Harvengt 1985)	Limited availability (Europe)
Mecillinam			IV	1978	Limited availability

IM, Intramuscular; IV, intravenous.
[a]FDA approval unless otherwise noted.
[b]Dates were updated from Medeiros (1997) (www.accessdata.fda.gov/scripts/cder/drugsatfda; www.drugs.com).

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spectrum of activity. They were used extensively to treat serious nosocomial infections, especially when combined with a β-lactamase inhibitor (see below).

Two parenteral penicillins with unusual chemical structures, mecillinam and temocillin (Table 2), were introduced to treat infections caused by enteric bacteria before the global emergence of extended-spectrum β-lactamases (ESBLs) in the late 1980s. Mecillinam (also known as amdinocillin), with a 6-β-amidino side chain, is a narrow-spectrum β-lactam that binds exclusively to PBP2 in enteric bacteria (Curtis et al. 1979). Because of this specificity, it shows synergy in vitro in combination with other β-lactams that bind to PBPs 1a/1b and/or PBP3 in Gram-negative bacteria (Hanberger et al. 1991), thus decreasing the possibility that a point mutation in a single PBP would lead to resistance (Hickman et al. 2014). Temocillin, the 6-α-methoxypenicillin analog of ticarcillin, had greater stability than ticarcillin to hydrolysis by serine β-lactamases, but lost antibacterial activity against Gram-positive bacteria, anaerobic Gram-negative pathogens, and some enteric bacteria that included the important pathogens *Enterobacter* spp. and *Serratia marcescens* (Martinez-Beltran et al. 1985). Mecillinam and temocillin are currently enjoying a resurgence in interest owing to their stability to many ESBLs (Livermore et al. 2006; Rodriguez-Villalobos et al. 2006), often resulting in greater than 90% susceptibility when tested against many contemporary ESBL-producing Enterobacteriaceae (Giske 2015; Zykov et al. 2016).

Because increasing numbers of β-lactamases have compromised the use of penicillins as single agents (Bush 2013), there is currently limited therapeutic use of the penicillins as monotherapy. Ampicillin, amoxicillin, piperacillin, and ticarcillin have continued to be useful, primarily as a result of their combination with an appropriate β-lactamase inhibitor (see below). However, even ampicillin, amoxicillin, penicillin G, and penicillin V are still active as monotherapy against Group A streptococci, and *Treponema pallidum*, two of the few bacterial species that do not produce β-lactamases (Schaar et al. 2014).

CEPHALOSPORINS

During the 1950s, the discovery of the naturally occurring penicillinase-stable cephalosporin C opened a new pathway to the development of hundreds of novel cephalosporins (Newton and Abraham 1956; Abraham 1987) to treat infections caused by the major penicillinase-producing pathogen of medical interest at that time, *S. aureus*. Dozens of cephalosporins were introduced into clinical practice (Abraham 1987), either as parenteral or oral agents. The molecules exhibited antibacterial activity with MICs often $\leq$4 μg/mL against not only staphylococci, but also *Streptococcus pneumoniae* and non-β-lactamase-producing enteric bacteria. The parenteral agents were generally eightfold more potent than the oral agents that were used in some cases to replace oral penicillins in penicillin-allergic patients. The early cephalosporins, for example, those in the cephalosporin I subclass (Bryskier et al. 1994) introduced before 1980, were labile to hydrolysis by many β-lactamases that emerged following their introduction into clinical practice, so that only a few of the early molecules remain in use (see Table 3), primarily to treat mild to moderate skin infections caused by methicillin-susceptible *S. aureus* (MSSA) (Giordano et al. 2006). Cefazolin with high biliary concentrations is still used for surgical prophylaxis and for treatment of abdominal infections (Sudo et al. 2014) and is effective as empiric therapy in 80% of Japanese children with their first upper urinary tract infection (Abe et al. 2016).

When the TEM-1 penicillinase began to appear on transmissible plasmids in *Neisseria gonorrhoeae* (Ashford et al. 1976) and *Haemophilus influenzae* (Gunn et al. 1974; Khan et al. 1974), it was quickly recognized that the penicillins and cephalosporins in medical use were becoming ineffective, not only in treating those TEM-1-producing organisms, but also for the enteric bacteria and *P. aeruginosa* that could all acquire this enzyme. Another surge of synthetic activity in the pharmaceutical industry provided both oral and parenteral cephalosporins with stability to this common enzyme. These agents tended to have decreased potency against the

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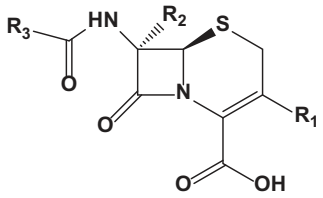
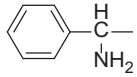
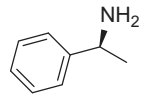
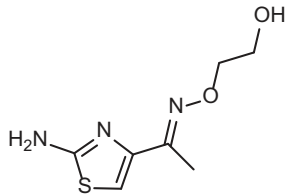
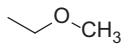
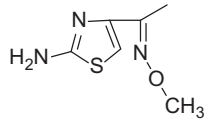
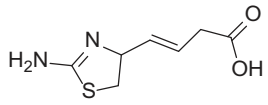
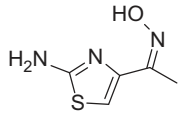
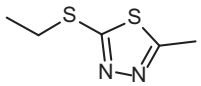
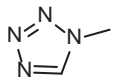
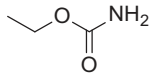
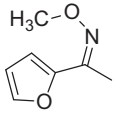
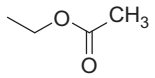
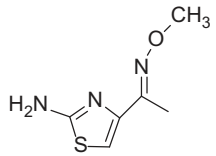
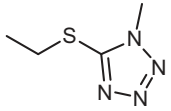
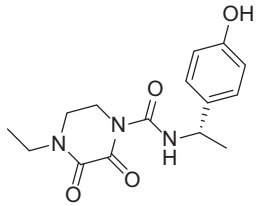
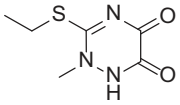
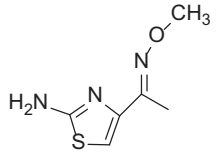
Table 3. Cephalosporins of current clinical utility or of historical interest



Name	Subclass[a]	R_1	R_2	R_3	Route of administration	Approval date[b,c]	Status
Cephalexin	Cephalosporin I		–H	$-CH_3$	Oral	1971	Limited availability
Cefaclor	Cephalosporin I	–Cl	–H		Oral	1979	Widely available
Cefixime	Cephalosporin V		–H		Oral	1989	Widely available
Cefpodoxime	Cephalosporin IV		–H		Oral	1992	Widely available
Ceftibutin	Cephalosporin III	–H	–H		Oral	1995	Widely available

Continued

Table 3. *Continued*

Name	Subclass[a]	R_1	R_2	R_3	Route of administration	Approval date[b,c]	Status
Cefdinir	Cephalosporin V		–H		Oral	1997	Widely available
Cefazolin	Cephalosporin I		–H		IV	1973	Widely available
Cefuroxime	Cephalosporin II		–H		Oral,[d] IV	1983	Widely available
Cefotaxime	Cephalosporin III		–H		IV	1981	Widely available
Cefoperazone	Cephalosporin III		–H		IV	1982	Widely available
Ceftriaxone	Cephalosporin III		–H		IV	1984	Widely available

Continued

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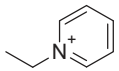
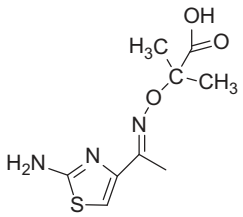
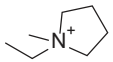
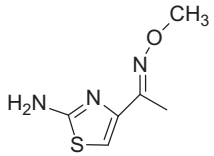
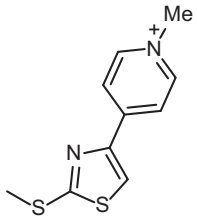
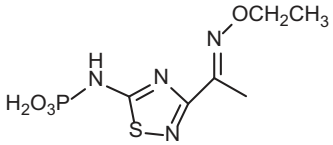
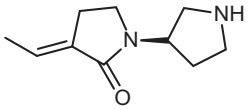
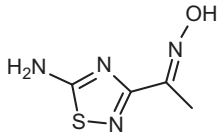
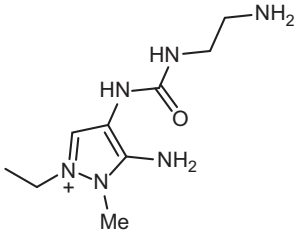
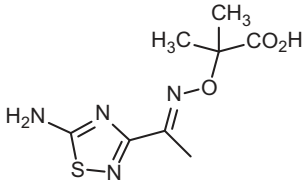
Table 3. *Continued*

Name	Subclass[a]	R_1	R_2	R_3	Route of administration	Approval date[b,c]	Status
Ceftazidime	Cephalosporin III		–H		IV	1985	Widely available
Cefepime	Cephalosporin IV		–H		IV	1996	Widely available
Ceftaroline (fosamil)	Anti-MRSA cephalosporin		–H		IV	2010	Widely available
Ceftobiprole	Anti-MRSA cephalosporin		–H		IV	2013 (Europe)	Limited availability
Ceftolozane	Antipseudomonal cephalosporin–cephalosporin VI		–H		IV	2014	Limited availability

Continued

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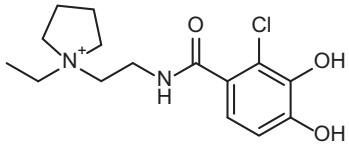
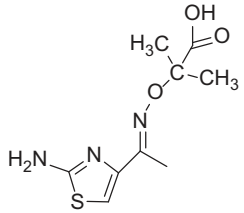
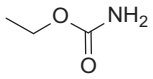
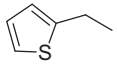
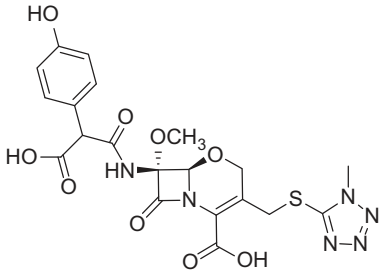
Table 3. *Continued*

Name	Subclass[a]	R_1	R_2	R_3	Route of administration	Approval date[b,c]	Status
S-649266	Siderophore cephalosporin–cephalosporin V		–H		IV	Not approved	Phase 2
Cefoxitin	Cephamycin		$-OCH_3$		IV	1978	Widely available
Moxalactam	Oxacephem				IV	1982[e]	Limited availability

IM, Intramuscular; IV, intravenous.

[a]Subclasses assigned according to CLSI (2016), Bryskier et al. (1994), or Bryskier and Belfiglio (1999).

[b]FDA approved unless otherwise noted.

[c]Dates were updated from Medeiros (1997) (www.accessdata.fda.gov/scripts/cder/drugsatfda; www.drugs.com; www.price-rx.com/lists/lantibiotics.shtml).

[d]Oral when dosed as cefuroxime axetil.

[e]Anonymous (1982).

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staphylococci, but gained antibacterial activity against Gram-negative pathogens. Cefuroxime, dosed parenterally or orally as the axetil ester, was the only member of the cephalosporin II class (Bryskier et al. 1994) with both oral and systemic dosage forms, but its stability to β-lactamase hydrolysis was diminished compared to later oral cephalosporins (Jacoby and Carreras 1990). As seen with cefuroxime, acceptable oral bioavailability of cefpodoxime required esterification through addition of a proxetil group to attain sufficient absorption for efficacy (Bryskier and Belfiglio 1999). Of the oral agents approved after 1983 in Table 3, cefdinir was generally more stable to hydrolysis, not only to the original TEM enzyme, but also to the AmpC cephalosporinases that are produced at a basal level in many enteric bacteria and *P. aeruginosa* (Payne and Amyes 1993; Labia and Morand 1994).

Among the parenteral agents introduced in the 1980s were the cephamycin cefoxitin, and cephalosporins in the cephalosporin III and cephalosporin IV subclasses (Bryskier et al. 1994), which continue to serve as important antibiotics for the treatment of serious infections caused by Gram-negative pathogens. The novel oxacephem moxalactam, or latamoxef, which had similar antimicrobial activity to the cephalosporin III/IV subclasses, has exquisite stability to hydrolysis by β-lactamases (Sato et al. 2015), but was not a highly successful antibiotic owing, in part, to a relatively high frequency of bleeding in patients treated with this drug (Brown et al. 1986). The cephamycin cefoxitin is notable for its characteristic 7-methoxy side chain that confers stability to the TEM-type β-lactamases, including ESBLs. It has useful antibacterial activity against MSSA and enteric bacteria that do not produce high levels of AmpC cephalosporinases (Jacoby and Han 1996). Cefotaxime, cefoperazone, ceftriaxone, and ceftazidime, designated as subclass cephalosporin III, and cefepime in the cephalosporin IV subclass, are also known as expanded-spectrum cephalosporins with increased hydrolytic stability to the common penicillinases, SHV-1 and TEM-1 β-lactamase (Martinez-Martinez et al. 1996). These agents have diminished activity against staphylococci and enterococci compared to earlier cephalosporins, but have more potent activity against Gram-negative organisms. Cefepime tends to have lower MICs against enteric bacteria than the other expanded-spectrum cephalosporins, attributed to greater penetration through the OmpF outer-membrane porin protein (Nikaido et al. 1990; Bellido et al. 1991). Cefotaxime and ceftriaxone are often used to treat susceptible streptococcal infections; all can be used to treat serious infections caused by enteric bacteria if the organisms test susceptible. Notably, ceftazidime and cefepime have maintained their observed activity against *P. aeruginosa*, with recent susceptibility rates exceeding 80% (Sader et al. 2015). A liability of the expanded-spectrum cephalosporins, however, began to emerge only a few years after the introduction of cefotaxime, when the ESBLs were identified with the ability to hydrolyze all of the β-lactams, with the exception of the carbapenems. These enzymes, in addition to both serine and metallo-carbapenemases, have severely compromised the activity of almost all penicillins and cephalosporins, necessitating the development of combination therapy with other β-lactams, β-lactamase inhibitors, or antibiotics from other classes.

Ceftolozane, recently approved in combination with tazobactam for the treatment of complicated urinary tract infections and complicated intraabdominal infections, shows potent antipseudomonal activity, and includes activity against enteric bacteria that produce some ESBLs (Zhanel et al. 2014), particularly CTX-M-producing isolates (Estabrook et al. 2014). Another recent addition to the cephalosporin family is the siderophore-substituted cephalosporin S-649266 with a catechol in the 3-position, thus allowing the molecule to enter the cells via an iron transport mechanism (Kohira et al. 2015). In addition to increased penetrability, the cephalosporin is stable to hydrolysis by many carbapenemases, resulting in activity against many β-lactam-resistant enteric bacteria (Kohira et al. 2015).

In the mid-1990s, reports began to emerge describing cephalosporins with MICs <4 μg/mL against MRSA (Hanaki et al. 1995) as a

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result of targeted binding to PBP2a. PBP2a is an acquired low-affinity PBP responsible for the observed lack of antibacterial activity of most β-lactams in MRSA isolates. Ceftobiprole (Hanaki et al. 1995; Hebeisen et al. 2001) and ceftaroline (Moisan et al. 2010), two cephalosporins with IC_{50} values <1 μg/mL for binding to the staphylococcal PBP2a, have been developed for clinical use (Table 3). Ceftaroline is approximately twofold to fourfold more potent than ceftobiprole in inhibiting staphylococcal and streptococcal growth (Karlowsky et al. 2011), but ceftobiprole is up to fourfold more potent against *Enterococcus faecalis* (Karlowsky et al. 2011). Ceftobiprole generally has at least fourfold to eightfold lower MICs than ceftaroline against enteric bacteria, *P. aeruginosa*, and *Acinetobacter* spp. (Pillar et al. 2008; Karlowsky et al. 2011). Neither cephalosporin is stable to hydrolysis by ESBLs or carbapenemases (Pillar et al. 2008; Castanheira et al. 2012), although the combination of ceftaroline with the β-lactamase inhibitor avibactam overcomes many of these issues (Mushtaq et al. 2010; Flamm et al. 2014) (see below). Both drugs are highly insoluble and have been derivatized as prodrugs for therapeutic use, as ceftaroline fosamil (Talbot et al. 2007) and ceftobiprole medocaril (Hebeisen et al. 2001), respectively.

CARBAPENEMS

Thienamycin was identified in the mid-1970s as a potent broad-spectrum antibiotic with the typical four-membered β-lactam structure fused to a novel five-membered ring in which carbon rather than sulfur was present at the 1-position (Kahan et al. 1979). Because of its chemical instability, this carbapenem was never developed as a therapeutic agent, but was stabilized by adding the *N*-formimidoyl group to the 2-position, resulting in imipenem (Table 4). Imipenem has been widely used for infections caused by Gram-positive, Gram-negative, nonfermentative, and anaerobic bacteria based on its sustained high activity against these organisms, particularly among non-carbapenemase-producing enteric bacteria (Bradley et al. 1999; Kiratisin et al. 2012). Carbapenems, in general, bind strongly to PBP2 in Gram-negative bacteria, but may also bind to PBP1a, 1b, and 3, thus providing supplemental killing mechanisms that may serve to lessen the emergence of resistance (Sumita and Fukasawa 1995; Yang et al. 1995). Carbapenems are notable for their stability to most β-lactamases (Bonfiglio et al. 2002), with the exception of the emerging carbapenemases found primarily in Gram-negative bacteria (Bush 2013). Because of the lability of imipenem to hydrolysis by the human renal dehydropeptidase (DHP) causing inactivation of the drug (Kropp et al. 1982), it is dosed in combination with cilastatin, a DHP inhibitor that also acts as a nephroprotectant (Kahan et al. 1983).

Based on the potent broad-spectrum activity of the early carbapenems, other related agents, including meropenem, ertapenem, and doripenem, have been developed for global use, with generally the same group of organisms included in their activity spectrum (Baughman 2009). All these carbapenems are more stable chemically than imipenem, thus allowing for a longer shelf life for the formulated drug and the potential for prolonged infusion times (Cielecka-Piontek et al. 2008; Prescott et al. 2011). Like imipenem, they are stable to most β-lactamases, other than the carbapenemases (Bush 2013). Following the introduction of imipenem, later carbapenems contained a 1β-methyl group that conferred stability to the human DHP, thus negating the necessity for coadministration of an inhibitor such as cilastatin (Zhanel et al. 2007). In terms of antibacterial activity, meropenem is generally twofold to fourfold more potent that imipenem against enteric bacteria (Jorgensen et al. 1991), is similar in potency against *P. aeruginosa*, but may have twofold to eightfold less antibacterial activity against Gram-positive bacteria (Neu et al. 1989). In addition, meropenem and doripenem retain greater activity against isolates of *P. aeruginosa* lacking the outer membrane porin protein OprD than imipenem (Riera et al. 2011). Meropenem is the only carbapenem approved for use in meningitis because of its excellent penetration into the meninges (Dagan et al. 1994). Doripenem, a carbapenem with somewhat

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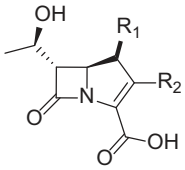
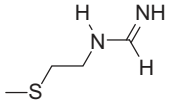
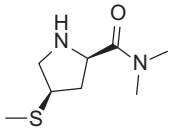
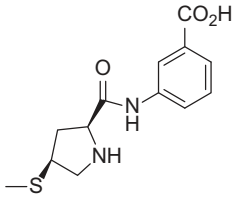
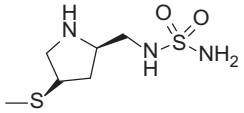
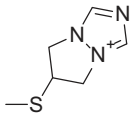
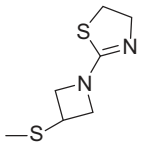
Table 4. Carbapenems of current clinical utility



Name	R_1	R_2	Approval date[a,b]	Status
Imipenem	H		1985	Widely available
Meropenem	CH_3		1996	Widely available
Ertapenem	CH_3		2001	Widely available
Doripenem	CH_3		2007	Widely available
Biapenem	CH_3		2001 (Japan)	Available in Japan
Tebipenem[c]	CH_3		2009 (Japan)	Available in Japan

[a]FDA approved unless otherwise noted.

[b]Dates were updated from Medeiros (1997) (www.accessdata.fda.gov/scripts/cder/drugsatfda; www.drugs.com; adisinsight.springer.com/drugs/800010812).

[c]Formulated as the pivoxil ester.

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higher chemical stability than imipenem or meropenem (Prescott et al. 2011), follows the antibacterial profile of meropenem, but is slightly more potent against Gram-negative organisms (Nordmann et al. 2011). Ertapenem, recognized for its long elimination half-life in humans because of its high protein binding (95%) (Majumdar et al. 2002), may be effectively administered once daily (Kattan et al. 2008) in contrast to the other carbapenems that are dosed most commonly two or three times a day. Although its antibacterial spectrum is similar to the other carbapenems against Enterobacteriaceae, ertapenem differs from imipenem, meropenem, and doripenem in that it has no useful activity against *P. aeruginosa* (Kohler et al. 1999). Two carbapenems approved for use only in Japan include biapenem, with an antimicrobial spectrum similar to meropenem and doripenem (Neu et al. 1992; Papp-Wallace et al.

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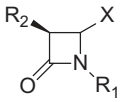
2011), and tebipenem, which lacks appreciable antipseudomonal activity (Fujimoto et al. 2013) (Table 4). Tebipenem is notable for its dosing as the pivoxil ester, rendering it orally bioavailable for use in pediatric respiratory infections (Kato et al. 2010). Like the other carbapenems, they are stable to hydrolysis by most serine β-lactamases, but can be hydrolyzed by both serine and metallo-carbapenemases. Biapenem has been reported to have better hydrolytic stability to metallo-β-lactamases (MBLs) compared to imipenem or meropenem (Neu et al. 1992; Inoue et al. 1995; Yang et al. 1995) with at least fourfold lower MICs than imipenem when tested against organisms producing IMP, VIM, or NDM MBLs (Livermore and Mushtaq 2013).

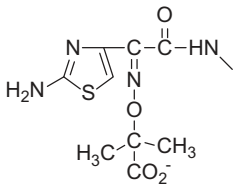
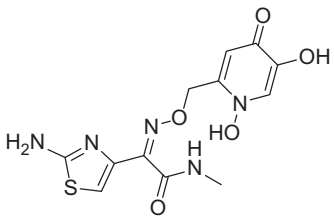
MONOCYCLIC β-LACTAMS

Aztreonam, a monocyclic β-lactam with an N1-sulfonic acid substituent, originated as a derivative from a novel antibiotic isolated from the New Jersey Pine Barrens (Cimarusti and Sykes 1983) (Table 5), and is the only monobactam to gain regulatory approval for therapeutic use. It has targeted activity against aerobic enteric bacteria and *P. aeruginosa*, with MICs against *S. aureus*, *S. pneumoniae*, and *E. faecalis* $\geq$50 μg/mL (Sykes et al. 1982). It binds tightly to PBP3 in Gram-negative rods, with weaker binding to PBP1a, leading to filamentation followed by cell lysis (Sykes et al. 1982). At the time that it was introduced into clinical practice, aztreonam was stable to hydrolysis by all of the common β-lactamases (Sykes et al. 1982); the emergence of ESBLs and the serine carbapenemases has since rendered it less effective against multidrug-resistant β-lactamase-producing organisms (Wang et al. 2014). However, the monobactam nucleus is not a good substrate for hydrolysis by MBLs, thus leading to a unique opportunity for this monobactam to be used in combination therapy with a serine β-lactamase inhibitor to treat infections caused by multi-β-lactamase-producing bacteria (see below) (Wang et al. 2014).

BAL30072 is a novel monosulfactam with an N1-*O*-sulfate group, an activity-enhancing 3-dihydropyridone siderophore substituent, and a 4-gem-dimethyl substitution on the azetidinone ring (Page et al. 2010) (Table 5). Its spectrum of activity is similar to aztreonam, but supplemented with activity against addi-

Table 5. Monocyclic β-lactams



Name	Subclass	R_1	R_2	Approval date	Status
Aztreonam X = α-methyl	Monobactam	—SO_3H		1986[a]	Widely available
BAL30072 X = gem-dimethyl	Monosulfactam	—OSO_3H		Not approved	Phase 1

[a]U.S. approval date provided in Medeiros (1997).

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tional nonfermentative bacteria. As a result of the increased penetration of BAL30072 via iron uptake mechanisms, it is more potent against some Gram-negative bacteria than other β-lactams, with activity against *Acinetobacter* spp. and *Burkholderia* spp. eightfold to >256-fold better than imipenem (Page et al. 2010). It is susceptible to hydrolysis by ESBLs and many carbapenemases, and has shown synergistic activity in combination with β-lactamase inhibitors (Mushtaq et al. 2013) or meropenem (Hofer et al. 2013; Hornsey et al. 2013). Like aztreonam, it is stable to hydrolysis by MBLs; additionally, it was hydrolyzed 3000-fold less efficiently by the KPC-2 serine carbapenemase compared to aztreonam (Page et al. 2010).

β-LACTAMASE INHIBITORS

Attempts to identify inhibitors of common β-lactamases began in the mid-1970s, triggered by the appearance of the transferable TEM-1 penicillinase in *Neisseria gonorrhoeae* (Ashford et al. 1976) and *Haemophilus influenzae* (Gunn et al. 1974; Khan et al. 1974). As the result of natural product screening, clavulanic acid with a novel clavam structure (Table 6) was identified as a broad spectrum inhibitor of the staphylococcal penicillinases and most of the recognized plasmid-encoded penicillinases found in enteric bacteria (Reading and Cole 1977; Cole 1982), including the highly prevalent TEM and SHV enzymes (Simpson et al. 1980). The TEM β-lactamase was shown to be inactivated by this suicide inhibitor that initially acylates the active site serine with transient inhibition that includes hydrolysis of the inhibitor before complete enzyme inactivation (Charnas et al. 1978; Charnas and Knowles 1981). The spectrum of the inhibitor is now recognized to include most class A β-lactamases, including ESBLs (Steward et al. 2001) and, to a lesser extent, serine carbapenemases (Nordmann and Poirel 2002; Yigit et al. 2003). Clavulanic acid acts synergistically with penicillins and cephalosporins against β-lactamase-producing enteric bacteria to inhibit sensitive β-lactamases, thus allowing the companion β-lactam to kill the bacteria. It has been combined with ticarcillin as a parenteral combination for nosocomial infections that include *P. aeruginosa* as a causative pathogen (Neu 1990), and with amoxicillin as an orally bioavailable formulation for therapeutic use especially in pediatric populations (Klein 2003). It is also used in phenotypic testing to determine the presence of ESBLs in *Escherichia coli* and *Klebsiella pneumoniae* (Steward et al. 2001).

Following the discovery of clavulanic acid, medicinal chemists synthesized a number of penicillanic acid sulfones (Table 6) with β-lactamase inhibitory activity (English et al. 1978; Fisher et al. 1981; Aronoff et al. 1984). Of these, sulbactam (English et al. 1978) and tazobactam (Aronoff et al. 1984) were successfully commercialized. Both had a similar spectrum of activity as clavulanic acid. Against class A β-lactamases, sulbactam had less inhibitory activity than clavulanic acid or tazobactam based on IC_{50} values, but both sulfones were better inhibitors of class C cephalosporinase β-lactamases (Bush et al. 1993). Each followed the same general inhibitory/inactivation-mechanism as for clavulanic acid (Easton and Knowles 1984; Bush et al. 1993). The number of hydrolytic events before inactivation was at least 25-fold higher for sulbactam than for clavulanic acid or tazobactam for the TEM-2 β-lactamase (Bush et al. 1993; Easton and Knowles 1984). In contrast to clavulanic acid, the sulfone inhibitors do not function as inducers of chromosomally mediated AmpC β-lactamase (Weber and Sanders 1990).

Sulbactam has been combined with ampicillin for general global use (Neu 1990) and with cefoperazone to provide additional synergistic activity against nonfermentative and anaerobic bacteria, primarily in Japan (Eliopoulos et al. 1989). Tazobactam has been combined with piperacillin and, more recently, with cefoperazone and ceftolozane for nosocomial infections, including those caused by *P. aeruginosa* (Lister 2000). In general, none of the inhibitors has useful antibacterial activity as monotherapy, although there are several notable exceptions. Clavulanic acid alone has been reported to have an MIC as low as 1 μg/mL against *N. gonorrhoeae* (Wise et al. 1978); sulbactam has modest activity against wild-type *Acinetobacter* spp. and *Burkholderia cepacia*, with MIC_{90} values

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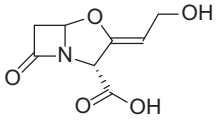
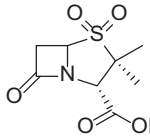
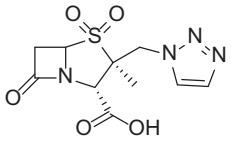
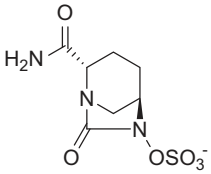
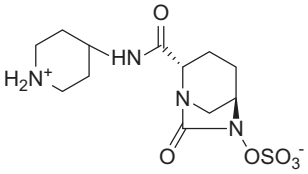
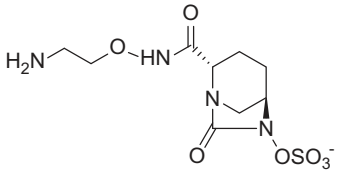
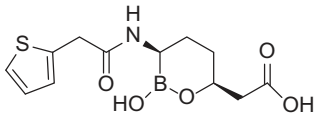
Table 6. β-lactamase inhibitors of current interest

Name	Structure	Subclass	Partner β-lactam	Approval date[a]	Status
Clavulanic acid[b]		Clavam	Amoxicillin	1984	Widely available
Sulbactam[c]		Penicillanic acid sulfone	Ampicillin	1986	Widely available
Tazobactam		Penicillanic acid sulfone	Piperacillin Ceftolozane	1993 2014	Widely available Available in the United States and Europe
Avibactam[d]		DBO[e]	Ceftazidime[d]	2015	Widely available
Relebactam		DBO	Imipenem	Not approved	Phase 3 in the United States
RG6080		DBO	Not selected	Not approved	Phase 1
RPX7009		Boronic acid	Meropenem	Not approved	Phase 3 in the United States

[a]Dates provided in Medeiros (1997) or www.accessdata.fda.gov/scripts/cder/drugsatfda.
[b]Also initially combined with ticarcilllin to provide parenteral activity against *Pseudomonas aeruginosa*.
[c]Also combined with cefoperazone outside the United States.
[d]Also in development with ceftaroline or aztreonam.
[e]Diazabicyclooctane.

≤8 and 10 μg/mL, respectively (Jacoby and Sutton 1989; Fass et al. 1990), but does not retain activity against isolates with multiple resistance mechanisms (Dong et al. 2014). None of these inhibitors is effective in inhibiting the hydrolytic activity of MBLs (Bush 2015), and their modest activity against serine carbapenemases does not translate into clinical susceptibility (Yigit et al. 2003; Woodford et al. 2004) owing, at least in part, to the presence of multiple β-lactamases in the producing organisms (Moland et al. 2007). Even the potent inhibitory

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activity against individual ESBLs that is observed with clavulanic acid and tazobactam is not sufficient to protect their accompanying penicillins in the presence of multiple β-lactamases (Jones-Dias et al. 2014).

Following a hiatus of approximately two decades, a unique class of non-β-lactam β-lactamase inhibitors emerged, based on a novel bridged diazabicyclooctane (DBO) structure (Table 6) (Coleman 2011). The first of these inhibitors, avibactam, has a broader spectrum of activity than clavulanic acid and the sulfone inhibitors. Not only are class A penicillinases, ESBLs, and serine carbapenemases potently inhibited, but class C cephalosporinases and some class D oxacillinases are also effectively inhibited (Ehmann et al. 2012, 2013). Unlike the previous inactivators described above, avibactam is a tight-binding, covalent, reversible inhibitor for most enzymes, with the KPC-2 enzyme, a notable exception for which slow avibactam hydrolysis was observed (Ehmann et al. 2012). In addition, avibactam does not induce AmpC β-lactamases at clinically relevant concentrations (Coleman 2011). Avibactam has been approved for therapeutic use in combination with ceftazidime, and is under development for ceftaroline–avibactam or aztreonam–avibactam combinations (Flamm et al. 2014; Biedenbach et al. 2015; Li et al. 2015). Other DBOs under development include RG6080 and relebactam (MK 7655), in combination with imipenem. The spectrum of relebactam shows a similar spectrum of activity to avibactam; however, it provides less potentiation against important class D β-lactamases such as OXA-48 (Livermore et al. 2013). RG6080 (formerly OP0565) is a DBO that has an inhibitory spectrum similar to the other DBOs but has the additional benefit of exhibiting some intrinsic antibacterial activity against enteric bacteria (Livermore et al. 2015).

The boronic acid inhibitor RPX7009 (Table 6) represents another novel class of synthetic non-β-lactam β-lactamase inhibitors (Hecker et al. 2015), although boronic acids have been known for many years to be effective inhibitors of serine β-lactamases (Kiener and Waley 1978). Despite the inhibitory activity of RPX7009 against many groups of serine β-lactamases (Hecker et al. 2015), it is being developed in combination with meropenem to target pathogens producing serine carbapenemases (Lapuebla et al. 2015).

β-LACTAM RESISTANCE: CONCLUDING REMARKS

Resistance to the β-lactams continues to increase, especially in Gram-negative organisms (Vasoo et al. 2015), because of the widespread therapeutic dependence on these efficacious and safe antibiotics (see Fig. 1). Major resistance mechanisms will be expanded on in other articles in this collection. PBP acquisition or mutation is the major β-lactam-resistance mechanism in Gram-positive bacteria (see Fisher and Mobashery 2016). The most prevalent and most damaging resistance mechanisms among Gram-negative pathogens are represented by the β-lactamases (Babic et al. 2006; Livermore 2012), both chromosomally encoded enzymes that may be produced at high levels and transferable enzymes that travel on mobile elements among species (Bush 2013). When these targeted mechanisms are combined with decreased uptake or increased efflux of the β-lactam, high-level resistance becomes a major clinical problem (see Bonomo 2016). Perhaps the most encouraging prospect in counteracting resistance is the emergence of new classes of β-lactamase inhibitors that will provide protection for some of the most valuable antibiotics in clinical practice, at least for the present time.

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β-Lactams and β-Lactamase Inhibitors: An Overview

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