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The Chemical Relationship Among Beta-Lactam Antibiotics and Potential Impacts on Reactivity and Decomposition

*Jonathan Turner[1,2], Alyssa Muraoka[2], Michael Bedenbaugh[3], Blaine Childress[4], Lauren Pernot[5], Mark Wiencek[5] and Yuri K. Peterson[2]**

[1] College of Medicine, Medical University of South Carolina, Charleston, SC, United States, [2] College of Pharmacy, Medical University of South Carolina, Charleston, SC, United States, [3] Intramed Plus, West Columbia, SC, United States, [4] South Carolina Research Authority, Greenville, SC, United States, [5] Contec, Inc., Spartanburg, SC, United States

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***Correspondence:**
Yuri K. Peterson
petersy@musc.edu

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Beta-lactam antibiotics remain one of the most commonly prescribed drug classes, but they are limited by their propensity to cause hypersensitivity reactions (e.g., from allergy to anaphylaxis) as well as by the emergence of bacteria with a myriad of resistance mechanisms such as β-lactamases. While development efforts continue to focus on overcoming resistance, there are ongoing concerns regarding cross-contamination of β-lactams during manufacturing and compounding of these drugs. Additionally, there is a need to reduce levels of drugs such as β-lactam antibiotics in waste-water to mitigate the risk of environmental exposure. To help address future development of effective remediation chemistries and processes, it is desired to better understand the structural relationship among the most common β-lactams. This study includes the creation of a class-wide structural ordering of the entire β-lactam series, including both United States Food and Drug Association (US-FDA)-approved drugs and experimental therapies. The result is a structural relational map: the "Lactamome," which positions each substance according to architecture and chemical end-group. We utilized a novel method to compare the structural relationships of β-lactam antibiotics among the radial cladogram and describe the positioning with respect to efficacy, resistance to hydrolysis, reported hypersensitivity, and Woodward height. The resulting classification scheme may help with the development of broad-spectrum treatments that reduce the risk of occupational exposure and negative environmental impacts, assist practitioners with avoiding adverse patient reactions, and help direct future drug research.

Keywords: hydrolysis, decomposition, chemical informatics, lactam antibiotics, antibiotic allergy (including penicillin and cephalosporin β-lactams), antimicrobial activity, deactivation

HISTORICAL OVERVIEW

Since the first clinical uses of penicillin G in the 1930s and 1940s, β-lactam antimicrobials have enjoyed marked success in the treatment of bacterial infections. By 1944 penicillin was being manufactured at the rate of over a billion doses a year (Aldridge et al., 1999). Shortly after the introduction of the penam penicillin, the first chemical compounds of the cephem group

were isolated from the fungus *Cephalosporium acremonium* by Giuseppe Brotzu in 1948, when crude filtrates of a culture were found to inhibit the growth of *Staphylococcus aureus* (Singh and Arrieta, 1999; Foye et al., 2008). The first cephem, cephalothin, became available for patients in the United States as a parenteral drug in 1964 (Greenwood, 2008). Interest in β-lactam antibiotics spurred scientists to explore a breadth of structural derivatives and platforms well beyond the above-mentioned natural substances in efforts to expand the spectrum. Those synthetic efforts have resulted in four major β-lactam classes: monobactam, penams, penems, and cephems (**Figure 1**).

STRUCTURAL PLATFORMS AND β-LACTAM CLASSES

The historical development process as well as structural and functional (e.g., spectra of activity) differences among the various classes of β-lactams are described in detail in several excellent reviews (Bush and Bradford, 2016; Ochoa-Aguilar et al., 2016; Lima et al., 2020). Aside from the impacts resulting from electron withdrawing substituents by different R groups, the key structural features of all β-lactam antibiotics include (1) the 2-azetidinone, a 4-membered cyclic amide required for their characteristic target acylation, (2) the level of cyclic amide ring strain imposed by bicyclic structural designs, and (3) an acidic moiety critical to their recognition by the transpeptidase active site (**Figure 2**).

While many previous studies have investigated the intricacies of drug binding and the impacts on efficacy and resistance, the relationship of molecular structure on the ability of chemical compounds and processes to decontaminate β-lactam residues from manufacturing and compounding facilities as well as terrestrial and aquatic environments has received less attention. Because of their perceived or actual potential to cause allergic responses in a substantial portion of the host population, governmental guidelines and regulations involve special precautions to reduce the risk of cross-contamination from β-lactams (Food and Drug Administration [FDA], 2013). The chemicals that might be candidates for decontamination of surfaces in facilities or for waste-water treatment should be effective against a broad range of drugs at levels that are already employed for disinfection and be readily biodegradable themselves.

As such, it was desired to assess the structural relationships among β-lactams to understand if a subset of drugs can serve as a proxy for others during development and testing. As a first step toward this attempt of a "read-across," the most widely used β-lactam antibiotics have been reviewed, molecularly modeled, and structurally organized into relational maps termed a "Lactamome."

β-Lactam Classes

The **monocyclic β-lactams** (or monobactam) class represents the simplest structural platform among these antibiotics. The monocyclic platform of this b-lactam was first isolated from *Chromobacterium violaceum* (Asai et al., 1981; Imada et al., 1981; Sykes et al., 1981; Decuyper et al., 2018; Goldberg et al., 2021). There are three major monocyclic β-lactams: aztreonam, tigemonam, nocardicin A, and two minor monocyclic β-lactams: carumonam (only approved in Japan) and tabtoxin. Tabtoxin, the only member retaining a nitrogen-hydrogen bond, is uniquely a glutamine synthetase inhibitor with lower activity against penicillin-binding proteins (PBPs). The others possess an *N*-sulfonic acid moiety or *N*-acetic acid moiety. Aztreonam (**Figure 1**), currently the only monocyclic β-lactams clinically used in the United States, exhibits potent inhibition of Gram-negative PBPs (Georgopapadakou et al., 1982; Sykes et al., 1982; Rittenbury, 1990; Cunha, 1993) but finds limited clinical utility owing to its lack of activity against Gram-positive or anaerobic bacteria. Because of its unique monocyclic β-lactam structure, aztreonam is thought to have no cross-sensitivity to patients allergic to penicillin (Gaeta et al., 2015). Currently there is pre-clinical research in aztreonam combination with other β-lactams and diazabicyclooctane monocyclic β-lactams against MDR/XDR Gram-negative bacteria (Bassetti et al., 2021; Bhatnagar et al., 2021). A second generation of monocyclic β-lactams is also under late stage clinical development (Osborn et al., 2019).

Penams are a class of β-lactams possessing an azabicyclo[3.2.0]heptane ring system, a carboxylic acid moiety at C3, and a sulfur atom at position one (**Figure 1**). The prototypic and most well-known penam is penicillin G (PNG or benzylpenicillin), isolated from *Penicillium chrysogenum* (Fleming, 2001). The other commonly used natural product penam is penicillin V, or phenoxymethylpenicillin. In the absence of β-lactamases, the natural penicillins show good Gram-positive activity but fail to inhibit the growth of many Gram-negative organisms (Libby and Holmberg, 1945; Eagle, 1946; Eagle and Technical Assistance of Arlyne D. Musselman, 1947; Nell and Hill, 1947; Thomsen and Larsen, 1962). A great deal of creative synthetic chemistry has been directed to the penam platform to modulate the spectrum of this class, predominantly *via* modifications at the C6 acylamino group (R_1 side chain). Clinically useful penam derivatives have geminal dimethyl groups at C2, except tazobactam which is used in combination therapies as a β-lactamase inhibitor. The penam amoxicillin is one of the most often prescribed antibiotics in the United States, many other countries, and in veterinary medicine (Tao et al., 2019).

Penems are direct analogs of penams but with 2,3-unsaturation within the fused five-membered ring (**Figure 1**). The thiapenems, which contain a sulfur atom in the fused ring at position one, do not exist naturally but were synthesized in 1978 by chemists including R.B. Woodward (Ernest et al., 1978). The penem class is one of a few β-lactam antibiotics still being researched, and includes faropenem, ritipenem, and sulopenem (Batchelder et al., 2020; Butler et al., 2022; Sato et al., 2022). While no members of the thiapenem class are currently used in United States clinical settings, safety and efficacy data required for FDA approval are forthcoming. However, there are several FDA-approved members of a subclass of penems called carbapenems, which possess a carbon atom in place of the sulfur "X" atom. The structure of ertapenem is shown in **Figure 1** as an example of this class. The C6

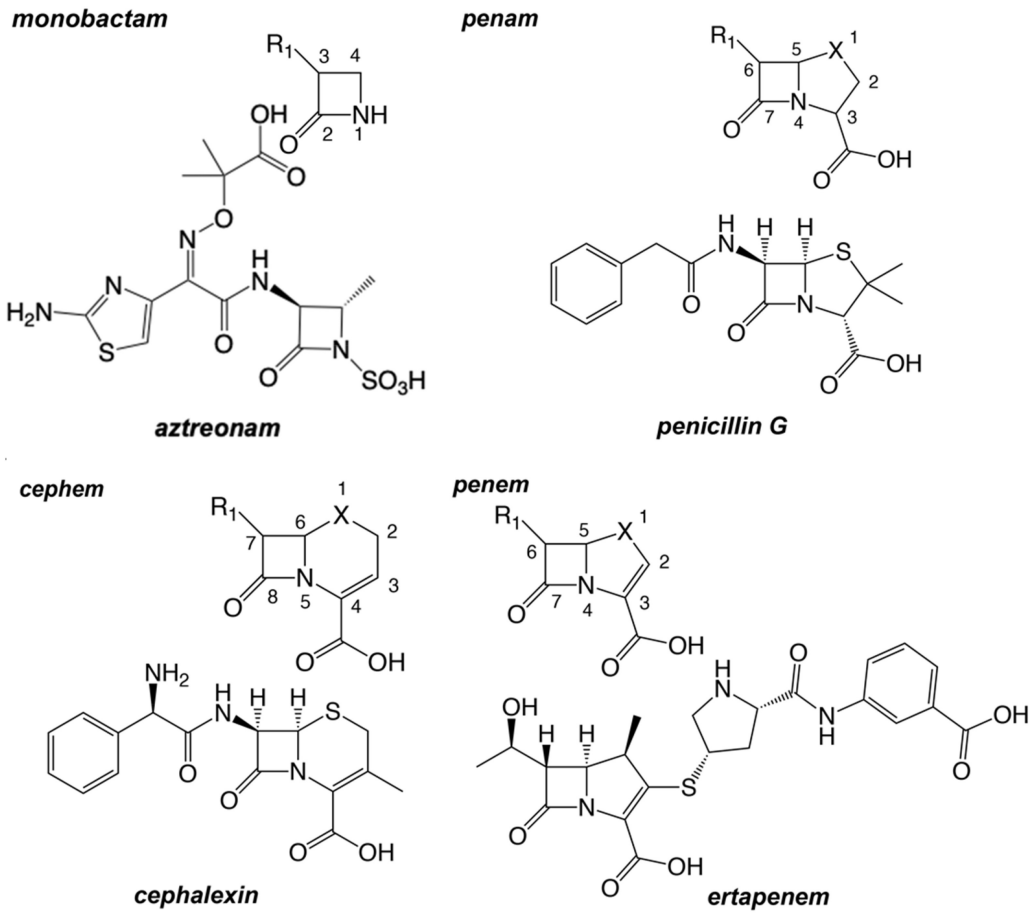

FIGURE 1 | The chemical graphs and scaffold of primary examples of major β-lactam antibiotic classes. Common atom numbering scheme of the chemotype is depicted and oriented above the example β-lactam ring. The X may be a carbon, an oxygen atom, or a sulfur atom. For example, penem structures with X=C are "carbapenems"; penem structures with X=O are "oxapenems"; and penem structures with X=S are "thiapenems," or more commonly, simply "penems."

hydroxyethyl substituent possessed by members of the penem class represents a significant departure from penams and cephems, which generally exhibit large and variable aminoacyl substituents at C6. Differences in activity and spectrum among compounds of this class are influenced by *cis* alignment of the vicinal R1 hydroxyl and C6 hydrogen and dictated by the C2 substituent. Given their broad spectrum, as well as the β-lactamase stability afforded by their C6 *R*-hydroxyethyl side chain and *trans* C5-C6 hydrogen geometry (Basker et al., 1980), the carbapenems have found most of their clinical utility as antimicrobials for infections with multidrug-resistant organisms.

Cephems, also known as cephalosporins, differ from penems by having a dihydrothiazine ring fused to the β-lactam ring (Hughes, 2017a,b). First generation cephems generally possess an aromatic acylamino side chain at C7 and exhibit potent Gram-positive activity (Godzeski et al., 1963; Spencer et al., 1966a,b; Ryan et al., 1969; Hsieh and Ho, 1975).

As cephems entered a second generation, drug developers explored other substituents at C7, such as the replacement of the acetoxy group with various nucleophiles (i.e., carbamates, heterocyclic mercaptans, and pyridines). These cephems exhibit broader spectrum than their earlier counterparts, with some showing potent inhibition of Gram-negatives (Eykyn et al., 1973; Kosmidis et al., 1973; Hamilton-Miller et al., 1974; Neu, 1974a,b; Nomura et al., 1974; Wallick and Hendlin, 1974; Tsuchiya et al., 1978). The broad cephem class also contains the cephamycin (and cephalosporin) class which also has the cephem nucleus and includes the second generation cefoxitin and cefotetan (Kosmidis et al., 1973; Neu, 1974b; Wallick and Hendlin, 1974).

In third generation designs, the aryl group was modified to an aminothiazole, a change found to enhance Gram-negative activity. One notable outlier is cefoperazone, which borrows its C7 acylamino group from the ureidopenicillin piperacillin. This group exhibits not only further expanded spectrum compared to previous generations, but maintains stability to serine β-lactamases (Sosna et al., 1978; Kojo et al., 1979; Matsubara et al., 1979; O'Callaghan et al., 1980; Reiner et al., 1980; Shannon et al., 1980; Verbist and Verhaegen, 1980; Wise et al., 1980; Neu et al., 1981, 1984, 1989; Kamimura et al., 1984; Inamoto et al., 1988, 1990a,b; Yokoo et al., 1991).

With fourth generation cephems, quaternary nitrogen substituents were incorporated at C3 to enhance passive transport through the Gram-negative outer membrane, decrease affinity for β-lactamases, and promote departure of the leaving group (Machka and Braveny, 1983; Seibert et al., 1983; Khan et al., 1984; Kessler et al., 1985; Limbert et al., 1991; Chin et al., 1992; Hancock and Bellido, 1992).

The fifth generation of cephems was specifically engineered to combat various resistance problems while attempting to maintain a broad spectrum of activity (Entenza et al., 2002; Wootton et al., 2002; Zbinden et al., 2002; Ishikawa et al., 2003; Iizawa et al., 2004; Issa et al., 2004; Sader et al., 2005; Takeda et al., 2007a,b; Toda et al., 2008; Ito et al., 2016; Kohira et al., 2016; Dobias et al., 2017; Aoki et al., 2018). In general, these cephems maintain the alkoxyimino group, exchange the aminothiazole for an aminothiadiazole, and install conjugation or extended ring systems in their C3 substituents.

A unique and small modification to the cephem class is the **oxacephem**, which possesses an azabicyclo[4.2.0]oct-2-ene ring system, a carboxylic acid moiety at C4, and, as the name suggests, an oxygen at position one in place of sulfur. The major oxacephems are moxalactam (latamoxef) and flomoxef. These compounds were developed to reduce blood coagulation defects and, more specifically, target the bacterial genus *Nocardia* (Yazawa et al., 1989; Cazzola et al., 1993).

b-lactamase inhibitors include subclasses of penam β-lactams resistant to hydrolysis by β-lactamases. While the success of β-lactam antibiotics has been extraordinary, their long-term usage has collided with the evolution of resistant microbial strains. Myriad resistance determinants can contribute to such resistance, but β-lactamases are of particular concern due to their high catalytic efficiency and their potential for rapid dissemination by horizontal transfer on plasmids. Major β-lactam-based β-lactamase inhibitors include sulbactam, clavulanate, and tazobactam. These β-lactam molecules exhibit little direct antibacterial properties by themselves but serve a sacrificial role by tenaciously binding to β-lactamases to thereby enable the unimpeded performance of a partner β-lactam such as amoxicillin (Pechere and Kohler, 1999; Shapiro et al., 2021).

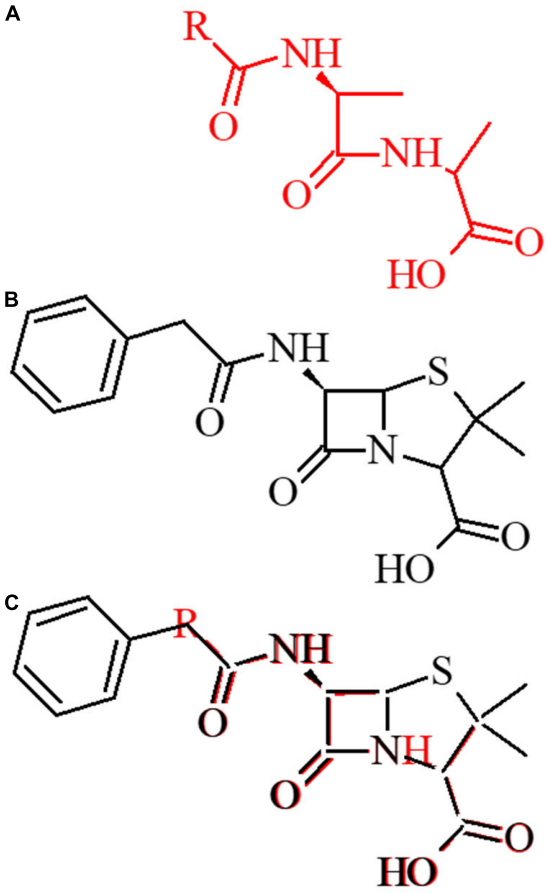

FIGURE 2 | Structural basis of lactam activity. **(A)** The D-Ala-D-Ala amino acid is depicted in red. **(B)** The 1st generation penam ampicillin is depicted in black. **(C)** D-Ala-D-Ala dipeptide overlay with the β-lactam ampicillin antibiotic.

Mechanism of Activity

β-lactam antibiotics act through structural mimicry of the D-alanine-D-alanine motif in peptidoglycans of the bacterial cell wall (**Figure 2**). They inhibit bacterial transpeptidases which catalyze the cross-linkage of peptidoglycan through the formation of isopeptide bonds (Goffin and Ghuysen, 1998; Macheboeuf et al., 2006; Sauvage et al., 2008). Peptidoglycan is an essential component of the bacterial cell wall and plays major roles in protecting bacteria from environmental stress, ensuring osmotic stability. Cell wall degradation and resynthesis are critical to bacterial cell growth and division. The major target of β-lactams are PBPs, which are essential peptide cross-linking enzymes and are essential for peptidoglycan synthesis. In the presence of a β-lactam, the serine nucleophile attacks the lactam carbonyl, resulting in a stable acyl-enzyme complex (Yocum et al., 1979; Waxman et al., 1980). This action interrupts the integrity of the bacterial cell wall, diminishing the capacity for growth and division and removing protection from osmotic or tensile stress. A second major mechanism of action, specific to carbapenem β-lactams are the L,D-transpeptidases. For example, faropenem efficacy against mycobacteria is due to L,D transpeptidase covalent adduct formation (Lohans et al., 2019; Lu et al., 2020).

While target affinity and site accumulation are important factors, the efficacy of β-lactams has canonically been dominated by their propensity for chemical acylation, and therefore, a consequence of their ease of entry into the PBP site (i.e., a diffusion-limited kinetic process). This chemical reactivity is strongly related to the geometry at the β-lactam nitrogen and the degree of ring strain. In monocyclic structures, such as monobactams, the amide bond is stabilized by conjugation between the nitrogen lone pair and the carbonyl group. In bicyclic structures, the amide stabilization is attenuated by a third bonding partner, which creates a trigonal pyramidal (sp^3) nitrogen geometry. The reduced amide resonance conferred by these bicyclic systems affords increased carbonyl electrophilicity and higher intrinsic reactivity to nucleophiles and nucleophile-containing enzymes such as transpeptidases, β-lactamases, and metallo-β-lactamases (Green et al., 1965; Morin et al., 1969;

Sweet and Dahl, 1970; Glover and Rosser, 2012; Szostak et al., 2015; Ismalaj, 2022).

Considering the trigonal pyramid, defined by the nitrogen (i.e., the apex) and its three bond-pair substituents (i.e., the base) (**Figure 3**), the distortion from a planar (sp^2) amide can be defined by a parameter known as the Woodward height (*h*-Woodward) (Ernest et al., 1978; Lang et al., 1978; Woodward, 1980; Meng et al., 2021; Ismalaj, 2022). Monocyclic monobactams, having an essentially planar geometry at nitrogen, tend to be the least reactive of the β-lactams with negligible *h*-Woodward values (Diaz et al., 2002).

Cephems are sterically predisposed toward Woodward heights of about 0.2–0.3 Å, due to conformational flexibility afforded by their six-membered ring fusion. However, cephalosporins have unique features that contribute to their chemical reactivities beyond *h*-Woodward. A competitive enamine resonance resulting from the delocalization of the nitrogen's lone electron pair into the π electron system of the dihydrothiazine ring contributes to attenuated amide resonance (Morin et al., 1969; Sweet and Dahl, 1970). In the setting of this resonance, heteroatomic moieties at the C3 position can act as leaving groups upon ring opening. Whether or not it is a leaving group, the C3 substituent can participate in long range inductive effects with the β-lactam amide moiety–strongly electron-withdrawing groups are postulated to enhance the electrophilicity of the carbonyl (Morin et al., 1969; Boyd et al., 1975; Boyd, 1984).

Penams exhibit still larger *h*-Woodward (∼0.4 Å) values than cephams due to the additional strain imposed by five-membered ring fusion, and as such exhibit higher intrinsic reactivity to nucleophiles. Interestingly, molecules of the penam class can exist in two distinct conformational states, one in which the C3 carboxylate is in an equatorial position in relation to the ring system and one in which it is axial (Abrahamsson et al., 1963; James et al., 1968; Dexter and van der Veen, 1978).

Structural analysis reveals carbapenems and thiapenems as having *h*-Woodward values of 0.50–0.60 Å; these drugs are recognized as among the most reactive β-lactams. Such higher values may be attributed to the additional geometric constraints introduced by the unsaturation between C2 and C3 of the pyrrolidine ring, as well as replacement of the position one sulfur atom with a carbon atom in carbapenems. Their rapid acylation of PBPs have been ascribed to this highly activated β-lactam ring system. Such ring opening propensity has been shown by examining the kinetics of base hydrolysis (Woodward, 1980). Results indicate the penems are the most readily hydrolyzed of known β-lactams (Knox, 1961; Frere et al., 1975; Graves-Woodward and Pratt, 1998; Hujer et al., 2005; Silvaggi et al., 2005; Jeong et al., 2018).

RESULTS AND DISCUSSION

Chemical Similarity Among β-Lactams

Considering the evolution and history of β-lactams, this study utilized a novel method to examine the chemical similarity and interrelatedness of β-lactam antibiotics. To perform this analysis, the complete pairwise chemical similarity was calculated among β-lactam drugs approved by the FDA or compounds in late-stage clinical trials, to create a radial cladogram analogous to the common method of how genes, strains or species are compared in a phylogeny. The analysis was performed using the industry standard Tanimoto coefficient similarity score calculated from keyed organic chemical groups using ChemMine and visualized using Dendroscope (Huson et al., 2007; Backman et al., 2011; Peterson et al., 2013). The resulting "Lactamome" (**Figure 4**) was depicted with benzylpenicillin (penicillin G) as the top-most molecule, owing to its place as a foundational member. The resulting circular chemogram (dendrogram of chemicals) was color-coded according to known β-lactam chemical classes. The utility of chemical clustering is that relationships are unbiased and based solely on organic chemistry. Broadly speaking, the Lactamome shows the major penam and cephem clusters in relation to the minor monobactam, β-lactam-based β-lactamase inhibitor, oxacephem, carbapenem and penem classes. The positioning reflects the similarity of the atomic arrangements in fused or unfused ring systems in relation to the β-lactam foundation, coupled with the electronic effects of substituent end groups. Beginning with benzylpenicillin, penems cluster in four distinct subclasses. This is followed by two major branches and five subgroups of the cephem class.

Monobactams fit in their own small cluster that branches from the cephem class. However, nocardicin has substituents with structural similarity to moxalactam and was positioned apart from other monobactams despite its single ring platform. β-lactamase inhibitors based on the core β-lactam structure (sulbactam, clavulanate, and tazobactam) make up their own cluster. Interestingly along with the penam mecillinam, members of this branch are highly related *via* their core chemistry (3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, **Figure 1** penam). Oxacephems (moxalactam and flomoxef) are uniquely located as branching off the cephem class.

While generational labeling is a common method for describing β-lactams, particularly cephems (cephalosporins), this convention is not always consistent among researchers or pharmaceutical companies. Using consensus information from multiple literature sources, the relevant drugs in the Lactamome were assigned colors according to a generational scheme (**Figure 5B**). However, the generational Lactamome did not reveal any apparent trends or relationships that signaled generation. In most cases, terminal clusters are the same generation or differ by only one generation. In the case of cephems, later generations exhibit a broader spectrum of activity and less cross-reactivity with penicillin (Trubiano et al., 2017). The carbapenem class, while important for multidrug resistant infections, does not readily conform to chemical generation labeling. Similarly, β-lactamase inhibitors, mecillinam, and monobactams do not conform to multigenerational binning.

Susceptibility to Hydrolysis

While factors like affinity, site accumulation, and pharmacokinetics affect *in vivo* efficacy, the minimum inhibitory concentrations (MICs) of antibiotics correlate with those having higher *h*-Woodward values. Correspondingly, higher *h*-Woodward value drugs are more prone to hydrolysis,

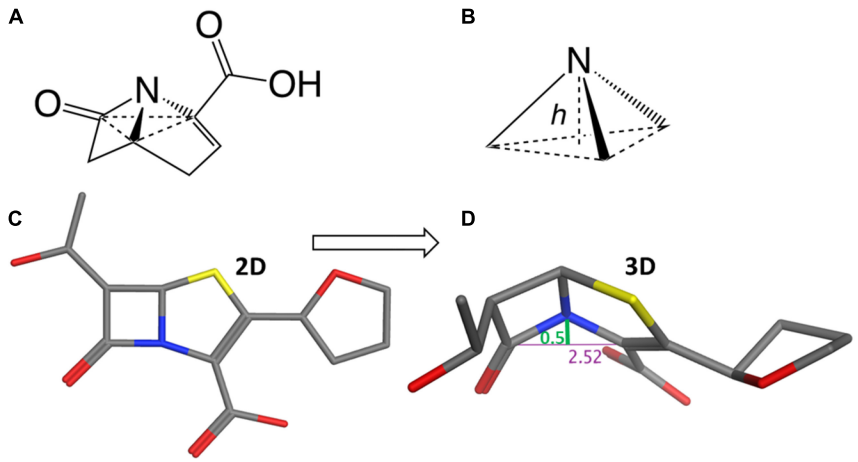

FIGURE 3 | Structural flexibility of β-lactams and the h-Woodward coefficient. **(A)** General bicyclic β-lactam structure rendered to show pyramidal nitrogen. **(B)** Depiction of h-Woodward, defined by height of nitrogen to trigonal pyramid ligand base. **(C)** Faropenem depicted in stick form. **(D)** Faropenem energy minimized (using MOE with the Amber10:ETH forcefield) and angle of the bent nitrogen bonds showing the h-Woodward of 0.5 Å.

exhibiting shorter aqueous and biological half-lives. For each compound examined, a self-consistent field calculation with geometry optimization was carried out using the modified neglect of diatomic overlap (MNDO) algorithm. The height of the trigonal pyramid with the lactam nitrogen at its apex and the nitrogen's three bonded substituents at its base (i.e., *h*-Woodward) was measured for the optimized structure. However, the trend is not perfect, for example, clavulanate, while among the most reactive of the β–lactams, exhibits poor antibacterial activity against many organisms.

When the Lactamome was colored according to *h*-Woodward, an interesting pattern emerged (**Figure 5C**). Monobactams, except for tigemonam, exhibited the lowest *h* values, most of the cephems exhibited relatively low *h* values, and the first-through-third generation penams occupied the middle range of Woodward height. Carbapenems and the oxapenem, clavulanate, with its additional ring strain from the unsaturation at C2, demonstrated the highest *h*-Woodward values of all of the β-lactams analyzed herein. Using the Woodward parameter as a measure of reactivity may therefore serve as a guide to the relative ease of hydrolytic decomposition of β-lactams, with monobactams representing the least susceptible.

Because the β-lactams are minimally metabolized *in vivo*, their serum half-lives are largely determined through primary renal clearance. As exceptions, the ureido class (e.g., cefoperazone, piperacillin) undergo significant biliary clearance. Lactams that are more susceptible to hydrolysis tend to have greater activity, but also exhibit shorter biological half-lives. For example, carbapenems and penams tend toward lower plasma stability than cephems. Hydrolytic instability is one of the main reasons that many β-lactam antimicrobials need to be administered parenterally, reconstituted at the bedside or refrigerated, and dosed on a strict and frequent schedule. Compounds possessing unique pharmacokinetic properties not representative of their class may have markedly divergent half-lives. For example, ceftriaxone, ertapenem, and temocillin exhibit extensive protein binding ($t_{1/2} > 6$ h), and both cephalothin and cefotaxime are rapidly converted to their desacetyl metabolites ($t_{1/2} < 1$ h). An interesting recent development involving the fermentation isolation of clavulanate focused heavily on the minimization of its hydrolysis to improve its yield during manufacturing (Veeraraghavan et al., 2021).

While short serum half-lives may present challenges during administration of β-lactams, the increased rate of degradation *in vivo* may reduce the risk of occupational and environmental exposure after excretion. Such susceptibility to hydrolysis *ex vivo* can be exploited by chemical processes to decontaminate residues during manufacturing, compounding, and administration, as well as by waste-water treatment facilities to further reduce environmental hazards.

Antibacterial Efficacy

While the optimal antibiotic strategy for patient care requires consideration of many factors, a primary criterion is the susceptibility of the infectious bacterial strain. Using The Sanford Guide to Antimicrobial Therapy (Gilbert et al., 2020), a "heat map" of susceptibility trends for β-lactam coverage by organism ultrastructure and metabolism was generated (**Figure 6**). When looking at the fractional activity against general classes of pathogenic bacteria, several specific patterns emerge. None of the β-lactams are particularly effective against cell wall-deficient microbes, which mostly include intracellular pathogens like mycoplasma and *Chlamydia trachomatis*. However, for infections typically caused by Gram-negative and Gram-positive bacteria, β-lactams present a myriad of options for good empiric or specific coverage. When comparing spectrum of activity versus *h*-Woodward values, a weak but correlative relationship is apparent. Beta-lactams with higher values generally exhibit broader spectrum of activity within and across groups of microbes than β-lactams with lower *h*-Woodward values. Notably, the monobactam aztreonam has the lowest *h*-Woodward value and a very narrow spectrum of activity.

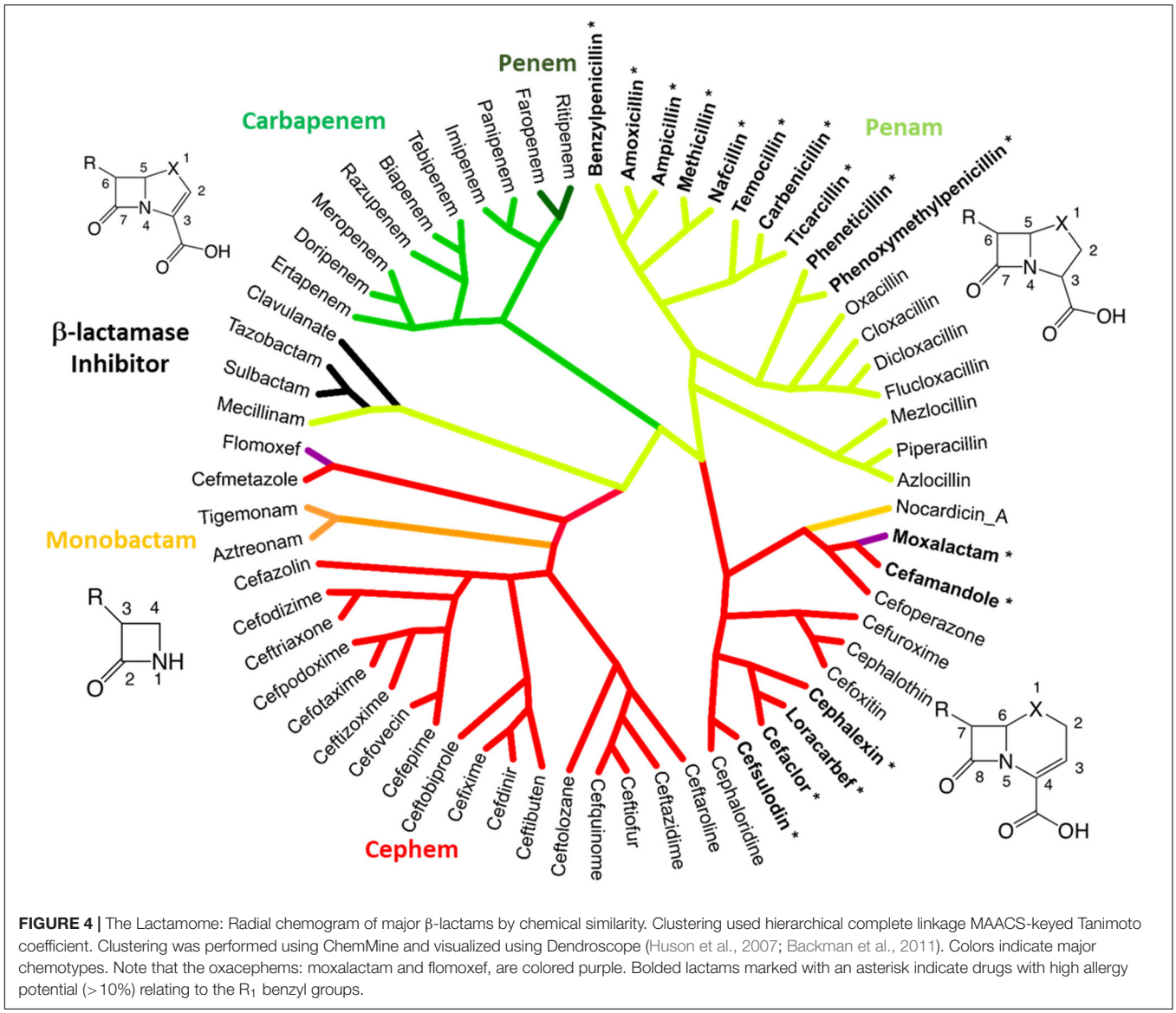

FIGURE 4 | The Lactamome: Radial chemogram of major β-lactams by chemical similarity. Clustering used hierarchical complete linkage MAACS-keyed Tanimoto coefficient. Clustering was performed using ChemMine and visualized using Dendroscope (Huson et al., 2007; Backman et al., 2011). Colors indicate major chemotypes. Note that the oxacephems: moxalactam and flomoxef, are colored purple. Bolded lactams marked with an asterisk indicate drugs with high allergy potential (>10%) relating to the R_1 benzyl groups.

However, there are several exceptions, notably the relatively narrow spectrum of activity with nafcillin and oxacillin. As mentioned previously, this is due to the many factors affecting microbial killing, including site accumulation (particularly relevant in Gram-negative pathogens) and target affinity.

Good antimicrobial stewardship requires the use of an antimicrobial with the narrowest possible spectrum, but which still provides a high likelihood of infection clearance. For this reason, clinicians need to think about the most likely pathogens involved in specific infectious processes to guide an appropriately targeted empiric therapy. Targeted therapy also highlights the sustained need for rapid, cost-effective, and accurate diagnostics. As an example, absent other risk factors, cellulitis is generally caused by *S. pyogenes* or methicillin-susceptible *S. aureus* (MSSA). This condition can be treated effectively with nafcillin, any of the oxacillin subclass, or a first-generation cephalosporin like cefazolin. Cefazolin is also a safe alternative for patients with nafcillin hypersensitivity (Gandhi et al., 2021). Coverage should be expanded only with good reason, including colonization with methicillin-resistant *S. aureus* (MRSA), open wounds, or specific exposures (e.g., *Vibrio vulnificus* with saltwater exposure or *Aeromonas hydrophila* with freshwater exposure). One of the key deficiencies of the β-lactam class is its minimal activity against atypical and intracellular pathogens, as they are more resistant to alterations in peptidoglycan synthases. Non-lactam drugs–tetracyclines, macrolides, and fluoroquinolones–are likely more appropriate treatments for these microorganisms due to the variety of anti-infective mechanisms.

Special consideration should be given to infections with highly resistant organisms that have been verified with culture-based methods or nucleic acid amplification testing (NAAT). Conditions in which *Pseudomonas aeruginosa* is commonly implicated include burn wounds, healthcare-associated pneumonia, diabetic ulcers, and cystic fibrosis. For

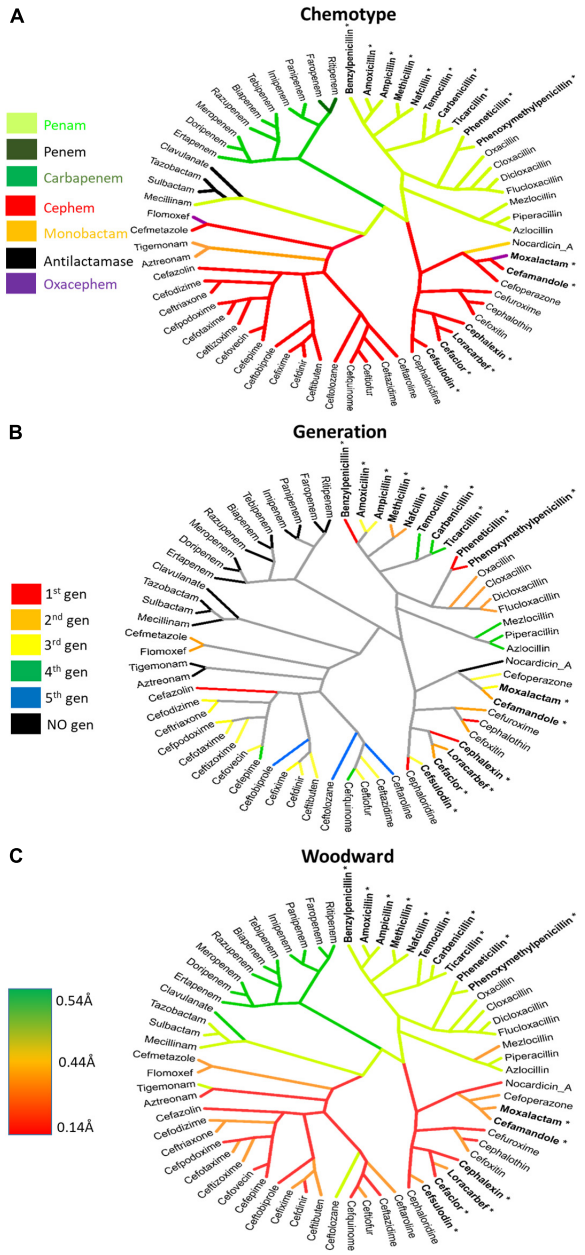

FIGURE 5 | Lactamomes depicting **(A)** chemotype, **(B)** compound generation, and **(C)** *h*-Woodward values. **(A)** The chemotype is a reproduction of **Figure 4** to aid comparisons to the other figures. **(B)** The generational lactamome assigns generation levels (1st–5th) to individual drugs based on how they most currently referenced in literature. Individual drugs that do not conform to generational naming are colored in black. **(C)** *h*-Woodward lactamome is colored using a heatmap with higher *h*-Woodward values in green and lower *h*-Woodward values in red. Bolded lactams marked with an asterisk indicate drugs with high allergy (>10%) relating to the R_1 benzyl groups.

patients with these conditions, only a handful of β-lactam options exist, including ceftolozane-tazobactam, piperacillin-tazobactam, ceftazidime, cefepime, and carbapenems (except for ertapenem). Until the approval of ceftaroline, β-lactams were largely ineffective against MRSA; and were less commonly used than glycopeptide macrocyclic agents like vancomycin and daptomycin. Guidelines stipulate ceftaroline as a last-resort option for treatment of microbiologically proven cases of vancomycin-intermediate *S. aureus* (VISA, generally defined as vancomycin MIC ≥ 2 μg/mL) for which daptomycin cannot be used (e.g., lung infections). Ceftobiprole, though not yet approved in the United States, will likely occupy a similar niche.

Extended-spectrum β-lactamase (ESBL) producing strains of *E. coli* and *Klebsiella* spp. have become increasingly common in intra-abdominal infections as well as urinary tract infections. Carbapenems retain activity against these strains due to their remarkable β-lactamase stability, and newer agents employing diazabicyclooctane (DBO) β-lactamase inhibitors (e.g., ceftazidime-avibactam, imipenem-relebactam, and aztreonam-avibactam, which is still in development) also are effective. Carbapenemase-producing Gram-negative enterics also have emerged, for which combinations of carbapenems with DBOs and boronic acids (e.g., imipenem-relebactam and meropenem-vaborbactam) remain clinically efficacious. As with all infectious treatments the spectrum, dose, route of administration, and drug allergy should be carefully considered.

Streptococcus pyogenes (also known as or Group A *Streptococcus* or GAS) is the causative pathogen in several human diseases, including pharyngitis, scarlet fever, and necrotizing fasciitis. The susceptibility of this organism to β-lactams has remained remarkably consistent over many decades although there are recent indications that mutations in the gene encoding a PBP are widespread and can result in reduced susceptibility (Macris et al., 1998; Musser et al., 2020). However, given the historically consistent susceptibility, it was selected as a model organism to examine further the potential relationship between *h*-Woodward values and susceptibility to β-lactam antibiotics. The data were extracted from 95 different studies involving 10 strains of *S. pyogenes* (Wallmark, 1962; Adams, 1963; Sidell et al., 1963; Gravenkemper et al., 1965; Thornhill et al., 1969; Bergeron et al., 1973; Eykyn et al., 1973, 1976; Neu, 1974b, 1976; Shibata et al., 1975; Ernst et al., 1976; Goto, 1977; Stewart and Bodey, 1977; Bodey and Le Blanc, 1978; Chabbert and Lutz, 1978; Verbist, 1978; Wise et al., 1978, 1980, 1988, 1991; Fass, 1979, 1990; Kamimura et al., 1979, 1984; Neu et al., 1979, 1981, 1984, 1989; Watanakunakorn and Glotzbecker, 1979; Weaver et al., 1979; Angehrn et al., 1980; Fu and Neu, 1980; Greenwood et al., 1980; Hinkle et al., 1980; Baker et al., 1981; Bodey et al., 1981, 1985; Cherubin et al., 1981; Eickhoff and Ehret, 1981; Istre et al., 1981; Jones et al., 1981, 1984; Stamm et al., 1981; Tsuchiya et al., 1981; Ahonkhai et al., 1982; Fainstein et al., 1982; Scully et al., 1983; Kessler et al., 1985; Toda et al., 1985; Une et al., 1985; Vuye and Pijck, 1985; Neu and Chin, 1986; Okamoto et al., 1987; Mine et al., 1988; Shelton and Nelson, 1988; Kayser et al., 1989; Yu and Neu, 1989; Arisawa et al., 1991; Chin et al., 1991, 1992; Emberton and Finlay, 1991; Limbert et al., 1991; Poch et al., 1992; Yan et al., 1993; Coonan and Kaplan, 1994; Tsuji et al., 1995, 1998; Suzuki et al., 1996; Cocuzza et al., 1997; Woodcock et al., 1997; Fontana et al., 1998; Kriebernegg et al., 1998; Sakagawa et al., 1998; Yamaguchi et al., 1998; Fuchs et al., 2001; Livermore et al., 2001; Pendland et al., 2002; Iizawa et al., 2004; Marchese et al., 2004;

Lev et al., 2005; Stefani et al., 2008; Tempera et al., 2010; Camara et al., 2013; Fujimoto et al., 2013; Sakata, 2013; Yang et al., 2015; Yanik et al., 2015; Cotroneo et al., 2020; Jean et al., 2020; Musser et al., 2020; Ubukata et al., 2020; Yanagihara et al., 2020).

As seen in the upper portion of **Figure 7**, β-lactams with higher *h*-Woodward values are the most potent options against *S. pyogenes*. Drugs with the lowest minimum inhibitory concentration values against 50% of the population (MIC_{50}) also exhibit the lowest variation among different strains. Median susceptibility decreases (increased MIC_{50}) at intermediate and higher *h*-Woodward values, although the overall trend suggests a parabolic relationship where drugs with intermediate *h*-Woodward values exhibit the lowest potency. Taken by class, penems are generally more biologically active than penams (0.007 vs. 0.024 μg/mL), and both exhibit greater efficacy than cephems (0.074 μg/ml). Aztreonam, the lone monobactam in use, was found to exhibit the lowest efficacy against *S. pyogenes* with a mean MIC_{50} of 16.5 μg/ml. The results of this analysis align with the previous observations related to the heat map, previously presented as **Figure 6**, that *h*-Woodward values impact antibacterial activity both within strains of *S. pyogenes* and across different groups of bacteria.

Allergy and Other Immune Reactions

Hypersensitivity to β-lactams is among the most commonly reported drug allergies, representing 42.6% of all drug-induced anaphylaxis (Zagursky and Pichichero, 2018). However, prevalence is likely over-reported due to misinterpretation of mild drug reactions (e.g., diarrhea, mild drug rash, attribution of illness symptoms to drug). In fact, many individuals with reported β-lactam allergy can tolerate β-lactams due to this misattribution, and many of those with remote history of true allergic reaction are sometimes able to tolerate the drugs years later due to waning sensitivity (Romano et al., 2014). Even so, β-lactam allergy remains a clinically relevant problem, with skin testing generally yielding confirmed rates around 8% (3–10%) for penicillins and 1% (1–2%) for cephalosporins. Hypersensitivity to carbapenems and monobactams is rarer.

Allergy is a result of immune activation in response to specific β-lactam substituents (**Figure 1** and **Supplementary Spreadsheet**). The 2-azetidinone ring acts as a hapten, covalently modifying nucleophilic residues on host proteins to elicit an IgE response in individuals with specific human leukocyte antigen allotypes (**Figure 8**). While this covalently bound β-lactamoyl protein adduct is the major determinant of hypersensitivity, hydrolyzed small molecule products also can elicit some response.

Beta-lactam allergy is an immunologic type I hypersensitivity reaction, meaning that it occurs through mast cell degranulation in response to preformed IgE binding antigen recognition receptors (FcRε) on the mast cell surface. Subsequent release of histamine results in symptoms related to vasodilation (warmth and erythema), increased capillary permeability (edema), bronchoconstriction (dyspnea), and nociceptive stimulation (pain and pruritus). These symptoms are potentiated by the release of inflammatory eicosanoid derivatives, including prostaglandin D2, leukotriene B4, and leukotriene C4. In mild cases, this manifests as hives or wheezing, but in patients with high IgE titers, the reaction may proceed to anaphylaxis or anaphylactic shock. Because of the potential severity of the reaction, in addition to the poor accuracy of self-reporting mentioned above, identification of patients with true allergy through skin testing or measuring IgE against β-lactam products is critical to avoiding significant morbidity and mortality.

While not part of the group of IgE-mediated allergic syndrome, other significant immune reactions to the β-lactam class exist as well that are thought to occur through parallel mechanisms. Drug-induced immune hemolytic anemia (DIIHA) is a type II hypersensitivity reaction mediated by direct binding of IgG to erythrocytes, seen with relatively high frequency in β-lactam-treated subjects. One longitudinal study, documenting causes of DIIHA in Southern California over 30 years estimates that over 80% of cases are due to β-lactams (Garratty, 2009). Eosinophilic reactions are common as well, including drug-induced hypersensitivity syndrome (DiHS) with multiorgan involvement (previously known as drug reaction with eosinophilia and systemic symptoms or DRESS) caused by covalent modification of host proteins. Mucocutaneous eruption syndromes with epidermal detachment are also possible, arising from the activation of cytotoxic T-cells against keratinocytes.

There is a growing body of evidence suggesting the substituent adjacent to the lactam carbonyl (**Figure 1**), referred to as R_1, is the primary driver of immunogenicity. Indeed, immunologic cross-reactivity is most often seen against structurally similar R_1 groups of penams and cephems (i.e., ampicillin and cephalexin). One of the most prominent β-lactams associated with allergy is cefamandole, whose R_1 is a hydroxybenzyl with a terminal aromatic. This structural relationship is not only common to such compounds as cephalexin (possessing an aminobenzyl moiety) but also to cephalothin, whose R_1 aromatic is a thiophene, and cefuroxime whose R_1 aromatic is a furan. These compounds, therefore, possess similar electronic and steric properties, or bioisosteric profiles. Such end group topology and electronic properties may play determinative roles in allergen character, possibly due to three-dimensional shape ("lock and key") factors.

Compounds with 10% allergy response and containing similar aromatic R_1 end groups have been bolded and tagged with asterisks in **Figure 4**. One careful study recommends skin reactivity testing for both penicillin and cephalosporin as 11% displayed positive skin test responses to the cephalosporin class, and 64% of cross-reactive patients responded negatively to cefamandole (Romano et al., 2004). In another study of 252 penicillin-allergic patients, ∼39% of patients treated with the cephalosporins cefaclor, cephalexin, cefadroxil, or cefamandole had an allergic response (Romano et al., 2018). Both studies show low cross-reactivity between penicillins and later-generation cephalosporins, such as ceftriaxone (∼3%). R_1 groups containing phenyloxazole and piperazine also account for ∼3% of allergies. In cases where a patient may react in tests to dissimilar β-lactams, it is likely not due to true cross-reactivity, but rather to independent sensitivity to each drug. The low rate of cross-reactivity seen between penicillin and carbapenems (<1%), which possess a unique hydroxyethyl side chain, further supports the hypothesis that not only does the R_1 bioisosterism play

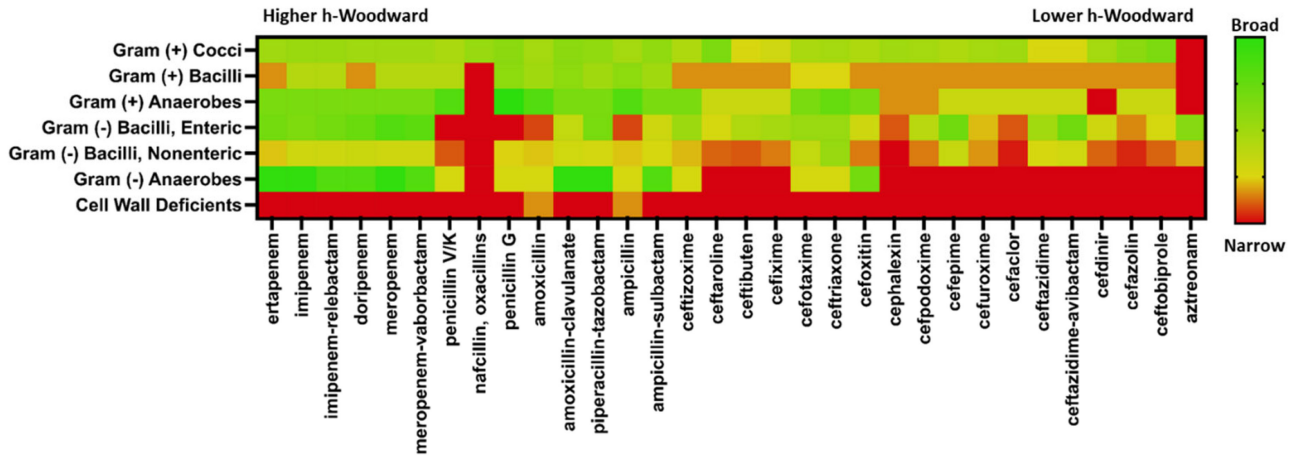

FIGURE 6 | Antimicrobial spectra of β-lactams. Clinical activity data were taken from The Stanford Guide to Antimicrobial Therapy. A fractional coverage index was calculated using a weighted average of categorical coverage values reported. Heatmap color range is from green indicating high coverage and red indicating low coverage. Beta-lactams are ordered from highest *h*-Woodward value (ertapenem) to lowest (aztreonam).

a dominant role, but aromatic end group chemistry appears causative (Romano et al., 2006, 2007; Atanaskovic-Markovic et al., 2008; Gaeta et al., 2015; Buonomo et al., 2016). Although not utilized on their own as an antibacterial therapy, β-lactam based β-lactam inhibitors also have been implicated in allergic reactions (Stover et al., 2019). The authors concluded that cross-allergenicity with β-lactams is likely with sulbactam and tazobactam. Cross-allergenicity is less likely with clavulanate, but still possible.

The involvement of the R_2 side group in allergic response is the subject of greater uncertainty. While structural similarity of R_2 has been considered as a possible factor, this group is frequently lost during ring opening, and any role it plays is generally quite small in comparison to the R_1 side group. In the context of a β-lactam allergy, clinicians often look to different antimicrobial classes as alternatives. However, if the agent to which the patient has had an immune reaction is known, they may be able to use β-lactams of similar spectrum but differing chemical structures, both with regard to class and R_1. For example, if a patient has had a severe reaction to amoxicillin in the past, cefpodoxime proxetil (a prodrug formulation) may be a suitable oral alternative due to its differently structured R_1.

Similarly, clinicians often cite an allergy to penicillin G or amoxicillin as reason to avoid other penams, occasionally utilizing drugs of last defense when they might not be needed. As a clinical example, piperacillin-tazobactam is frequently avoided in the setting of a penicillin G allergy in favor of cefepime for similar Gram-negative enteric and pseudomonads coverage. Many clinicians, wary of cross-reactivity, will even avoid the cephalosporin class and prescribe a carbapenem. However, penicillin allergy may not preclude the use of piperacillin-tazobactam, as the benzyl functionality of penicillin G, to which the reaction likely occurred, is structurally very different from the R_1 groups of cefepime or nitrogen-substituted R_1 of piperacillin. For this reason, it is critical to keep accurate record of the β-lactam-based drugs to which the patient has reacted, as well as the type and severity of said reaction, so as to determine which other agents they are not likely to tolerate.

Exposure and Environmental Concerns

Although β-lactam antibiotics do not meet the criteria for hazardous drugs established by the National Institute of Occupational Safety and Health (NIOSH), manufacturing and compounding of these drugs requires attention to reduce the risk of cross-contamination or occupational exposure to sensitive individuals. Current good manufacturing practice (cGMP) regulations require the use of methods to address cross-contamination [e.g., Title 21, Sections 211.42(d), 211.46(d), and 211.176 of the Code of Federal Regulations]. To further assist manufacturers, the FDA issued a draft guideline in 2013 entitled "Non-Penicillin Beta-Lactam Drugs: A cGMP Framework for Preventing Cross-Contamination" (Food and Drug Administration [FDA], 2013). Although most compounding pharmacies are 503a-type facilities and not required to operate under cGMP, the FDA often applies the described guidelines to pharmacy compounders. The guidelines are quite restrictive, including requiring segregation of "facilities" for "operations relating to the manufacture, processing, and packing" of β-lactam antibiotics. Additionally, an updated guidance document regarding insanitary conditions at compounding facilities was issued in November 2020 (Food and Drug Administration [FDA], 2020). It lists several examples of insanitary conditions applicable to the production of sterile and non-sterile drug, including: "Processing of β-lactams without complete and comprehensive separation from non-β-lactam products." While segregation may not be absolutely required (or feasible) for all compounding activities, it is important to reduce the risk of cross-contamination through effective decontamination of surfaces and equipment after manipulations involving β-lactam antibiotics.

Another concern involves the environmental persistence of antibiotics, including β-lactams, in the environment. Antibiotics

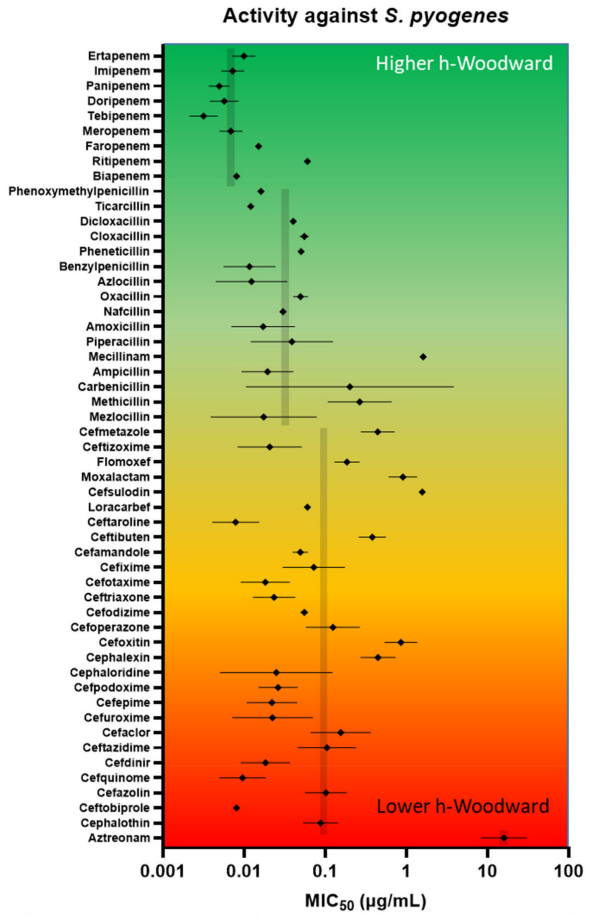

FIGURE 7 | *In vitro* antimicrobial activity of lactams against *S. pyogenes*. A review of the literature on Gram-positive β-lactam activity was conducted in which susceptibility data were gleaned from 95 studies reporting data for at least 10 strains. MIC_{50} (presented as log values) were amassed, and geometric mean and geometric standard deviation were calculated. Geometric means for entire classes (e.g., penems) are shown in gray. Beta-lactams are ordered from highest *h*-Woodward value (ertapenem) to lowest (aztreonam).

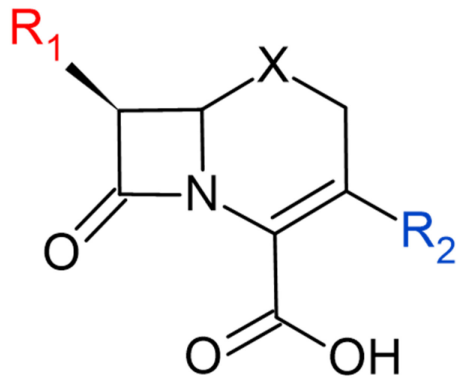

FIGURE 8 | Structural representation of R_1 and R_2 chemical groups in cephem backbone.

used to treat humans and livestock can escape into the environment by several routes, including improper disposal and excretion through urine and feces (Kivits et al., 2018; Szekeres et al., 2018). Conventional waste-water treatment processes are not effective at removing or destroying these drugs (Song et al., 2019). Persistence of these drugs in the environment can therefore result in selective pressures on environmental bacteria, leading to development of resistance genes which then may be transferred to human or animal pathogens (Bengtsson-Palme et al., 2018). β-lactams with intermediate or high *h*-Woodward values are more susceptible to decontamination *via* alkaline or acid hydrolysis at the 2-azetidinone ring (Lang et al., 1978). The kinetics of inactivation by such processes are related to the extent of ring activation. Thus, cephems tend to be more resistant to degradation, followed by penams, while carbapenems are the most susceptible.

While further studies are needed, there is evidence that oxidizing agents may decontaminate β-lactam antibiotics (Lorcheim, 2011; He et al., 2014; Zhang et al., 2017). These chemicals commonly are used for disinfection of surfaces contaminated with β-lactam antibiotics as well as in waste-water treatment systems. Additional research should establish how oxidizers such as peracetic acid, hydrogen peroxide, and hypochlorous acid would perform as decontamination strategies within the four major classes of β-lactam antibiotics, and whether such oxidants would differ in efficacy by pH and h-Woodward.

CONCLUSION

β-lactams remain an important and highly utilized class of antibiotics. In the outpatient setting, amoxicillin and cephalexin are consistently among the most prescribed drugs in the United States, and ceftriaxone and piperacillin-tazobactam are staples of empiric inpatient treatment. Over their decades of prominence, however, concerns have arisen among clinicians and laboratories regarding their efficacy and environmental persistence. Among these concerns are serious allergic responses and acquisition of drug resistance by environmental bacteria.

While non-β-lactam antibiotics have gained increased attention, the utility of β-lactam antibiotics remains important, not only in the human clinical situation but also in a wide array of veterinary uses. The current 5th generation β-lactam are undergoing clinical trials and new β-lactams are expected to see less development, as non-β-lactam antibiotics, and combinations of β-lactams with lactamase inhibitors take center stage (**Figure 5B**). The current work structurally classified the β-lactam class of antimicrobials to aid clinical decision making, as well as inform patient, worker, and environmental safety. We have organized our structural analysis into an easily visualized tool, the Lactamome (**Figure 4**), which can be colorized according to several chemical properties, including overall molecular shape (**Figures 3**, **5A**) and propensity for

reaction with nucleophiles, i.e., *h*-Woodward (**Figure 3**). It should also be noted that when colored by allergic potential, one would obtain a chemogram strongly resembling **Figure 5C**, depicting h-Woodward.

The *h*-Woodward colored Lactamome (**Figure 5C**) indicates that higher values for penems and penams (**Figures 2**, **5**) would be the most susceptible to chemically catalyzed degradation. This greater propensity for hydrolysis is important in reducing occupational exposures, especially given that the highest rate of reported β-lactam hypersensitivity is to the penam class. Logically, more stringent cleaning is needed if a more allergy-prone lactam is used, but fortunately, the penams' high *h*-Woodward values indicate decontamination protocols involving hydrolysis should be efficient. In the case of cephems, while their overall rate of allergenicity is somewhat lower than that of penams, many first-generation agents from this subclass have high structural similarity to the first-generation penams (e.g., penicillin and cephalexin) and are, therefore, more likely to be allergens (**Figure 5B**). Therefore, care should be taken in the decontamination of surfaces or areas exposed to those cephems with a higher possibility for cross-reactivity.

Antibacterial efficacy also appears to trend with *h*-Woodward values. Drugs with higher h-Woodward values tend to have lower MICs against *S. pyogenes* and activity against a broader spectrum of bacteria (**Figure 7**). However, given the multitude of mechanisms involved with susceptibility across different species and types of bacteria, it is not clear if *h*-Woodward values would be a reliable criterion for matching β-lactams with particular pathogens (**Figure 6**). It is apparent that the "generational" nomenclature is a function of product development over time and generally is not well correlated with molecular structure or activity.

Unlike the correlation of *h*-Woodward values with both high intrinsic potency and high hydrolysis potential, allergenicity is impacted by additional factors, including the position of the R_1 group (**Figure 8**). In terms of selecting alternate β-lactams due to allergy, the Lactamome, when used in combination with the spectrum data (**Figure 6**) provides information for treatment options. These analyses also may guide future studies of efficacy to broaden recommended uses of known β-lactams. For example, if a patient with spontaneous bacterial peritonitis has a documented anaphylactic response to empiric cefotaxime, they are likely to have an adverse reaction to structurally similar ceftriaxone as well. In these situations, guidelines suggest a fluoroquinolone as the next suitable option. Using the structure and spectrum data presented, however, one might consider ampicillin-sulbactam, a decision for which positive data exists but a full-scale prospective non-inferiority trial has not been conducted (Guo et al., 2019).

The structural characterization presented in this study may provide a helpful guide to selecting antibiotic agents, especially for persons having certain allergic response histories, as well as to inform proper decontamination methods. The Lactamome may assist clinicians in assessing structural similarity and therefore help recognize, relatively speaking, which drug would be most effective, but exhibit lower risks of clinical cross-sensitivity. By first grouping the β-lactam antibiotics and then using coloring schemes, it is possible to quickly probe the entire genus. The Lactamome should also be useful in alerting practitioners to potential workplace hazards and assist in the development of decontamination strategies to reduce the risk of cross-contamination, occupational exposure, and environmental persistence.

AUTHOR CONTRIBUTIONS

All authors conceived and wrote the manuscript together. JT generated the spectrum and activity graphs. YP and AM generated the lactamome chemograms.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmicb.2022.807955/full#supplementary-material

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LP and MW were employed by Contec, Inc. MB was employed by Intramed Plus.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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