Egypt. J. Chem. **Vol.** 68, SI: Z. M. Nofal, pp. 1161- 1174(2025)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Cephalosporins: Broad Spectrum Antibiotics-An Updated Review for Healthcare Professionals

Mohammed Rashed Aldhahri[1*], Ahmed Abdulkarim Sulaiman Alnughaymishi[1], Bandar Zaben Muhammad Alharbi[1], Rashed Obaid Al-Harbi[1], Thamer H. Aljuaid, Waleed Abdullah Alghamdi[2], Abdulrahman Abdullah Nazal Al-Anzi[2], Reem Mahmoud Nashar[2], Waad Ali Alshehri[2], Wejdan Saleh Alghamdi[2], Njoud Abdulrhman Almousa[2], Alhanouf Saad Bin Serran[2], Malath Ali Salami[2], Reema Ali Salami[2], Amal Hajjan Alanazi[2], Abdullah Mohammed Asiri[2]

[1]*Ministry of National Guard Health Affairs, Saudi Arabia*
[2]*Ministry of Defense, Saudi Arabia*

Abstract

Background: Cephalosporins are cornerstone β-lactam antibiotics arranged into five generations that progressively expand gram-negative activity while preserving gram-positive coverage across common and severe infections.

Aim: To synthesize practice-oriented guidance on spectrum, mechanisms, pharmacokinetics, indications, safety, contraindications, monitoring, and toxicity.

Methods: Narrative review of the supplied article integrating generational profiles, cefiderocol approvals, population-specific dosing, adverse effects, and stewardship themes.

Results: First generation targets staphylococci/streptococci; second adds respiratory gram-negatives and anaerobes; third broadens Enterobacteriaceae with CNS penetration (ceftazidime provides antipseudomonal activity); fourth-generation cefepime adds β-lactamase stability and antipseudomonal activity; fifth-generation ceftaroline uniquely covers MRSA. Cefiderocol, a siderophore cephalosporin, is FDA-approved for complicated UTI and ventilator-associated pneumonia due to resistant gram-negative bacilli. Safety issues include hypersensitivity, drug-induced immune hemolytic anemia, N-methyl-thiotetrazole–associated hypoprothrombinemia and disulfiram-like reactions, and antibiotic-associated *Clostridioides difficile* colitis. Contraindications include cephalosporin allergy, anaphylaxis to β-lactams, and neonatal ceftriaxone in hyperbilirubinemia or with calcium. Monitoring focuses on renal function, PT/INR, and hemolysis labs; cefepime neurotoxicity is the hallmark of overdose, and careful dose adjustment in renal impairment is essential.

Conclusion: Cephalosporins remain versatile and effective; optimal outcomes require tailored selection and stewardship, while cefiderocol extends options against carbapenem-resistant gram-negatives.

Keywords: cephalosporins; β-lactam; cefiderocol; MRSA; *Pseudomonas aeruginosa*; pharmacokinetics; drug interactions; contraindications; toxicity; antimicrobial stewardship.

1. Introduction

Cephalosporins constitute a major class of β-lactam antibacterial agents that are widely deployed in the management of infections caused by both gram-positive and gram-negative organisms. As with other β-lactams, their core pharmacodynamic effect arises from the inhibition of bacterial cell-wall synthesis through binding to penicillin-binding proteins, culminating in defective peptidoglycan cross-linking and bactericidal activity. Over decades of development, cephalosporins have been systematically organized into five "generations," a convention that reflects both their chronological introduction and, more importantly, the progressive broadening and shifting of their antimicrobial spectra. This generational framework, while a simplification, remains clinically useful for anticipating coverage patterns and selecting empiric or targeted therapy in diverse settings. Across these generations, agents have demonstrated proven efficacy in common and serious infections alike, including but not limited to skin and soft tissue infections, community- and hospital-acquired pneumonia, meningitis, and other invasive syndromes in which reliable bactericidal therapy is required. The distinction among generations is anchored in observable differences in activity against gram-positive cocci and gram-negative bacilli, together with meaningful enhancements in stability to β-lactamases and, for certain agents, improved penetration into sanctuary sites such as the central nervous system. First-generation compounds concentrate their activity on gram-positive pathogens, with modest gram-negative coverage; subsequent generations introduce stepwise expansion against respiratory and enteric gram-negative organisms, as well as, in later generations, improved resilience to β-lactamase–mediated resistance. Notably, the fifth generation includes agents specifically engineered to retain broad coverage while addressing clinically important resistant gram-positive organisms. Taken together, cephalosporins offer a versatile therapeutic armamentarium whose selection is guided by the suspected pathogen profile, local epidemiology, site of infection, and patient-specific considerations such as route of administration and organ function.

*Corresponding author e-mail: aldhahrymo@mngha.med.sa (Mohammed Rashed Aldhahri)
Receive Date: 15 July 2025, Revise Date: 17 September 2025, Accept Date: 02 October 2025
DOI: 10.21608/ejchem.2025.404366.12049

First generation. The first-generation cephalosporins—comprising cefazolin, cephalothin, cephapirin, cephradine, cefadroxil, and cephalexin—exemplify strong activity against most gram-positive cocci, particularly *Staphylococcus* (methicillin-susceptible) and *Streptococcus* species. Their gram-negative spectrum is comparatively limited but reliably includes *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae*. In clinical practice, these characteristics translate into frequent use for uncomplicated skin and soft tissue infections, such as cellulitis and purulent abscesses, where the etiologic agents are most commonly staphylococci or streptococci. The availability of oral formulations (e.g., cephalexin, cefadroxil) facilitates outpatient management of such infections, whereas parenteral cefazolin is favored when intravenous therapy is indicated, whether due to disease severity, concerns about absorption, or the need for high and consistent serum concentrations. Beyond dermatologic applications, first-generation agents are deployed across a range of infectious syndromes in which susceptible organisms are likely or confirmed. These include osteoarticular infections, select respiratory tract infections, urinary and biliary tract infections, bacteremia when the pathogen is susceptible, and otitis media. A particularly salient and enduring role is surgical prophylaxis: cefazolin has emerged as the cephalosporin of choice for many clean-contaminated procedures because of its favorable pharmacokinetic profile, broad staphylococcal and streptococcal coverage, and safety record. In specific circumstances, first-generation cephalosporins are also utilized off-label for endocarditis prophylaxis in at-risk individuals undergoing dental or respiratory tract procedures, reflecting their reliable activity against common oropharyngeal flora when indicated [1][2][3].

Second generation. Second-generation cephalosporins are historically stratified into two subgroups: the "true" second-generation agents, represented by cefuroxime and cefprozil, and the cephamycins, including cefmetazole, cefotetan, and cefoxitin. This subdivision mirrors important microbiologic distinctions. Within the first subgroup, cefuroxime demonstrates enhanced efficacy against *Haemophilus influenzae* and is therefore frequently selected in scenarios where this pathogen is suspected. Clinically, an additional niche for cefuroxime is as a therapeutic option for Lyme disease in pregnant women and children, offering a β-lactam alternative to tetracyclines in populations where those agents are contraindicated. The cephamycin subgroup is notable for increased anaerobic activity, particularly against *Bacteroides* species, thereby extending utility to infections arising in anatomic sites where anaerobes contribute materially to the pathogen mix. Relative to the first generation, second-generation cephalosporins generally exhibit slightly reduced potency against gram-positive cocci; however, this is offset by significantly improved activity against gram-negative bacilli. As a result, these agents are often selected for respiratory tract infections, including bronchiolitis and pneumonia, especially when *H. influenzae* and *Moraxella catarrhalis* are epidemiologically prominent contributors. Their therapeutic footprint otherwise overlaps with first-generation indications—spanning bone and joint infections, lower respiratory tract infections, urinary and biliary tract infections, bacteremia from susceptible organisms, otitis media, and perioperative prophylaxis—while extending gram-negative coverage to include *H. influenzae*, *Enterobacter aerogenes*, *Neisseria* species, and *Serratia marcescens* [4].

Third generation. The third-generation cephalosporins—such as cefotaxime, ceftazidime, cefdinir, ceftriaxone, cefpodoxime, cefoperazone, and cefixime—represent a major evolutionary step, characterized by further expansion of gram-negative activity and improved stability against β-lactamases produced by members of the Enterobacteriaceae. Because of this broadened spectrum, third-generation agents are frequently employed when infections are suspected or proven to be caused by gram-negative organisms resistant to earlier cephalosporins or other β-lactams. A defining pharmacologic feature of parenteral representatives like ceftriaxone and cefotaxime is their capacity to achieve therapeutic concentrations in cerebrospinal fluid, a property that positions them as foundational therapies for bacterial meningitis. In this context, ceftriaxone, in particular, is a standard agent for meningitis due to *H. influenzae*, *Neisseria meningitidis*, or *Streptococcus pneumoniae*, capitalizing on its robust activity against these pathogens and its favorable dosing characteristics. Beyond the central nervous system, ceftriaxone also maintains an important role in the management of gonorrhea and in disseminated Lyme disease, reflecting its potency against *Neisseria gonorrhoeae* and *Borrelia burgdorferi*, respectively. Within this generation, ceftazidime warrants special mention for its activity against *Pseudomonas aeruginosa*, a notoriously drug-resistant non-fermenting gram-negative bacillus that complicates many nosocomial infections and demands agents with dependable antipseudomonal performance [5]. The clinical utility of third-generation cephalosporins therefore spans a broad array of syndromes, from severe community-acquired infections to healthcare-associated bacteremias and complicated intra-abdominal or urinary tract infections caused by susceptible organisms. Their use, however, must be balanced against stewardship principles: the very attributes that make them powerful—broad gram-negative coverage and central nervous system penetration—also heighten selection pressure for resistance if overused. Consequently, targeted de-escalation once culture and susceptibility results are available remains a cornerstone of best practice.

Fourth generation. The fourth-generation cephalosporin class is represented by cefepime, a broad-spectrum agent that, like certain third-generation congeners, penetrates the cerebrospinal fluid, thereby enabling use in central nervous system infections when appropriate. Structurally, cefepime contains a quaternary ammonium moiety that enhances its ability to traverse the outer membrane of gram-negative organisms, a design feature that contributes to its potency against problematic hospital pathogens. In terms of gram-positive coverage, cefepime retains activity against *S. pneumoniae* and methicillin-susceptible *Staphylococcus aureus* (MSSA), akin to the profiles observed with cefotaxime and ceftriaxone. Of critical importance, cefepime also demonstrates reliable activity against *P. aeruginosa*, paralleling the antipseudomonal capacity of ceftazidime. Furthermore, cefepime's spectrum includes many β-lactamase–producing gram-negative bacilli, thereby offering a therapeutic option in settings where resistance to earlier cephalosporins is anticipated. Given these attributes, cefepime is commonly reserved for severe systemic infections, particularly in patients at risk for or proven to have infections with multidrug-resistant organisms, aligning its use with institutional stewardship policies to preserve its effectiveness [6]. **Fifth generation.** The fifth-generation cephalosporins currently include ceftaroline and ceftobiprole. Ceftaroline is a broad-spectrum agent that maintains activity against a range of susceptible gram-positive and gram-negative organisms; what differentiates it from earlier cephalosporins is its clinically meaningful activity against methicillin-resistant *Staphylococcus aureus* (MRSA). This distinctive attribute stems from its affinity for altered penicillin-binding proteins that confer methicillin resistance, thereby enabling ceftaroline to address a key gap in cephalosporin spectra. In addition to MRSA, ceftaroline

provides coverage of *Listeria monocytogenes* and *Enterococcus faecalis*, expanding its relevance to clinical scenarios where these organisms may be implicated. However, unlike certain earlier agents, ceftaroline does not possess activity against *P. aeruginosa*, a consideration that must inform empiric regimens when antipseudomonal coverage is required [7]. Ceftobiprole—at present pending approval by the U.S. Food and Drug Administration—likewise offers activity against MRSA, *E. faecalis*, and penicillin-resistant *S. pneumoniae*, positioning it, once approved, as a versatile option at the interface of resistant gram-positive pathogens and broader cephalosporin utility [8][9][10].

Synthesis and clinical application:

The generational trajectory of cephalosporins encapsulates a coherent strategy: preserve or refine reliable gram-positive activity where clinically vital, while progressively strengthening the ability to confront gram-negative pathogens and emerging resistance mechanisms. In everyday practice, this translates into nuanced therapeutic choices. For superficial cellulitis in an otherwise stable outpatient, an oral first-generation agent often suffices, based on the high likelihood of staphylococcal or streptococcal etiologies. By contrast, community-onset pneumonia where *H. influenzae* is suspected may favor a second-generation option such as cefuroxime, leveraging its enhanced respiratory pathogen coverage. When facing suspected meningitis, ceftriaxone or cefotaxime becomes central to initial therapy because of dependable cerebrospinal fluid penetration and targeted activity against leading meningeal pathogens; if complicating risk factors suggest *P. aeruginosa*, antipseudomonal cephalosporins like ceftazidime or cefepime must be considered. In institutions grappling with β-lactamase–producing Enterobacteriaceae or non-fermenters, cefepime stands out for serious systemic infections, whereas MRSA-predominant severe skin and soft tissue infections may prompt selection of ceftaroline when a cephalosporin backbone is preferred.

Throughout these decisions, two principles are paramount. First, the "generation" label guides but does not replace pathogen- and site-specific reasoning; the precise agent within a generation may differ meaningfully in pharmacokinetics, tissue distribution, and unique coverage nuances (e.g., ceftazidime's antipseudomonal activity within the third generation, or ceftaroline's anti-MRSA profile in the fifth). Second, antimicrobial stewardship remains essential to preserve class efficacy. Because broad-spectrum agents accelerate selection pressure for resistance, clinicians should adopt a disciplined approach: choose empiric therapy that appropriately addresses likely pathogens and severity, pursue microbiologic diagnosis expeditiously, and de-escalate to the narrowest effective agent as soon as susceptibility data permit. Such practice not only optimizes individual patient outcomes by minimizing toxicity and collateral damage to the microbiome but also contributes to the broader public health objective of curbing antimicrobial resistance.

In addition, practical considerations frequently shape cephalosporin selection. Route of administration is central: oral options in the first and second generations facilitate step-down therapy and outpatient management when patients are clinically improving and able to absorb medication reliably. Parenteral formulations, especially in the third and fourth generations, are indispensable for severe disease, bacteremia, and central nervous system involvement, where rapid attainment of high serum and tissue levels is crucial. Tissue penetration varies among agents, informing choices in osteoarticular infections, pulmonary disease, and intra-abdominal pathology. Furthermore, predictable safety profiles—most notably hypersensitivity reactions shared with other β-lactams—necessitate careful history-taking, though cross-reactivity with penicillins is lower than once feared and must be weighed against the therapeutic advantages of cephalosporins when they are otherwise indicated.

From a mechanistic perspective, the enhanced gram-negative activity observed as one progress from earlier to later generations reflects structural adaptations that facilitate traversal of the gram-negative outer membrane and reduce hydrolysis by prevalent β-lactamases. The quaternary ammonium group in cefepime is a salient example of such design, enabling robust penetration and binding that translate to reliable activity against difficult hospital pathogens. Conversely, the emergence of MRSA—driven by altered penicillin-binding proteins—necessitated a different innovation: ceftaroline's capacity to bind these modified targets restores β-lactam utility against a canonical resistant gram-positive organism. These examples underscore the dynamic interplay between microbial evolution and antibiotic development that has shaped the cephalosporin class. Finally, while the generational schema offers a practical scaffold, contemporary clinical microbiology increasingly emphasizes local resistance phenotypes and organism-specific susceptibilities over class generalizations. Thus, even as the first through fifth generations provide an essential map of expected coverage, the most precise compass is the local antibiogram coupled with patient-level culture results. Using this information to calibrate therapy—initiating appropriately broad coverage and then narrowing with intention—ensures that cephalosporins continue to deliver their well-established benefits across the spectrum of infectious diseases. In this way, the class maintains its central role in modern antimicrobial therapeutics: versatile, potent, and continuously refined to meet the shifting challenges posed by bacterial pathogens in community and healthcare settings alike.

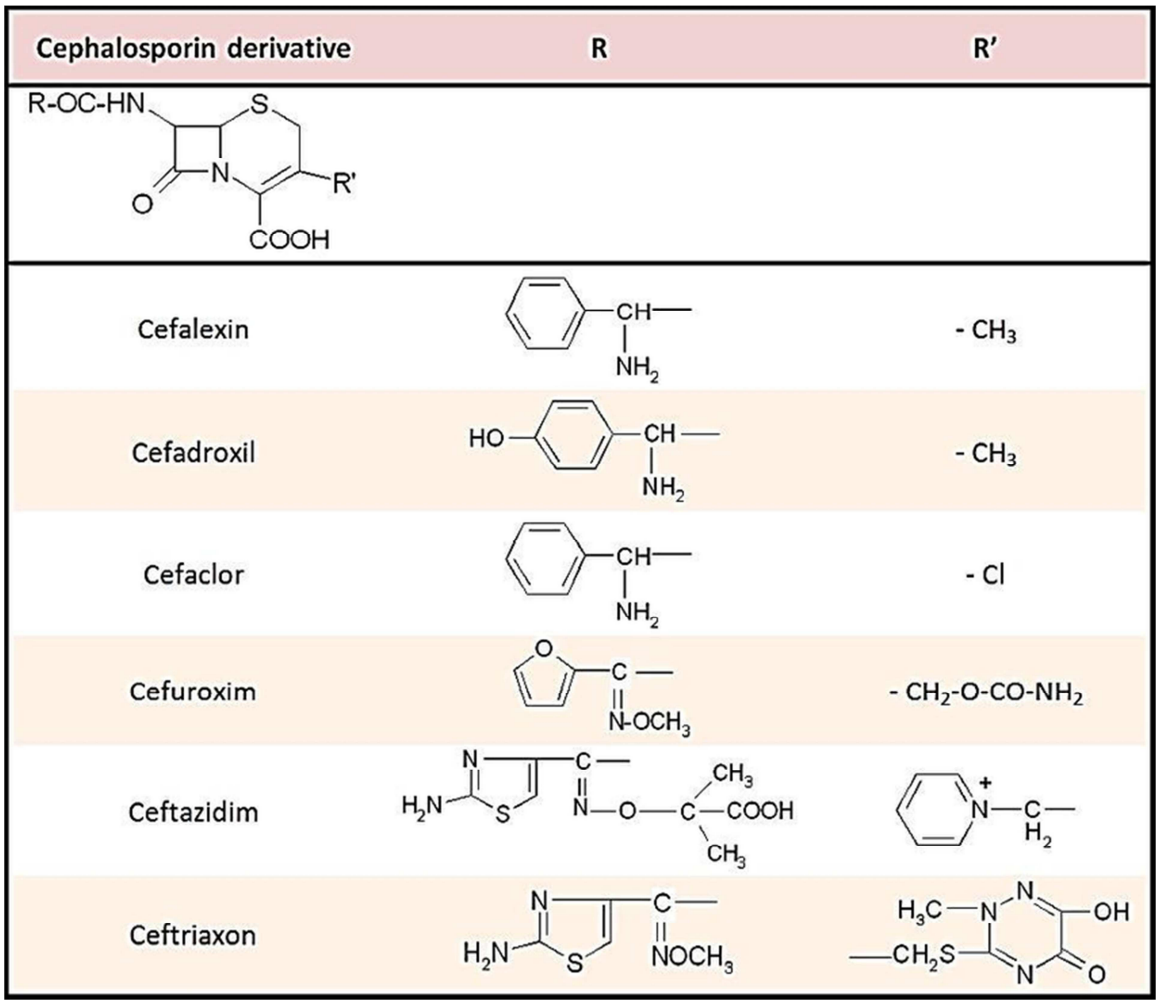

Figure-1: Cephalosporins Structure.

FDA-Approved Indications

Cefiderocol is a first-in-class siderophore cephalosporin distinguished by potent antibacterial activity against challenging gram-negative pathogens. In November 2019, the U.S. Food and Drug Administration (FDA) granted approval for its clinical use in two difficult settings: complicated urinary tract infections and ventilator-associated pneumonia arising from highly drug-resistant gram-negative bacteria. The authorization is purposefully circumscribed to infections attributable to susceptible gram-negative organisms and explicitly encompasses key nosocomial and community-associated pathogens, including *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Acinetobacter baumannii*. By aligning the label with organism-level susceptibility rather than broad syndromic categories alone, the approval underscores the agent's role as a targeted option where conventional β-lactams may fail due to resistance pressures. Accumulating evidence places cefiderocol at the forefront of therapeutic strategies for infections caused by multidrug-resistant gram-negative bacilli, with particular relevance when carbapenem resistance is suspected or confirmed. Across contemporary literature syntheses, the drug consistently demonstrates robust in vitro and clinical activity against organisms that have eroded the effectiveness of earlier-generation β-lactams, positioning it as a rational selection when carbapenem-refractory phenotypes are encountered [11][12]. This profile is especially salient in settings characterized by high burdens of β-lactamase–mediated resistance, where therapeutic options narrow and the risks of clinical deterioration and adverse outcomes escalate. Within such contexts, cefiderocol's demonstrated performance expands the clinician's armamentarium, offering an empirically defensible and mechanistically sound alternative that can be integrated into evidence-informed treatment algorithms for severe urinary and pulmonary infections due to resistant gram-negative organisms.

A defining attribute of cefiderocol's current clinical significance is its singular status among recently approved β-lactam agents with in vitro activity against carbapenem-resistant *A. baumannii* (CRAB), a pathogen notorious for limited susceptibility profiles and association with protracted hospitalizations, intensive care utilization, and elevated mortality. Recognizing both the promise and the stewardship implications of this capability, the Infectious Diseases Society of America advises a judicious deployment framework: cefiderocol should be reserved for CRAB infections that do not respond adequately to alternative agents or in clinical scenarios where intolerance, toxicity, or contraindications preclude the use of

other therapies [13]. This guidance reflects a calibrated balance—maximizing patient benefit in refractory disease while minimizing unnecessary selection pressure that could erode the drug's utility. Accordingly, in practice, cefiderocol's FDA-approved indications and expert-society recommendations converge to define a clear place in therapy: a focused, susceptibility-driven option for complicated urinary tract infections and ventilator-associated pneumonia caused by documented susceptible gram-negative pathogens, with particular strategic value when carbapenem resistance—and especially CRAB—is at issue [11][12][13].

Table 1. Generational profile of cephalosporins: spectrum, distinguishing features, and typical uses.

Generation	Representative agents	Key gram-positive activity	Key gram-negative activity	Distinctive features	Common clinical uses
First	Cefazolin, cephalothin, cephapirin, cephradine, cefadroxil, cephalexin	Strong vs. MSSA, streptococci	Limited: *E. coli, P. mirabilis, K. pneumoniae*	Reliable skin/soft-tissue coverage; cefazolin preferred for surgical prophylaxis	Cellulitis/abscess, surgical prophylaxis, osteoarticular infection, selected UTI/RTI, biliary infection
Second (true)	Cefuroxime, cefprozil	Slightly reduced vs. gram-positives vs. 1st gen	Enhanced: *H. influenzae, M. catarrhalis*	Cefuroxime option for Lyme in pregnancy/children	Community RTI (bronchitis/pneumonia), otitis media; step-down therapy
Second (cephamycins)	Cefmetazole, cefotetan, cefoxitin	As above	Adds anaerobes incl. *Bacteroides* spp.	Useful in intra-abdominal/pelvic infections	Intra-abdominal, gynecologic procedures; mixed aerobic–anaerobic infections
Third	Cefotaxime, ceftriaxone, ceftazidime, cefdinir, cefpodoxime, cefixime, cefoperazone	Less vs. many gram-positives (except pneumococcus with cefotaxime/ceftriaxone)	Broad Enterobacteriaceae; *H. influenzae*, *Neisseria* spp.; ceftazidime covers *P. aeruginosa*	Reliable CSF penetration (ceftriaxone/cefotaxime)	Meningitis, gonorrhea, disseminated Lyme, complicated UTI/intra-abdominal/RTI
Fourth	Cefepime	Pneumococcus, MSSA	Broad incl. *P. aeruginosa*; β-lactamase producers	Quaternary ammonium group improves outer-membrane penetration; CSF penetration	Severe nosocomial infections, febrile neutropenia, suspected MDR gram-negatives
Fifth	Ceftaroline; (ceftobiprole pending FDA)	Adds MRSA; *E. faecalis*; *Listeria* (*ceftaroline*)	Selected gram-negatives (not *Pseudomonas*)	Only cephalosporin with MRSA activity (ceftaroline)	Severe SSTI with MRSA, CAP with resistant pneumococcus
Siderophore	Cefiderocol	Minimal gram-positive role	MDR gram-negatives incl. *P. aeruginosa, A. baumannii, K. pneumoniae, E. coli, P. mirabilis*	"Trojan-horse" iron transport; FDA-approved for cUTI and VAP	Difficult-to-treat resistant gram-negative cUTI and

Mechanism of Action

Bacterial survival depends on the integrity of the peptidoglycan cell wall, a lattice strengthened by cross-linking reactions catalyzed by penicillin-binding proteins (PBPs), the peptidoglycan transpeptidases that finalize cell-wall assembly. Cephalosporins, originally derived from the fungus *Cephalosporium* spp., comprise a broad family of bactericidal agents whose core β-lactam ring is structurally poised to acylate PBP active sites. By covalently occupying these enzymes, β-lactams interrupt transpeptidation, halt new cell-wall synthesis, and precipitate osmotic instability, lysis, and bacterial death. The lethality results from the combined failure to maintain peptidoglycan homeostasis and the activation of autolytic pathways, such that cells unable to rebuild the wall predictably succumb. Against this backdrop of conserved mechanism, *Staphylococcus aureus* illustrates how bacteria evade cephalosporin pressure. Strains initially susceptible can acquire resistance by altering their PBPs; the paradigmatic example is expression of a gene encoding a modified PBP with markedly reduced affinity for β-lactams. This remodeling prevents the cephalosporin β-lactam ring from effectively inactivating the target enzyme, thereby permitting continued cross-linking despite drug exposure. Organisms harboring this mechanism are classified as methicillin-resistant *S. aureus* (MRSA). Within the cephalosporin class, clinically meaningful activity against MRSA is largely confined to the fifth-generation agent ceftaroline, which was designed to bind the altered PBP with sufficient affinity to restore β-lactam functionality in this resistant setting. A second, widely distributed resistance strategy is enzymatic: production of β-lactamases that hydrolyze the β-lactam ring before it can acylate PBPs, effectively neutralizing the drug. One

way to mitigate this threat is to co-formulate β-lactamase inhibitors with cephalosporins, as in ceftazidime/avibactam and ceftolozane/tazobactam, which broaden spectrum by protecting the partner cephalosporin from enzymatic degradation.

Cefiderocol exemplifies an advanced structural solution to the twin challenges of outer-membrane permeability and β-lactamase–mediated resistance. Classified as a siderophore cephalosporin, it bears a chlorocatechol moiety that confers high-affinity iron-chelating capacity—hence its designation as a "siderophore." This distinct handle co-opts bacterial iron uptake systems at the outer membrane, enabling active transport of the drug–iron complex across permeability barriers into the periplasmic space. There, cefiderocol avidly binds PBPs—most prominently PBP-3—disrupting peptidoglycan cross-linking much like earlier cephalosporins but with superior periplasmic access. This iron-facilitated translocation has been aptly termed a "trojan horse" strategy because it circumvents porin channel loss or restriction, a common outer-membrane resistance adaptation in gram-negative bacilli [12][14]. Beyond the siderophore motif, cefiderocol incorporates additional substitutions that reinforce its stability and transport. Analogous to cefepime and ceftazidime, it features a pyrrolidine group at the C3 position, which enhances resistance to certain β-lactamases and optimizes physicochemical properties. At C7, the carboxy-propanoxyamino substituent further aids outer-membrane trafficking and complements the iron-mediated entry route. Together, these structural elements produce a molecule that is not only adept at penetrating gram-negative envelopes but is also intrinsically robust against a broad array of β-lactamases, including some carbapenemases at lower activity levels. The net effect is reliable PBP access and inhibition despite porin alterations and enzymatic threats, translating into potent antibacterial activity against multidrug-resistant gram-negative pathogens [12][14].

Pharmacokinetics

Although many cephalosporins are administered parenterally to ensure predictable exposure in moderate to severe infections, several agents achieve therapeutically useful concentrations following oral dosing. These include cephalexin, cephradine, cefaclor, cefixime, cefadroxil, cefprozil, cefpodoxime, ceftibuten, and cefuroxime, each demonstrating effective gastrointestinal absorption when taken by mouth. The availability of oral formulations facilitates step-down therapy from intravenous regimens and supports ambulatory management of appropriately selected infections, provided pathogen susceptibility and clinical stability are established. Tissue penetration varies across the class and often dictates agent selection for specific infectious syndromes. Parenteral third- and fourth-generation agents such as ceftriaxone, cefotaxime, ceftazidime, and cefepime achieve concentrations in cerebrospinal fluid sufficient to treat meningitis, a property that underpins their frequent inclusion in empiric and targeted central nervous system regimens [15][16]. Cephalosporins also traverse the placenta, and many attain high levels in synovial fluid, aligning with their established roles in obstetric prophylaxis when indicated and in osteoarticular infections, respectively [17]. Following systemic administration of third-generation drugs, meaningful penetration into the aqueous humor has been documented, supporting use in certain ophthalmologic contexts. For pulmonary infections—particularly when gram-negative pathogens are suspected—agents such as ceftolozane/tazobactam, ceftobiprole, ceftazidime/avibactam, and ceftaroline demonstrate excellent lung tissue penetration, which enhances clinical efficacy in pneumonia and related lower respiratory tract diseases [18].

While most cephalosporins undergo minimal metabolic transformation, notable exceptions influence both pharmacodynamics and dosing considerations. Cefotaxime is converted to desacetyl-cefotaxime, an active metabolite with its own antibacterial effect, favorable distribution into extravascular compartments, and synergistic interplay with the parent drug, thereby augmenting overall therapeutic activity. In terms of elimination pathways, cefoperazone, ceftazidime, and ceftriaxone show substantial biliary excretion, a feature that can be advantageous in biliary infections but also raises considerations regarding cholestatic conditions and drug interactions in the hepatobiliary tract [19][20][21]. Renal clearance is the predominant elimination route for most cephalosporins, and dose adjustments are therefore often required in the setting of impaired kidney function to avoid accumulation and toxicity. Exceptions include cefpiramide and cefoperazone, which are primarily excreted in bile, while ceftriaxone displays dual (mixed renal/nonrenal) elimination. As with penicillins, coadministration of probenecid diminishes renal tubular secretion of cephalosporins, thereby prolonging serum concentrations—a pharmacologic interaction occasionally leveraged in clinical practice but more often considered when anticipating drug–drug interactions and adjusting dosing strategies [22].

In sum, the cephalosporin class exerts bactericidal activity by irreversibly disabling PBPs and halting peptidoglycan cross-linking, yet bacterial countermeasures—altered PBPs and β-lactamases—necessitate continuous structural innovation. Ceftaroline demonstrates how targeted binding to modified PBPs can reclaim activity against MRSA, while cefiderocol showcases a dual-pronged solution to gram-negative defenses: siderophore-guided entry that overcomes porin-based exclusion and substituent-driven resilience to β-lactamases. Appreciating the pharmacokinetic diversity across agents—spanning oral bioavailability, CNS and pulmonary penetration, metabolic activation, and distinct elimination routes—enables rational, site-specific selection and optimized dosing, ensuring that these versatile β-lactams are deployed with maximal efficacy and stewardship.

Administration

Available Dosage Forms, Routes, and Adult Use

Cephalosporins are available across oral and parenteral formulations, with route selection driven by severity of illness, target site penetration, and pharmacokinetic properties characteristic of each agent and generation. Among first-generation agents, cefazolin, cephalothin, and cephapirin are administered exclusively by the parenteral route, supporting their use in moderate to severe infections or when rapid, predictable serum levels are required. By contrast, cefadroxil and cephalexin are formulated for oral administration, enabling outpatient and step-down therapy once clinical stability is achieved. Cephradine is distinctive in its dual availability, permitting either oral or parenteral use depending on clinical context and the necessity for higher bioavailability or tissue concentrations. Second-generation cephalosporins likewise span routes of delivery. Cefuroxime can be given orally or parenterally, making it a versatile choice as care transitions from inpatient to outpatient settings. Cefprozil is available for oral use and is well suited to mild to moderate infections amenable to ambulatory management. In contrast, the cephamycins—cefmetazole, cefotetan, and cefoxitin—are administered parenterally,

reflecting their common deployment in intra-abdominal and pelvic infections where anaerobic coverage and reliable tissue penetration are pivotal.

Third-generation agents are stratified by route in a clinically meaningful way. Cefotaxime, ceftazidime, and ceftriaxone are parenteral agents, favored for severe infections requiring high serum levels and, in the case of cefotaxime and ceftriaxone, dependable cerebrospinal fluid penetration. Oral third-generation options—cefdinir, cefixime, and cefpodoxime—facilitate continuation therapy once the patient's condition stabilizes and culture data permit de-escalation. Notably, ceftriaxone retains a unique role in sexually transmitted infection management: a single intramuscular dose of 125 or 250 mg is sufficient to treat uncomplicated gonococcal infection and related complications such as pelvic inflammatory disease or epididymo-orchitis [23][24][25]. Fourth-generation therapy is represented by cefepime, which is administered parenterally and positioned for serious hospital-acquired infections, including those involving *Pseudomonas aeruginosa*, where robust gram-negative activity and central nervous system penetration can be critical. The fifth generation includes ceftaroline, also administered parenterally, selected when coverage for methicillin-resistant *Staphylococcus aureus* is required alongside broad gram-positive and select gram-negative activity. Finally, cefiderocol—a siderophore cephalosporin designed to overcome gram-negative permeability barriers and β-lactamase threats—is delivered parenterally for difficult-to-treat infections due to resistant gram-negative bacilli [13].

Considerations in Specific Patient Populations

Hepatic impairment

As a class, cephalosporins are associated with a low intrinsic risk of hepatotoxicity; idiosyncratic drug-induced liver injury has been reported only infrequently. An important exception is ceftriaxone, which has been linked—particularly with parenteral administration—to biliary sludging and a clinical picture that can mimic cholecystitis or cholestatic jaundice [26]. The clinical implications range from transient biliary precipitates detected on imaging to overt abdominal pain and laboratory cholestasis; vigilance is warranted, especially in patients with biliary stasis or concomitant risk factors. Pharmacokinetic investigations in patients with cirrhosis have yielded variable effects on the elimination half-life of cefotaxime, reflecting heterogeneity in hepatic dysfunction and portosystemic shunting among study populations. Nonetheless, cefotaxime's wide therapeutic index generally obviates the need for dose reduction solely on the basis of hepatic impairment. This property, combined with high ascitic fluid concentrations after standard dosing, underpins cefotaxime's role as a preferred agent in the empiric treatment of spontaneous bacterial peritonitis, where administration every 8 hours achieves reliable intraperitoneal exposure and favorable clinical outcomes [27].

Renal impairment

Renal handling is the principal route of elimination for most cephalosporins, and many parenteral agents exhibit relatively short half-lives in individuals with normal kidney function, necessitating frequent dosing to sustain therapeutic concentrations. Two agents diverge from this pattern: cefazolin and ceftriaxone possess longer half-lives, permitting less frequent administration even in the absence of renal dysfunction. Ceftriaxone in particular does not require dose adjustment for isolated renal failure; however, in the combined presence of renal and hepatic impairment, the total daily dose should not exceed 2 g to mitigate accumulation risk [28]. In chronic kidney disease, individualized dose optimization is essential to avert toxicity stemming from drug accumulation. Cefepime, a fourth-generation agent, is notable for dose-dependent neurotoxicity—manifesting as altered mental status, myoclonus, and seizures—when accumulation occurs in renal impairment; close monitoring of kidney function and systematic dose adjustment are therefore imperative. Conversely, agents that are predominantly renally excreted, such as cefazolin and ceftazidime, can be operationalized efficiently in patients receiving intermittent hemodialysis: post-dialysis administration three times weekly streamlines care and enhances adherence while achieving pharmacodynamic targets. Ultimately, regimen selection and interval adjustments should integrate patient-specific variables (residual renal function, dialysis modality, infection severity) with current nephrotoxicity risk guidance to balance efficacy and safety [29].

Pregnancy

For intrapartum prophylaxis against early-onset Group B Streptococcal disease, the American College of Obstetricians and Gynecologists recommends a first-generation cephalosporin—specifically cefazolin—for pregnant individuals with a documented penicillin allergy that confers a low risk of anaphylaxis or in whom the severity of penicillin allergy is uncertain [30]. This recommendation reflects cefazolin's reliable activity against streptococci, favorable safety profile in pregnancy, and low cross-reactivity risk relative to penicillins when IgE-mediated reactions are unlikely.

Breastfeeding

Cephalosporins are generally compatible with lactation. Empirical data indicate that agents such as cefadroxil, cefazolin, cefepime, cefiderocol, cefixime, cefotaxime, cefpodoxime, ceftaroline, and ceftazidime achieve low concentrations in human milk and are not expected to precipitate clinically significant adverse effects in breastfed infants [31][32][33]. Rare case reports and small case series have described perturbations of the infant gastrointestinal flora—manifesting as diarrhea or oral thrush—which are consistent with the class's impact on microbiota; however, these events appear uncommon and typically self-limited. On balance, the class is considered suitable for use in nursing mothers when therapy is indicated for maternal infection, with routine observation for minor gastrointestinal symptoms in the infant as a pragmatic precaution [34][35][36].

Pediatric patients

In the pediatric setting, pathogen-directed therapy remains central to optimizing outcomes and minimizing collateral effects. For acute bacterial arthritis due to methicillin-susceptible *S. aureus* (MSSA), the preferred initial intravenous therapy is a β-lactam, typically cefazolin, which offers excellent anti-staphylococcal activity, favorable joint penetration, and a well-characterized safety profile. Following clinical improvement and based on culture and susceptibility data, cephalexin is commonly employed as the oral step-down agent because of its reliable MSSA coverage and palatability. In cases where methicillin-resistant *S. aureus* (MRSA) is implicated, ceftaroline represents a reasonable alternative to clindamycin, providing β-lactam bactericidal activity against MRSA with a tolerability profile suited to pediatric care [37].

Older adults

Advanced age compounds vulnerability to adverse central nervous system effects of β-lactams, particularly in the presence of renal insufficiency or baseline neurologic disease. Older patients with reduced glomerular filtration and coexisting CNS disorders are at heightened risk for neurotoxicity. Cefepime is the prototypical agent associated with this phenomenon; toxicity may present as fluctuating confusion, agitation or somnolence, myoclonus, and overt seizures. Recognition hinges on a high index of suspicion in the appropriate clinical milieu, especially when dosing has not been adjusted for declining renal function or when unanticipated accumulation is possible due to acute kidney injury. Management entails prompt dose correction or discontinuation, supportive care, and, when necessary, hemodialysis to hasten drug removal, with subsequent substitution of an alternative agent tailored to pathogen susceptibility and the patient's renal profile [38].

Practical synthesis:

Route selection across cephalosporin generations reflects a balance of pharmacology and clinical need: oral agents (e.g., cephalexin, cefuroxime axetil, cefdinir, cefixime, cefpodoxime) facilitate ambulatory therapy and step-down care; parenteral options (e.g., cefazolin, cefotaxime, ceftriaxone, ceftazidime, cefepime, ceftaroline, cefiderocol) anchor initial management of severe or deep-seated infections and those requiring high serum or CNS levels. Special populations require calibrated dosing and agent choice: monitor hepatobiliary effects with ceftriaxone; use cefotaxime confidently in cirrhosis for spontaneous bacterial peritonitis; tailor regimens meticulously in renal impairment to avert neurotoxicity, particularly with cefepime; adopt cefazolin for intrapartum GBS prophylaxis in appropriate penicillin-allergic patients; continue breastfeeding with usual precautions; and favor cefazolin→cephalexin transitions for pediatric MSSA septic arthritis while reserving ceftaroline for MRSA. Such patient-centered, stewardship-aligned application ensures cephalosporins are leveraged to their full therapeutic potential while minimizing preventable harms [13][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38].

Adverse Effects

Cephalosporins are generally regarded as safe antimicrobial agents with a favorable therapeutic index. Across the class, most patients tolerate therapy without significant complications, and observed adverse events are often mild and self-limited. The reactions encountered most frequently involve the gastrointestinal tract—namely nausea, emesis, reduced appetite, and abdominal discomfort—reflecting class effects that are typically transient and manageable with supportive care. Nonetheless, clinicians should remain vigilant for a set of well-characterized adverse drug reactions that, although less common, have meaningful clinical implications for diagnosis, monitoring, and co-prescribing practices. The principal concerns are summarized below, with attention to mechanisms, relative risk across generations, and practical considerations for patient management.

Hypersensitivity reactions. Allergic phenomena with cephalosporins occur infrequently and appear to cluster more prominently with first- and second-generation agents than with later generations. Clinical presentations range from benign cutaneous eruptions—such as morbilliform rashes and urticaria—to angioedema; anaphylaxis is rare but has been described. Immunologic cross-reactivity in individuals with a documented penicillin allergy remains an enduring point of clinical debate. The risk is highest for first- and second-generation drugs, a pattern plausibly linked to greater structural similarity in the side-chain (R-group) moieties to penicillin G, whereas agents from the third generation onward demonstrate minimal cross-reactivity and are often used safely in many patients who report penicillin allergy [39][40]. Careful allergy history, attention to the type and timing of prior reactions, and consideration of alternative agents or graded challenges where appropriate can minimize unnecessary avoidance while preserving patient safety.

Drug-induced immune hemolytic anemia (DIIHA). Although uncommon, DIIHA represents a serious immune-mediated complication associated with cephalosporin exposure. The prevailing mechanistic model posits that the drug adsorbs to the erythrocyte membrane without intrinsic toxicity; pathologic hemolysis is precipitated when the host mounts an IgG response directed against the drug–cell complex. Antibody-coated erythrocytes are subsequently recognized and cleared by the reticuloendothelial system, culminating in hemolysis. Among cephalosporins, cefotetan and ceftriaxone are most frequently implicated, and clinical suspicion should be heightened when patients develop acute anemia, jaundice, or hemoglobinuria during or shortly after exposure to these agents [41]. Prompt drug discontinuation, supportive management, and, in severe cases, transfusion or immunomodulatory therapy may be required.

Disulfiram-like reactions. Certain cephalosporins share a structural side chain—methyl-tetrazole-thiol—that can inhibit aldehyde dehydrogenase and thereby impede the metabolism of acetaldehyde. When ethanol is ingested, this enzymatic blockade can trigger a disulfiram-like reaction characterized by flushing, throbbing headache, nausea, vomiting, chest discomfort, tachycardia, and hypotension. Cefamandole, cefoperazone, and moxalactam are the prototypical culprits, and patients receiving these agents should be counseled to abstain from alcohol during therapy and for a brief period thereafter to avoid precipitating symptoms [42].

Vitamin K deficiency and hypoprothrombinemia. A subset of cephalosporins has been associated with inhibition of vitamin K epoxide reductase, thereby limiting regeneration of the reduced, active form of vitamin K necessary for γ-carboxylation of coagulation factors II, VII, IX, and X. The downstream effect is diminished synthesis of functional clotting proteins and a predisposition to hypoprothrombinemia, which clinically may manifest as easy bruising, mucosal bleeding, or prolonged prothrombin time. Risk appears to be higher with agents carrying specific side chains and may be accentuated in patients with poor nutritional status, hepatic dysfunction, or concurrent anticoagulant therapy [43]. Monitoring coagulation parameters and vitamin K supplementation in high-risk scenarios are reasonable safeguards.

Pseudomembranous colitis. Although classically linked to clindamycin and ampicillin, antibiotic-associated pseudomembranous colitis—overwhelmingly due to *Clostridioides difficile*—is also a recognized complication of cephalosporin therapy, with particularly strong associations reported for third-generation agents. The pathogenesis reflects antibiotic-induced disruption of normal colonic microbiota, followed by overgrowth of toxigenic *C. difficile* and toxin-mediated mucosal injury. Clinicians should maintain a high index of suspicion for new-onset diarrhea, abdominal pain, or

leukocytosis during or after cephalosporin exposure; timely stool toxin testing and prompt initiation of guideline-concordant therapy are critical to reduce morbidity and transmission [44][45].

Drug–Drug Interactions

Warfarin. Cephalosporins harboring an N-methyl-thiotetrazole (NMTT) side chain—classically cefotetan, cefamandole, cefmetazole, cefoperazone, and moxalactam—are associated with hemostatic disturbances, including prolongation of prothrombin time, hypoprothrombinemia, and clinically significant bleeding. The NMTT moiety is thought to perturb vitamin K metabolism, compounding anticoagulant effects when co-administered with warfarin and thereby magnifying bleeding risk [46]. Beyond NMTT-bearing agents, emerging reports suggest that ceftaroline may also interact with warfarin, contributing to supratherapeutic international normalized ratio (INR) values and heightened bleeding potential. In addition, Saum et al. observed notable INR elevations with ceftriaxone compared with other antibiotics, underscoring the need for more frequent INR surveillance and conservative warfarin dose adjustments when cephalosporins—particularly ceftriaxone or ceftaroline—are introduced in chronically anticoagulated patients [47][48]. In practice, close laboratory monitoring, scrutiny for signs of bleeding, and proactive coordination with anticoagulation services are advisable during co-therapy.

Furosemide. Concomitant administration of cephalosporins with loop diuretics such as furosemide has been linked to an increased risk of nephrotoxicity. The mechanistic basis is not fully delineated, but additive or synergistic renal insults—hemodynamic changes, tubular stress, or idiosyncratic susceptibility—may be contributory [49][50]. Clinicians should consider renal function monitoring, judicious hydration, and avoidance of additional nephrotoxins where feasible when this combination is clinically necessary.

Aminoglycosides. Reports of nephrotoxicity during combined cephalosporin–aminoglycoside therapy exist, although the causal contribution of each agent can be confounded by severity of illness, hypotension, or concurrent nephrotoxic exposures common in critically ill populations. Consequently, the extent to which these drugs exert synergistic nephrotoxic effects remains uncertain [45][51]. Despite this ambiguity, prudence dictates close renal surveillance and attention to pharmacokinetic targets (e.g., aminoglycoside peak and trough concentrations) when combination therapy is indicated for synergistic bactericidal activity. Of note, simultaneous use of cefepime with aminoglycosides may heighten the likelihood of kidney injury, amplifying the case for conservative dosing, therapeutic drug monitoring, and early de-escalation when culture data permit [52][53].

Clinical Integration and Risk Mitigation

The overarching safety profile of cephalosporins is reassuring, yet thoughtful prescribing requires anticipation of the relatively uncommon but clinically important toxicities and interactions outlined above. Several practical strategies can meaningfully reduce risk:

1. **Allergy risk stratification.** A detailed allergy history distinguishes IgE-mediated reactions from nonspecific intolerance and identifies patients in whom later-generation cephalosporins can be used safely despite a penicillin allergy label. When uncertainty persists, targeted allergy testing or graded challenge under supervision may reclaim valuable β-lactam options while minimizing risk [39][40].
2. **Judicious selection by patient factors.** In patients with preexisting coagulopathy, malnutrition, or concurrent vitamin K antagonism, preference for agents without NMTT side chains and early consideration of vitamin K supplementation can help avert coagulopathic events [43][46]—particularly when warfarin is co-prescribed [47][48].
3. **Renal stewardship.** Baseline and periodic assessment of kidney function is essential when cephalosporins are combined with recognized nephrotoxins such as loop diuretics or aminoglycosides. Where possible, avoid triple-nephrotoxin combinations, limit therapy duration to the minimum effective course, and employ therapeutic drug monitoring for aminoglycosides to align exposure with efficacy while curbing toxicity [49][50][51][52][53].
4. **Monitoring for *C. difficile*.** Any new or worsening diarrhea during or after therapy warrants evaluation for *C. difficile* infection, with prompt initiation of appropriate treatment and infection control measures if confirmed. Stewardship practices—narrowing spectrum based on culture results and avoiding unnecessary prolonged courses—further diminish risk [44][45].
5. **Hemolysis vigilance.** Sudden anemia, hyperbilirubinemia, or hemoglobinuria in patients receiving cefotetan or ceftriaxone should prompt consideration of DIIHA; immediate drug cessation and supportive care are central to management [41].

In sum, cephalosporins combine broad clinical utility with comparatively low inherent toxicity. When adverse events do occur, they are often predictable based on structural features (e.g., NMTT side chains), concomitant therapies (e.g., warfarin, aminoglycosides, furosemide), or well-described immunologic mechanisms (e.g., DIIHA, allergic reactions). By tailoring drug selection to individual risk profiles, monitoring thoughtfully, and practicing antimicrobial stewardship, clinicians can preserve the benefits of this vital class while minimizing preventable harm [39][40][41][42][43][44][45][46][47][48][49][50][51][52][53].

Contraindications

Cephalosporins are contraindicated in any patient with a known allergy to a cephalosporin or with a documented anaphylactic reaction to penicillin or other β-lactam antibiotics. Although β-lactams share a core ring, contemporary understanding attributes most clinically relevant cross-reactivity to similarities in the R-side chains rather than to the β-lactam nucleus itself. Consequently, safe use depends less on the class label and more on side-chain concordance between the culprit drug and the proposed cephalosporin. To operationalize this principle, clinicians should align decisions with the latest expert recommendations. The American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) provide practical guidance for evaluating and managing patients who report cephalosporin or penicillin allergies, emphasizing structured history-taking, side-chain analysis, and judicious test dosing strategies [54].

For patients reporting a nonanaphylactic cephalosporin allergy (eg, benign exanthem, pruritus without systemic features), AAAAI/ACAAI guidelines endorse performing a direct oral or parenteral clinical challenge with a cephalosporin that has a dissimilar R1 side chain to the implicated agent; routine skin testing before such a direct challenge is not recommended in this context [54]. In contrast, when the history is consistent with true anaphylaxis to a cephalosporin, the guidelines advise confirming a negative cephalosporin skin test before administering a parenteral cephalosporin that bears a nonidentical R1 group, thereby mitigating the risk of immediate hypersensitivity while permitting access to desired β-lactam therapy [54]. Notably, for patients with a history of penicillin anaphylaxis, the same expert consensus supports administering a cephalosporin that is structurally dissimilar at the R1 side chain—without the need for preliminary testing or additional precautions—provided the assessment confirms the absence of concerning side-chain overlap. Where ambiguity persists regarding allergy phenotyping, test characteristics, or side-chain concordance, consultation with an allergist/immunologist is prudent. A detailed explanation of algorithms, test performance, and decision pathways appears in the published guidelines [54].

Ceftriaxone carries two important, age-specific contraindications. First, in neonates with hyperbilirubinemia, ceftriaxone can displace bilirubin from albumin binding sites, raising the concentration of unbound bilirubin and thereby increasing the risk of bilirubin-related neurotoxicity; accordingly, its use is contraindicated in this population [55][56]. Second, ceftriaxone can form insoluble calcium–ceftriaxone complexes when co-administered with, or closely followed/preceded by, calcium-containing solutions. In infants younger than 28 days, these precipitates have been reported in the lungs and kidneys and can be life-threatening; thus, ceftriaxone is contraindicated in neonates under 28 days of age who are expected to receive calcium-containing products [57]. These restrictions underscore the need for careful agent selection in neonatal care and meticulous review of concurrent parenteral therapies.

Monitoring

Active surveillance for hypersensitivity is essential during cephalosporin therapy. Clinicians should counsel patients and observe for early manifestations of immediate or delayed allergy—urticaria, pruritus, flushing, angioedema, bronchospasm, hypotension—as well as for less specific cutaneous eruptions. Any signs suggestive of anaphylaxis warrant urgent discontinuation of the agent, prompt initiation of standard anaphylaxis management, and documentation to prevent future re-exposure [58]. In parallel, pharmacists and prescribers should periodically evaluate renal function, because most cephalosporins are cleared renally and may require dose or interval adjustments to avoid accumulation and attendant neurotoxicity or other adverse events; ceftriaxone is a notable exception and typically does not require renal dose modification in isolation [58]. When drug-induced immune hemolytic anemia (DIIHA) is in the differential—classically heralded by sudden fatigue, pallor, dyspnea, back pain, dark urine, or jaundice during or shortly after therapy—laboratory monitoring should include a complete blood count (looking for falling hemoglobin and reticulocytosis), total and indirect bilirubin, haptoglobin (often low or undetectable), and lactate dehydrogenase (often elevated); these tests support the diagnosis and guide the urgency of intervention [59]. Recognizing DIIHA early is critical because cessation of the offending cephalosporin is the cornerstone of management, and additional supportive measures (eg, transfusion) may be lifesaving.

Clinicians should also remain alert to adverse events linked to particular structural motifs and class effects. For agents capable of producing a disulfiram-like reaction, patients should be monitored for flushing, nausea, vomiting, tachycardia, and hypotension if inadvertent alcohol exposure occurs, with counseling provided to avoid ethanol during therapy and for a short period thereafter [60]. Likewise, vigilance for antibiotic-associated diarrhea—especially new-onset or persistent diarrhea with abdominal pain or leukocytosis—should prompt evaluation for pseudomembranous colitis due to *Clostridioides difficile* and early initiation of guideline-concordant therapy if confirmed [61]. Prevention hinges on antimicrobial stewardship: narrowing therapy based on culture results and limiting duration to the minimum effective course. Finally, coagulation parameters merit attention in patients at risk for hypoprothrombinemia, particularly when receiving cephalosporins known to interfere with vitamin K metabolism or when concomitant factors (poor nutrition, hepatic dysfunction, concurrent warfarin) compound bleeding risk. Monitoring prothrombin time/international normalized ratio (PT/INR) at baseline and periodically thereafter facilitates timely detection of coagulopathy and informs supplementation or therapeutic adjustments where indicated [62][63]. Integrating these monitoring practices—structured allergy surveillance, renal function checks, targeted hematologic and coagulation testing, and symptom-driven evaluation for gastrointestinal complications—supports safe, effective cephalosporin use across diverse care settings while minimizing preventable harm.

Toxicity

Signs and Symptoms of Overdose. Experimental and clinical data converge on the conclusion that cephalosporin toxicity is largely exposure-dependent and organ specific. In animal models, supratherapeutic dosing has demonstrated direct renal injury: rabbits given high cephalosporin doses develop mitochondrial dysfunction within renal tubular cells, illuminating a mechanistic basis for nephrotoxicity and the kidney's particular vulnerability to β-lactam accumulation and oxidative stress [64]. In humans, cefepime is the best characterized precipitant of neurotoxicity when overdosed or in the setting of impaired clearance. Reported presentations include encephalopathy, fluctuating confusion, agitation, myoclonus, and generalized seizures. The prevailing pathophysiologic hypothesis is that excessive cefepime crosses the blood–brain barrier and exerts concentration-dependent antagonism at ϒ-aminobutyric acid (GABA) receptors—an effect also described with toxic doses of penicillin G—thereby lowering seizure threshold and provoking cortical irritability [65][66]. Electroencephalography may reveal characteristic triphasic waveforms or other epileptiform discharges, and a consistent clinical observation is resolution or marked improvement in mental status after discontinuation of cefepime, supporting a causal role of drug accumulation [65][66]. Predisposing conditions include renal dysfunction (acute or chronic), excessive dosing relative to creatinine clearance, and co-administration of neuroactive agents that reduce seizure threshold.

Population-level pharmacovigilance provides additional perspective on risk factors and implicated agents. A review of 511 severe adverse drug reaction reports recorded in the French Pharmacovigilance database from 1987 to 2017 found that affected patients were predominantly older adults—mostly men—with compromised renal function, a profile that biologically aligns with drug accumulation and neurotoxicity. The central nervous system syndromes cataloged encompassed

encephalopathy, confusional states, convulsions, and myoclonia. Among cephalosporins, cefepime and ceftriaxone were most frequently implicated, underscoring that even widely used, guideline-concordant agents can provoke serious neurologic events when clearance is reduced or dosing is not appropriately individualized [67]. Although ceftriaxone is not classically neurotoxic, impaired biliary and renal handling in frail or multimorbid patients may contribute to elevated exposures, and clinicians should maintain vigilance for neurologic change whenever β-lactams are administered to high-risk populations.

Management of Overdose. The first principles of management are immediate cessation of the offending cephalosporin and institution of supportive care. Stabilization priorities include airway protection, adequate oxygenation, and hemodynamic support, alongside prompt correction of metabolic derangements—hypoxemia, uremia, hypocalcemia, or electrolyte abnormalities—that can independently lower seizure threshold. If seizures develop, or if encephalopathy is accompanied by electrographic abnormalities, standard anticonvulsant therapy should be initiated without delay, following contemporary status epilepticus protocols and selecting agents with favorable pharmacokinetics in renal impairment [68]. Continuous or serial EEG monitoring can aid in detecting non-convulsive status epilepticus and in tracking response to therapy. Because most cephalosporins are renally cleared, hemodialysis may be considered in severe cases—particularly when neurotoxicity occurs in the context of kidney failure—to enhance drug removal and hasten clinical recovery; this decision should incorporate the pharmacokinetic properties of the specific cephalosporin and the patient's dialysis modality. Concomitantly, clinicians should reassess the need for ongoing antibacterial therapy and substitute an alternative agent guided by culture data and susceptibility, with careful attention to dose individualization. Documentation of the adverse reaction in the medical record and communication to the patient and outpatient care team reduce the risk of inadvertent re-exposure.

Enhancing Healthcare Team Outcomes. Prevention, early recognition, and effective treatment of cephalosporin toxicity are optimized through coordinated interprofessional practice. Clear shared goals, explicit role delineation, and reliable, bidirectional communication enable earlier detection of subtle cognitive changes and accelerate escalation of care. Prescribers should confirm indications, calculate doses using weight and contemporaneous kidney function, and counsel patients and caregivers about early neurologic warning signs. Nurses frequently detect the first changes in mental status or new myoclonus during routine observation and are pivotal in triggering rapid evaluation. Pharmacists mitigate risk by verifying renal dose adjustments, flagging potential drug–drug interactions that may compound neurotoxicity or nephrotoxicity, and educating staff and patients about characteristic adverse effects. Infectious diseases specialists add value by refining antimicrobial choices and durations, balancing efficacy with safety in complex hosts.

Antimicrobial stewardship programs knit these efforts together at the system level. A recent study of pharmacist-led stewardship interventions focused on antibiotics demonstrated durable improvements: increased procurement of blood cultures before therapy, more frequent de-escalation of agents once microbiology results were available, and a significant reduction in hospital-acquired infections [69]. Embedding stewardship practices within electronic clinical decision support—renal dosing calculators, automated alerts for declining glomerular filtration rate while on cefepime and prompts to reassess therapy at defined intervals—further reduces preventable overexposure. Standardized post-dialysis dosing protocols and order sets that default to creatinine-clearance–based intervals can streamline safe prescribing on busy inpatient services. Patients are indispensable partners in this safety net. They should be urged to report promptly any new confusion, agitation, hallucinations, tremors, myoclonus, seizures, abdominal distress, reduced urine output, or signs of bleeding, and to disclose over-the-counter products or supplements that may affect renal function or seizure threshold. Incorporating teach-back techniques, providing written action plans, and performing careful medication reconciliation during transitions of care can prevent delayed recognition of toxicity after discharge. In aggregate, cephalosporin toxicity most often reflects a predictable pharmacokinetic–pharmacodynamic mismatch—overexposure in the setting of renal impairment—superimposed on drug-specific liabilities such as cefepime's GABA antagonism. Rapid recognition and discontinuation of the culprit agent, targeted seizure management, consideration of dialysis when appropriate, and robust interprofessional coordination constitute the pillars of harm reduction and translate directly into improved clinical outcomes [64][65][66][67][68][69].

Conclusion:

Cephalosporins remain foundational to modern anti-infective practice because their pharmacology aligns with everyday clinical needs: predictable bactericidal activity via PBP inhibition, tissue penetration, and a laddered spectrum spanning community pathogens to difficult hospital organisms. Understanding the strengths and limitations within—and between—generations is essential for rational choices and confident de-escalation. First-generation agents cover methicillin-susceptible staphylococci and streptococci; second-generation options extend activity to respiratory gram-negatives and selected anaerobes; third-generation drugs add Enterobacteriaceae coverage and CNS penetration, with ceftazidime providing antipseudomonal activity; fourth-generation cefepime adds antipseudomonal coverage and resists many β-lactamases; fifth-generation ceftaroline also adds activity against MRSA, while cefiderocol targets resistant gram-negatives. Population-specific considerations matter: renal elimination drives dose adjustment and interval selection; biliary issues constrain ceftriaxone in neonates; and age-related vulnerability to cefepime-associated neurotoxicity compels vigilant monitoring. Adverse effects are generally infrequent—hypersensitivity, drug-induced immune hemolysis with cefotetan or ceftriaxone, vitamin-K-dependent coagulopathy and disulfiram-like reactions from specific side chains, and antibiotic-associated *Clostridioides difficile* colitis. These risks underscore the value of targeted laboratory surveillance, medication reconciliation, and patient counseling. Cefiderocol's siderophore-mediated entry and resilience to multiple β-lactamases expand options for carbapenem-resistant gram-negative infections when alternatives fail or are poorly tolerated. Sustaining class utility requires disciplined stewardship: pair therapy with local epidemiology, secure cultures early, narrow when possible, and use the shortest effective course. When clinicians integrate drug properties, pathogen probabilities, and patient factors, cephalosporins deliver high value while minimizing preventable harm—an equilibrium central to durable infectious-disease care. Clear communication among clinicians, pharmacists, and nurses enhances early detection of toxicity and optimizes dosing safely.

References:

1. Hsieh WC, Ho SW. Evaluation of antibacterial activities of cephalosporin antibiotics: cefazolin, cephaloridine, cephalothin, and cephalexin. Zhonghua Min Guo Wei Sheng Wu Xue Za Zhi. 1975 Mar;8(1):1-11.

2. Griffith RS. The pharmacology of cephalexin. Postgrad Med J. 1983;59 Suppl 5:16-27.
3. Bergeron MG, Brusch JL, Barza M, Weinstein L. Bactericidal activity and pharmacology of cefazolin. Antimicrob Agents Chemother. 1973 Oct;4(4):396-401.
4. Tartaglione TA, Polk RE. Review of the new second-generation cephalosporins: cefonicid, ceforanide, and cefuroxime. Drug Intell Clin Pharm. 1985 Mar;19(3):188-98.
5. Klein NC, Cunha BA. Third-generation cephalosporins. Med Clin North Am. 1995 Jul;79(4):705-19.
6. Okamoto MP, Nakahiro RK, Chin A, Bedikian A, Gill MA. Cefepime: a new fourth-generation cephalosporin. Am J Hosp Pharm. 1994 Feb 15;51(4):463-77; quiz 541-2.
7. Zhanel GG, Sniezek G, Schweizer F, Zelenitsky S, Lagacé-Wiens PR, Rubinstein E, Gin AS, Hoban DJ, Karlowsky JA. Ceftaroline: a novel broad-spectrum cephalosporin with activity against meticillin-resistant Staphylococcus aureus. Drugs. 2009;69(7):809-31.
8. Mahmoud E, Al Mansour S, Bosaeed M, Alharbi A, Alsaedy A, Aljohani S, Alalwan B, Alothman A. Ceftobiprole for Treatment of MRSA Blood Stream Infection: A Case Series. Infect Drug Resist. 2020;13:2667-2672.
9. Hsu WH, Hsu CK, Lai CC. Ceftobiprole medocaril for the treatment of pneumonia. Expert Rev Anti Infect Ther. 2023 Jun;21(6):551-563.
10. Lupia T, Pallotto C, Corcione S, Boglione L, De Rosa FG. Ceftobiprole Perspective: Current and Potential Future Indications. Antibiotics (Basel). 2021 Feb 08;10(2)
11. Wang C, Yang D, Wang Y, Ni W. Cefiderocol for the Treatment of Multidrug-Resistant Gram-Negative Bacteria: A Systematic Review of Currently Available Evidence. Front Pharmacol. 2022;13:896971.
12. Domingues S, Lima T, Saavedra MJ, Da Silva GJ. An Overview of Cefiderocol's Therapeutic Potential and Underlying Resistance Mechanisms. Life (Basel). 2023 Jun 21;13(7)
13. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of AmpC β-Lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Clin Infect Dis. 2022 Jul 06;74(12):2089-2114.
14. Ito A, Nishikawa T, Matsumoto S, Yoshizawa H, Sato T, Nakamura R, Tsuji M, Yamano Y. Siderophore Cephalosporin Cefiderocol Utilizes Ferric Iron Transporter Systems for Antibacterial Activity against Pseudomonas aeruginosa. Antimicrob Agents Chemother. 2016 Dec;60(12):7396-7401.
15. Rhoney DH, Tam VH, Parker D, McKinnon PS, Coplin WM. Disposition of cefepime in the central nervous system of patients with external ventricular drains. Pharmacotherapy. 2003 Mar;23(3):310-4.
16. Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clin Microbiol Rev. 2010 Oct;23(4):858-83.
17. Thabit AK, Fatani DF, Bamakhrama MS, Barnawi OA, Basudan LO, Alhejaili SF. Antibiotic penetration into bone and joints: An updated review. Int J Infect Dis. 2019 Apr;81:128-136.
18. Lupia T, Corcione S, Mornese Pinna S, De Rosa FG. New cephalosporins for the treatment of pneumonia in internal medicine wards. J Thorac Dis. 2020 Jul;12(7):3747-3763.
19. Leung JW, Chan RC, Cheung SW, Sung JY, Chung SC, French GL. The effect of obstruction on the biliary excretion of cefoperazone and ceftazidime. J Antimicrob Chemother. 1990 Mar;25(3):399-406.
20. Ramchandani M, Pal P, Reddy DN. Endoscopic management of acute cholangitis as a result of common bile duct stones. Dig Endosc. 2017 Apr;29 Suppl 2:78-87.
21. Ustyol L, Bulut MD, Agengin K, Bala KA, Yavuz A, Bora A, Demiroren K, Dogan M. Comparative evaluation of ceftriaxone- and cefotaxime-induced biliary pseudolithiasis or nephrolithiasis: A prospective study in 154 children. Hum Exp Toxicol. 2017 Jun;36(6):547-553.
22. Alasmari F, Alasmari MS, Muwainea HM, Alomar HA, Alasmari AF, Alsanea S, Alshamsan A, Rasool MF, Alqahtani F. Physiologically-based pharmacokinetic modeling for single and multiple dosing regimens of ceftriaxone in healthy and chronic kidney disease populations: a tool for model-informed precision dosing. Front Pharmacol. 2023;14:1200828.
23. Judson FN. Treatment of uncomplicated gonorrhea with ceftriaxone: a review. Sex Transm Dis. 1986 Jul-Sep;13(3 Suppl):199-202.
24. Jennings LK, Krywko DM. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Mar 13, 2023. Pelvic Inflammatory Disease.
25. Rupp TJ, Leslie SW. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Jul 17, 2023. Epididymitis.
26. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda (MD): Dec 20, 2021. Cephalosporins.
27. Zoratti C, Moretti R, Rebuzzi L, Albergati IV, Di Somma A, Decorti G, Di Bella S, Crocè LS, Giuffrè M. Antibiotics and Liver Cirrhosis: What the Physicians Need to Know. Antibiotics (Basel). 2021 Dec 28;11(1)
28. Andriole VT. Pharmacokinetics of cephalosporins in patients with normal or reduced renal function. J Infect Dis. 1978 May;137 Suppl:S88-S99.
29. Vondracek SF, Teitelbaum I, Kiser TH. Principles of Kidney Pharmacotherapy for the Nephrologist: Core Curriculum 2021. Am J Kidney Dis. 2021 Sep;78(3):442-458.
30. Prevention of Group B Streptococcal Early-Onset Disease in Newborns: ACOG Committee Opinion Summary, Number 782. Obstet Gynecol. 2019 Jul;134(1):1.
31. Drugs and Lactation Database (LactMed®) [Internet]. National Institute of Child Health and Human Development; Bethesda (MD): Nov 15, 2024. Cefadroxil.
32. Drugs and Lactation Database (LactMed®) [Internet]. National Institute of Child Health and Human Development; Bethesda (MD): Nov 15, 2024. Cefazolin.
33. Drugs and Lactation Database (LactMed®) [Internet]. National Institute of Child Health and Human Development; Bethesda (MD): Apr 15, 2024. Cefepime.

34. Drugs and Lactation Database (LactMed®) [Internet]. National Institute of Child Health and Human Development; Bethesda (MD): Aug 15, 2024. Cefpodoxime.
35. Drugs and Lactation Database (LactMed®) [Internet]. National Institute of Child Health and Human Development; Bethesda (MD): Jul 20, 2020. Ceftaroline.
36. Drugs and Lactation Database (LactMed®) [Internet]. National Institute of Child Health and Human Development; Bethesda (MD): Nov 15, 2024. Ceftazidime.
37. Woods CR, Bradley JS, Chatterjee A, Kronman MP, Arnold SR, Robinson J, Copley LA, Arrieta AC, Fowler SL, Harrison C, Eppes SC, Creech CB, Stadler LP, Shah SS, Mazur LJ, Carrillo-Marquez MA, Allen CH, Lavergne V. Clinical Practice Guideline by the Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA): 2023 Guideline on Diagnosis and Management of Acute Bacterial Arthritis in Pediatrics. J Pediatric Infect Dis Soc. 2024 Jan 29;13(1):1-59.
38. Grill MF, Maganti R. Cephalosporin-induced neurotoxicity: clinical manifestations, potential pathogenic mechanisms, and the role of electroencephalographic monitoring. Ann Pharmacother. 2008 Dec;42(12):1843-50.
39. Moreno E, Macías E, Dávila I, Laffond E, Ruiz A, Lorente F. Hypersensitivity reactions to cephalosporins. Expert Opin Drug Saf. 2008 May;7(3):295-304.
40. Dickson SD, Salazar KC. Diagnosis and management of immediate hypersensitivity reactions to cephalosporins. Clin Rev Allergy Immunol. 2013 Aug;45(1):131-42.
41. Garratty G. Drug-induced immune hemolytic anemia. Hematology Am Soc Hematol Educ Program. 2009:73-9.
42. Uri JV, Parks DB. Disulfiram-like reaction to certain cephalosporins. Ther Drug Monit. 1983 Jun;5(2):219-24.
43. Shearer MJ, Bechtold H, Andrassy K, Koderisch J, McCarthy PT, Trenk D, Jähnchen E, Ritz E. Mechanism of cephalosporin-induced hypoprothrombinemia: relation to cephalosporin side chain, vitamin K metabolism, and vitamin K status. J Clin Pharmacol. 1988 Jan;28(1):88-95.
44. de Lalla F, Privitera G, Ortisi G, Rizzardini G, Santoro D, Pagano A, Rinaldi E, Scarpellini P. Third generation cephalosporins as a risk factor for Clostridium difficile-associated disease: a four-year survey in a general hospital. J Antimicrob Chemother. 1989 Apr;23(4):623-31.
45. Rankin GO, Sutherland CH. Nephrotoxicity of aminoglycosides and cephalosporins in combination. Adverse Drug React Acute Poisoning Rev. 1989 Summer;8(2):73-88.
46. Park GH, Kim S, Kim MS, Yu YM, Kim GH, Lee JS, Lee E. The Association Between Cephalosporin and Hypoprothrombinemia: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2019 Oct 16;16(20)
47. Baillargeon J, Holmes HM, Lin YL, Raji MA, Sharma G, Kuo YF. Concurrent use of warfarin and antibiotics and the risk of bleeding in older adults. Am J Med. 2012 Feb;125(2):183-9.
48. Vega AJ, Smith C, Matejowsky HG, Thornhill KJ, Borne GE, Mosieri CN, Shekoohi S, Cornett EM, Kaye AD. Warfarin and Antibiotics: Drug Interactions and Clinical Considerations. Life (Basel). 2023 Jul 30;13(8)
49. Maideen NMP, Balasubramanian R, Muthusamy S. A Comprehensive Review of the Pharmacologic Perspective on Loop Diuretic Drug Interactions with Therapeutically Used Drugs. Curr Drug Metab. 2022;23(3):188-199.
50. Pea F, Furlanut M. Pharmacokinetic aspects of treating infections in the intensive care unit: focus on drug interactions. Clin Pharmacokinet. 2001;40(11):833-68.
51. Silverblatt F. Pathogenesis of nephrotoxicity of cephalosporins and aminoglycosides: a review of current concepts. Rev Infect Dis. 1982 Sep-Oct;4 Suppl:S360-5.
52. Zhang Q, Matsumura Y, Teratani T, Yoshimoto S, Mineno T, Nakagawa K, Nagahama M, Kuwata S, Takeda H. The application of an institutional clinical data warehouse to the assessment of adverse drug reactions (ADRs). Evaluation of aminoglycoside and cephalosporin associated nephrotoxicity. Methods Inf Med. 2007;46(5):516-22.
53. Krcméry V, Fuchsberger P, Gocár M, Salát T, Bodnárová J, Sobota R, Koza I, Svec J. Nephrotoxicity of aminoglycosides, polypeptides and cephalosporins in cancer patients. Chemotherapy. 1991;37(4):287-91.
54. Khan DA, Banerji A, Blumenthal KG, Phillips EJ, Solensky R, White AA, Bernstein JA, Chu DK, Ellis AK, Golden DBK, Greenhawt MJ, Horner CC, Ledford D, Lieberman JA, Oppenheimer J, Rank MA, Shaker MS, Stukus DR, Wallace D, Wang J, Chief Editor(s): Khan DA, Golden DBK, Shaker M, Stukus DR, Workgroup Contributors: Khan DA, Banerji A, Blumenthal KG, Phillips EJ, Solensky R, White AA, Joint Task Force on Practice Parameters Reviewers: Bernstein JA, Chu DK, Ellis AK, Golden DBK, Greenhawt MJ, Horner CC, Ledford D, Lieberman JA, Oppenheimer J, Rank MA, Shaker MS, Stukus DR, Wallace D, Wang J. Drug allergy: A 2022 practice parameter update. J Allergy Clin Immunol. 2022 Dec;150(6):1333-1393.
55. Gulian JM, Gonard V, Dalmasso C, Palix C. Bilirubin displacement by ceftriaxone in neonates: evaluation by determination of 'free' bilirubin and erythrocyte-bound bilirubin. J Antimicrob Chemother. 1987 Jun;19(6):823-9.
56. Bickford CL, Spencer AP. Biliary sludge and hyperbilirubinemia associated with ceftriaxone in an adult: case report and review of the literature. Pharmacotherapy. 2005 Oct;25(10):1389-95.
57. Bradley JS, Wassel RT, Lee L, Nambiar S. Intravenous ceftriaxone and calcium in the neonate: assessing the risk for cardiopulmonary adverse events. Pediatrics. 2009 Apr;123(4):e609-13.
58. Spyker DA, Thomas BL, Sande MA, Bolton WK. Pharmacokinetics of cefaclor and cephalexin: dosage nomograms for impaired renal function. Antimicrob Agents Chemother. 1978 Aug;14(2):172-7.
59. Barcellini W, Fattizzo B. Novel pharmacotherapy for drug-induced immune hemolytic anemia. Expert Opin Pharmacother. 2023 Sep-Dec;24(18):1927-1931.
60. Farooq PD, Urrunaga NH, Tang DM, von Rosenvinge EC. Pseudomembranous colitis. Dis Mon. 2015 May;61(5):181-206.
61. Ren S, Cao Y, Zhang X, Jiao S, Qian S, Liu P. Cephalosporin induced disulfiram-like reaction: a retrospective review of 78 cases. Int Surg. 2014 Mar-Apr;99(2):142-6.

62. Haba Y, Akizuki H, Hashiguchi N, Naito T. Hypoprothrombinemia During Cefmetazole Treatment: A Case Report. Am J Case Rep. 2022 Jul 27;23:e936712.
63. Chen LJ, Hsiao FY, Shen LJ, Wu FL, Tsay W, Hung CC, Lin SW. Use of Hypoprothrombinemia-Inducing Cephalosporins and the Risk of Hemorrhagic Events: A Nationwide Nested Case-Control Study. PLoS One. 2016;11(7):e0158407.
64. Tune BM, Fravert D. Cephalosporin nephrotoxicity. Transport, cytotoxicity and mitochondrial toxicity of cephaloglycin. J Pharmacol Exp Ther. 1980 Oct;215(1):186-90.
65. Payne LE, Gagnon DJ, Riker RR, Seder DB, Glisic EK, Morris JG, Fraser GL. Cefepime-induced neurotoxicity: a systematic review. Crit Care. 2017 Nov 14;21(1):276.
66. Tchapyjnikov D, Luedke MW. Cefepime-Induced Encephalopathy and Nonconvulsive Status Epilepticus: Dispelling an Artificial Dichotomy. Neurohospitalist. 2019 Apr;9(2):100-104.
67. Lacroix C, Kheloufi F, Montastruc F, Bennis Y, Pizzoglio V, Micallef J. Serious central nervous system side effects of cephalosporins: A national analysis of serious reports registered in the French Pharmacovigilance Database. J Neurol Sci. 2019 Mar 15;398:196-201.
68. Bora I, Demir AB, Uzun P. Nonconvulsive status epilepticus cases arising in connection with cephalosporins. Epilepsy Behav Case Rep. 2016;6:23-7.
69. Uda A, Ebisawa K, Sakon H, Kusuki M, Izuta R, Yahata M, Yano I, Miyara T. Sustained Improvements in Antimicrobial Therapy and Clinical Outcomes following a Pharmacist-Led Antimicrobial Stewardship Intervention: Uncontrolled Before-After Study. J Clin Med. 2022 Jan 23;11(3)

.