Int. J. Pharm. Investigation, 2024; 14(2):289-298.
https://www.jpionline.org

Review Article

Sulbactam and Durlobactam Combination as a Newer Antibiotic for Carbapenem-Resistant *Acinetobacter baumannii* Infections

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ABSTRACT

This review explores the evolution of the concept of Healthcare-Associated Pneumonia (HCAP) in light of the 2016 guidelines from the Infectious Diseases Society of America (IDSA). These updated guidelines prioritize patient-specific risk factors over healthcare system interactions in pneumonia classification. Recent research has revealed that the risk of contracting Multidrug-Resistant (MDR) pathogens is more closely linked to individual patient risk factors than to healthcare system interactions. Consequently, administering empiric antibiotic therapy targeting MDR bacteria for patients meeting HCAP criteria is discouraged unless specific risk factors for MDR infections are identifiable. Hospital-Acquired Pneumonia (HAP) is a significant challenge, particularly in intensive care units, leading to elevated hospitalization costs and extended inpatient care. The review also delves into the emergence and global prevalence of Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) infections, known for their high mortality rates. In response to the rising threat of CRAB infections, the review introduces Sulbactam-Durlobactam (SUL-DUR) as a promising therapeutic solution. It examines the unique characteristics of Sulbactam and Durlobactam, both individually and in combination, and their potential in treating CRAB infections. Clinical trial data is presented to demonstrate the effectiveness and safety of SUL-DUR in addressing Hospital-Acquired Bacterial Pneumonia (HABP), Ventilator-Associated Bacterial Pneumonia (VABP), and bacteremia caused by the *Acinetobacter baumannii*-Calcoaceticus complex. The review also covers FDA-approved prescribing guidelines, dosage recommendations, adverse reactions, drug interactions, and usage in specific populations, including pregnant and lactating individuals. The management of renal and hepatic impairment and underscores the importance of monitoring for potential overdosage. While initial clinical evidence is promising, further research is essential to establish the full efficacy and safety profile of SUL-DUR.

Keywords: Hospital Acquired Bacterial Pneumonia, Hospital Acquired Pneumonia, Ventilator Associated Bacterial Pneumonia, Carbapenem Resistant *Acinetobacter baumannii*, Multidrug Resistant, Sulbactam, Durlobactam.

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Received: 13-10-2023;
Revised: 18-12-2023;
Accepted: 03-02-2024.

INTRODUCTION

Pneumonia is characterized by the emergence of novel lung infiltrates coupled with clinical signs suggestive of an infectious origin, including recent-onset fever, purulent sputum, elevated leukocyte count, and deteriorating oxygen levels.[1] Hospital-Acquired Pneumonia (HAP), also known as nosocomial pneumonia, refers to lower respiratory tract infections that were not in the incubation phase at the time of a patient's hospital admission and become symptomatic two or more days after admission. Cases of pneumonia with symptoms occurring sooner should be classified as instances of community-acquired pneumonia. Ventilator-Associated Pneumonia (VAP) specifically pertains to nosocomial pneumonia that develops in patients who have been receiving ventilator support for more than 48 hr.[1,2]

In the context of a literature review, it's essential to highlight the evolution of the concept of Healthcare-Associated Pneumonia (HCAP) based on the latest guidelines, specifically the Infectious Diseases Society of America (IDSA) guideline from 2016. The term "HCAP" has been deprecated in recent pneumonia classifications according to these guidelines. The updated guidelines emphasize a more refined and individualized approach to categorizing pneumonia cases by considering various risk factors and patient-specific characteristics. Nevertheless, recent research has revealed that a considerable number of individuals

DOI: 10.5530/ijpi.14.2.36

meeting the HCAP criteria did not have actual infections caused by MDR pathogens.[3] The past research, retrospective studies have indicated that the use of broad-spectrum antibiotics in such cases may lead to less favorable outcomes. It seems that the risk of infection with Multidrug-Resistant (MDR) organisms is more closely linked to individual patient risk factors rather than interactions within the healthcare system. As a result, it is advisable not to administer empiric antibiotic therapy aimed at Multidrug-Resistant (MDR) bacteria to patients who fullfill HCAP criteria, unless credible risk factors for acquiring MDR infections are evident.[4,5]

Hospital-Acquired Pneumonia (HAP) is a commonly observed bacterial infection acquired within healthcare facilities, notably prominent in both medical and surgical Intensive Care Units (ICUs). As a result, HAP substantially contributes to escalated hospitalization costs and prolonged durations of inpatient care.[6]

Carbapenem-Resistant *Acinetobacter baumannii* (CRAB)

The group of Gram-negative bacteria known as the *Acinetobacter baumannii*-Calcoaceticus Complex (ABC) represents a collection of closely related *Acinetobacter* species acknowledged for their tendency to cause formidable and serious infections.[7] This Gram-negative bacillus, *Acinetobacter baumannii*, displays an aerobic nature, pleomorphic morphology, and limited motility. Operating as an opportunistic pathogen, *A. baumannii* poses a significant threat to individuals with compromised immune systems, particularly those enduring extended hospitalization exceeding 90 days.[8] These microorganisms instigate an array of skin and soft tissue infections, intricate urinary tract infections, Ventilator-Associated Pneumonia (VAP), bacteremia and various other maladies afflicting both immune compromised and healthy populations alike.[9] Despite its typical aquatic habitat, *A. baumannii* has demonstrated a capacity to establish colonization on the skin and has been extensively recovered from the respiratory and oropharyngeal secretions of afflicted individuals.[10]

The preponderance of Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) infections are concentrated within healthcare facilities, notably affecting patients in critical care units who often contend with a multitude of medical comorbidities. Nonetheless, infections do sporadically emerge within community settings, particularly in the Asia Pacific region, as well as in long-term acute care environments.[11,12] The mortality rates stemming from Acinetobacter infections, which frequently follow a chronic trajectory, commonly range from 40% to 60%.[13] The prevalence of these infections varies markedly worldwide, encompassing scenarios such as Surgical site infections account for 1% of cases, while Ventilator-Associated Pneumonia (VAP) represents 12% of instances in the United States,[14] to as much as in China, hospital-acquired drug-resistant infections make up 35% of the total cases.[15] In the realm of afflicted patients, substantial quantities of *baumannii* have been retrieved from their respiratory and oropharyngeal secretions, with the pathogen showcasing an adeptness for skin colonization.[10]

The primary cause of carbapenem resistance in *A. baumannii* is unequivocally associated with the horizontal integration of class D (OXA-type) carbapenemase genes.[16] In addition to carbapenem resistance, additional pathways include obtaining class B (VIM-, IMP-, and NDM-type) carbapenemases, the lack of the outer membrane protein CarO, and alterations to the AdeABC resistance-nodulation-division efflux pump.[17] Although these alternative pathways of resistance are less frequently observed, their impact on shaping the concerning phenotype is eclipsed by the significant potency exhibited by the class D carbapenemase genes.

Remarkably, a significant portion of CRAB isolates exhibit either an exceedingly high level of drug resistance, rendering them susceptible solely to polymyxins, aminoglycosides, or tigecycline, or they manifest multidrug resistance, further compounding the complexities of therapeutic interventions.[18] Within the realm of CRAB infections, patients are confronted with a daunting reality, as their susceptibility to mortality is at least twofold compared to individuals afflicted by *A. baumannii* strains that retain sensitivity to carbapenem treatments.[19]

Presently, a substantial array of ABC isolates prominently displays multidrug resistance, extending its reach to encompass even formidable resistance against Carbapenems. Notably, infections stemming from Carbapenem-Resistant ABC have ascended to become the fourth foremost contributor to mortality entwined with antimicrobial resistance worldwide.[20] The categorization of *A. baumannii* as an imminent peril and a prime focus for urgent action has underscored its role as a prioritized pathogen, underscoring the imperativeness of cultivating novel antibiotics to counter its menace.[21]

In the backdrop of escalating antimicrobial resistance, individuals grappling with severe infections originating from Carbapenem-Resistant ABC, encompassing conditions like HABP, VABP, and bloodstream infections, often find themselves subjected to inadequate initial antimicrobial treatment, a circumstance that precipitates adverse consequences and amplifies the burden of healthcare expenditure.[22,23]

Navigating the most effective strategy to address grave infections stemming from Carbapenem-Resistant ABC remains a conundrum marked by uncertainty.[24] Established guidelines advocate for the utilization of combination antibiotic therapies, which might encompass amalgams centered around Colistin, Tigecycline, Minocycline, and Sulbactam, contingent upon factors like the site of infection and *in vitro* susceptibility profiles.[24,25] Nevertheless, the utilization of Colistin often incurs dose-dependent toxicity, most notably nephrotoxicity, and

exhibits suboptimal efficacy at recommended dosages due to limitations in tissue penetration.[16]

Cefiderocol approved for HABP and VABP caused by gram-negative agents, including *A. baumannii*.[26] Nevertheless, instances of cefiderocol-resistant *A. baumannii* have already emerged, driven by mutations affecting Iron transporter, β-Lactamases Enzyme, and Penicillin-Binding Proteins (PBPs).[27] Furthermore, the effectiveness of Cefiderocol against CRAB infections yielded unsatisfactory outcomes, revealing a disparity in mortality when compared to the comparator (best available therapy).[23]

Although Tigecycline exhibits robust *in vitro* antimicrobial activity against CRAB, its practicality is hindered by limitations like limited tissue distribution, low plasma concentration, ADR particularly GI complications. Consequently, the urgent need for innovative treatment approaches for CRAB infections remains steadfast.

Sulbactum

Initially developed by Pfizer as a sulfone β-lactamase inhibitor, Sulbactam has shown a unique dual function as a cell wall synthesis inhibitor. It effectively targets crucial Penicillin-Binding Proteins (PBPs) in Acinetobacter spp. and certain Gram-negative bacteria like *Neisseria* spp., ultimately leading to cell death. This distinctive amalgamation of a bactericidal β-Lactamase Inhibitor, Sulbactam, boasts favorable pharmacological attributes that render it a promising contender for advancement within clinical realms. A frequent application entails its utilization as a β-Lactamase inhibitor in tandem with β-Lactams like Ampicillin, thereby culminating in the formulation of Ampicillin-Sulbactam.

Sulbactam's inhibitory process remains confined to a distinct subset of class A serine β-Lactamases, as evidenced by its nuanced mechanism of action.[28] An alluring facet of Sulbactam lies in its inherent antibacterial efficacy, which is meticulously reserved for Acinetobacter and a select cohort of bacterial species, a direct outcome of its astute interception of pivotal enzymes pivotal to bacterial peptidoglycan synthesis. Within the Acinetobacter domain, Sulbactam specifically zeroes in on PBP1a, PBP1b, and PBP3, all while sparing the influence upon PBP2. The eloquence of this selectivity is effectively showcased through its preferential inhibition of BOCILLIN FL penicillin labeling within *A. baumannii* membranes, concurrently inducing cell filamentation-an unequivocal testament to the nuanced inhibition of Gram-negative PBP1/PBP3 interactions.[29]

Frequently integrated in tandem with Ampicillin, Sulbactam emerges as a stalwart component of amalgamated strategies against CRAB, catalyzing the inception of diverse combinations such as Polymyxin-B-Meropenem-Sulbactam and Colistin-Doripenem-Sulbactam, to name a few.[30] In an enlightening study by Wang *et al*., emphasis was placed on the nuanced interplay between Sulbactam ratios and the subsequent escalation of *in vitro* antimicrobial activity within Sulbactam-based ensembles, a phenomenon particularly pertinent in the context of *A. baumannii*.[31] Within this dynamic spectrum of combinations, the Cefoperazone-Sulbactam partnership, anchored at a 1:3 ratio, rose as the preeminent contender, showcasing the most potent *in vitro* activity that effectively surpassed the performance of numerous comparator agents.

Although further in-depth research is required to explore the intricate mechanistic underpinnings that govern the effectiveness of Sulbactam and other β-lactam combinations against CRAB, there is an encouraging aspect in the promising 50% inhibitory concentration of Sulbactam concerning PBP3, which could potentially play a role in its impact.[32] Moreover, the potential for concurrent inhibition of multiple PBPs in the context of co-administering diverse β-Lactams remains an enigma that beckons further elucidation. It's important to highlight that the vulnerability of Sulbactam to enzymatic degradation by various β-Lactamases found in Acinetobacter spp. raises valid concerns.[28] Therefore; a prudent approach involves combining Sulbactam with an innovative, wide-ranging β-Lactamase inhibitor-a logical step poised to address the ongoing challenge posed by CRAB.

Durlobactam

Distinguished by its nomenclature as Durlobactam, alternatively known as DUR or ETX2514, this compound stands out from the cohort of recently endorsed β-Lactamase inhibitors through its unique attributes. Revealing itself as an innovative broad-spectrum Diazabicyclooctane (DBO), Durlobactam exhibits a wide-ranging capability by effectively countering Ambler class A, C, and D β-lactamases, including the prevalent OXA-type Carbapenemases often found in Carbapenem-resistant ABC. Durlobactam apart from its market counterparts is its capacity to extend its activity across a broader spectrum. The development and creation of Durlobactam were founded on a combination of structure-based drug design, computational chemistry, and medicinal chemistry. This integrated approach was guided by the principle of enhancing chemical reactivity, increasing enzymatic affinity, improving permeability through Gram-negative barriers, and optimizing physico-chemical properties to facilitate intravenous administration.[33]

Durlobactam's eminent status as an exceedingly potent Diazabicyclooctane (DBO) β-Lactamase inhibitor has been substantiated through a multitude of inquiries, unequivocally highlighting its expansive scope in contrast to its DBO inhibitor counterparts. Adding to its intrigue, Durlobactam unfolds an inherent antibacterial prowess against select bacterial species.[33-35] An intriguing aspect comes to light as Durlobactam interacts with Penicillin-Binding Proteins (PBPs), as revealed by rapid acylation rate constants and microscopy examinations using phase contrast. These changes reveal notable modifications in morphology,

Table 1: Depiction of therapy, complications and effectiveness of the drug in various phases of clinical trials.

Author, Year of Publishing	Phases	Study	Therapy	Complication	Effectiveness
Olexiy Sagan *et al*., 2020	Phase 1-2	Clinical studies	Sulbactam-Durlobactam was well-received without significant adverse effects and displayed favorable pharmacokinetic characteristics when administered alone or in conjunction with Imipenem-Cilastatin in healthy adults.	Urinary Tract Infections (UTIs) or Acute Pyelonephritis.	Sulbactam-Durlobactam demonstrated effective penetration of lung epithelium in healthy adults, indicating its potential for further investigation as a novel treatment for pneumonia caused by multidrug-resistant *A. baumannii*.[39]
Keith S Kaye *et al*., 2023	Phase 3	Pathogen-specific, Randomised clinical trial	The use of Sulbactam-Durlobactam in combination with colistin for the treatment of severe infections caused by carbapenem-resistant *A. baumannii*-Calcoaceticus complex (ABC).	A reduced occurrence of nephrotoxicity in comparison to colistin.	Sulbactam-Durlobactam achieved the primary non-inferiority endpoint of 28-day all-cause mortality.[40]

especially the emergence of spherical structures that signify PBP2 inhibition. However, this effect on Acinetobacter Minimum Inhibitory Concentrations (MICs) becomes less prominent when Durlobactam is examined independently. In the context of its distinct role against CRAB, Durlobactam solidifies its position as an exceptionally effective antagonist to Acinetobacter-associated Cephalosporinase and class D β-Lactamases, encompasing the OXA lineage Carbapenemases (OXA-23, OXA-24/40) that remain pervasive within CRAB. Notably, *in vitro* explorations have laid bare Durlobactam's potential to reinstate the efficacy of Sulbactam against multidrug-resistant *A. baumannii*.[33]

Sulbactam-Durlobactam

The prospect of a potent therapeutic solution to combat CRAB is firmly rooted in the synergy between Sulbactam and Durlobactam, culminating in the creation of the innovative amalgam, Sulbactam-Durlobactam (SUL-DUR). Notably, the efficacy of Sulbactam-Durlobactam has been substantiated by its remarkable capacity for lung epithelium penetration within healthy adults, a compelling testament to its potential for tackling pneumonia induced by multidrug-resistant *A. baumannii*.[36] Through worldwide surveillance initiatives, the *in vitro* effectiveness of Sulbactam-Durlobactam against Carbapenem-Resistant ABC isolates has proven to be impressive, with fewer than 4% exhibiting a Minimum Inhibitory Concentration (MIC) exceeding the suggested susceptibility threshold of 4 µg/mL.[37,38]

In the realm of limited clinical trial experiences, early glimpses within case reports have illuminated a pathway toward promising outcomes. A noteworthy illustration is provided in the case study documented by Zaidan *et al*., which highlights a successful treatment outcome for extensively drug-resistant *A. baumannii* pneumonia and septic shock. The strategy employed a combination of Cefiderocol and SUL-DUR, with the process expedited through an investigational new drug application pathway.[41] It is noteworthy to underscore that the simultaneous administration of Cefiderocol adds layers of complexity to the quest for pinpointing the chief architect of microbial eradication. The authors venture into speculation, contemplating the multifaceted role of DUR, which beyond fortifying SUL, could conceivably have bolstered the efficacy of Cefiderocol as well. This remarkable achievement finds an echo in the tenets of the ATTACK trial, where the orchestration of combination therapies, designed to assail multiple fronts, culminated in heightened efficacy (Table 1).[40]

Amidst the landscape of pharmaceutical innovations, Cefiderocol (FetrojaR) emerges as a recent milestone, securing approval to combat the tenacious challenge posed by drug-resistant Gram-negative pathogens, with particular resilience displayed against MDR Acinetobacter.[42] However, the translation of its robust *in vitro* potential to preclinical models encounters nuances, as *in vivo* efficacy against Cefiderocol-susceptible *Acinetobacter baumannii* surfaces with an element of variability.[43] Expanding on this storyline, clinical trials have revealed a concerning aspect where Cefiderocol treatment is associated with increased mortality rates when compared to the best available therapy. This situation has been observed in patients dealing with *A. baumannii* bloodstream infections or nosocomial pneumonia.[23] The intricacies of these outcomes have found alignment with

challenges woven around siderophore-mediated uptake and the ensuing specter of heteroresistance.[44] At present, a promising prospect in the advanced phases of clinical development focuses on a singular combination: the potent pairing of Sulbactam, a first-generation β-Lactamase inhibitor with inherent antibacterial effectiveness against Acinetobacter spp., and Durlobactam, a next-generation Diazabicyclooctane β-Lactamase inhibitor that exerts a broad-spectrum influence encompassing Class A, C, and D β-Lactamases.[33]

Clinical Trial Details

Summary

This comprehensive study unfolds in two distinct phases. Part A encompasses a meticulously orchestrated randomized controlled segment, meticulously designed to delve into patients grappling with HABP, VABP, or Bacteremia emanating from the *Acinetobacter baumannii*-Calcoaceticus complex. The subsequent Part B constitutes a single-group facet, which strategically focuses on addressing infections attributable to *Acinetobacter baumannii*-Calcoaceticus complex that have exhibited resistance or have proven unresponsive to Colistin or polymyxin B interventions, meticulously adhering to the predefined inclusion criteria.

Study Type: Interventional

Phase: Phase 3

Study Design

Allocation: Randomized

Masking: None (Open Label)

Description of Masking: While logistical constraints may prevent the complete masking of study drugs, rigorous efforts will be made to maintain confidentiality involving patients, site staff, and the Sponsor. This confidentiality will be upheld, with the exception of the attending physician and immediate healthcare providers.

Primary Purpose: Therapeutic Intervention

ABC Complex, HABP, VABP, Bacteremia, and Colistin Resistant ABC.

Interventions

Sulbactam: Administered intravenously as a 1.0 g infusion over duration of 3 hr, repeated at 6 hr intervals (q6h).

Durlobactam: Administered intravenously as a 1.0 g infusion over duration of 3 hr, repeated at 6 hr intervals (q6h).

Sulbactam-Durlobactam: Administered for a therapeutic duration ranging from 7 to 14 days, tailored to individual clinical requirements.

Colistin: Treatment for 7 to 14 days as needed

Imipenem/Cilastatin: 1.0 g Imipenem/1.0 g Cilastatin IV infusion over 1 hr q6h

Study Arms

Experimental: Part A-Group 1 (Assessor-blind).

Sulbactam-Durlobactam+Imipenem/Cilastatin.

Active Comparator: Part A-Group 2 (Control).

Colistin+Imipenem/Cilastatin.

Experimental Arm: Part B-Group 3 (Open-label).

Treatment with the combination of Sulbactam-Durlobactam along with Imipenem/Cilastatin.

Active Comparator Arm: Part B-Group 3 (Open-label).

Administration of the combination of Sulbactam-Durlobactam together with Imipenem/Cilastatin.

Sex and Gender: Both sexes are eligible for the study.

Ages: Participants must be 18 years and older (Adult, Older Adult).[45]

Prescribing Information (FDA Approved)

Therapeutic Indications

Sulbactam-Durlobactam is an innovative co-packaged formulation that combines the synergistic potential of Sulbactam, a Beta-Lactam antibacterial with strong Beta-Lactamase inhibitory properties, with Durlobactam, an advanced Beta-Lactamase Inhibitor. This medication is utilized for the treatment of HABP or VABP caused by susceptible strains of *Acinetobacter baumannii*-Calcoaceticus complex in patients who are 18 years of age and older.

Limitations of Use

Sulbactam-Durlobactam's formulation is specifically designed to target HABP or VABP caused by strains of the ABC complex that are susceptible to it. To safeguard against the emergence of drug-resistant bacterial strains and uphold the therapeutic efficacy of Sulbactam-Durlobactam, as well as other antibacterial agents, its usage should be restricted to the treatment or prevention of infections that have been definitively diagnosed as bacterial or display compelling signs suggesting a bacterial origin.

Dosage and Application Guidelines

Individuals with CLcr between 45 and 129 mL/min are recommended to follow a dosing regimen that entails the intravenous infusion of 1 g of each Sulbactam and Durlobactam every 6 hr. This administration should be conducted carefully over 3 hr duration. Modifications to the dosing schedule are

Table 2: Shows specific Adverse Reactions that occur at a frequency exceeding 5%.

Adverse drug Reactions	Sulbactam-durlobactam (*N*=91) n (%)
Any Adverse Reaction	80 (88)
Liver test abnormalities*	17 (19)
Diarrhea	15 (17)
Anemia	12 (13)
Hypokalemia	11 (12)
Arrhythmia	8 (9)
Acute kidney injury*	5 (6)
Thrombocytopenia	5 (6)
Constipation	5 (6)

necessary for those with CLcr values below 45 mL/min or above 130 mL/min.

Moreover, the administration protocol mandates that all doses of Sulbactam-Durlobactam be meticulously infused intravenously over a standardized 3 hr interval.

Dosage Forms and Strengths

Contained within the packaging is a singular, impeccably clear vial housing a single dose of Sulbactam for injection, impeccably dosed at 1 g potency. Complementing this, the ensemble also comprises two individual amber vials, each meticulously calibrated at 0.5 g strength, encapsulating doses of Durlobactam for injection.

Absolute Preclusions

The utilization of Sulbactam-Durlobactam is absolutely not recommended for patients who have a confirmed and severe allergic reaction to any of the components present in the product.

Cautions and Vigilance

Notably, Beta-Lactam antibacterial drugs have been associated with instances of severe and on occasion fatal hypersensitivity (anaphylactic) reactions. Such hypersensitivity reactions were also observed in individuals undergoing treatment with Sulbactam-Durlobactam. Should an allergic response manifest, it is imperative to promptly cease the utilization of Sulbactam-Durlobactam.

Clostridioides difficile-Associated Diarrhea (CDAD)

Nearly all systemic antibacterial agents, including Sulbactam-Durlobactam, have been associated with cases of CDAD. Patients should be assessed in case of the occurrence of Diarrhea.

Adverse drug reactions

*Liver test abnormalities encompass a spectrum of adverse reactions, encapsulating manifestations such as anomalies in liver function tests, deviations in hepatic function, heightened transaminase levels, elevated ALT, and escalated AST readings.

On the other hand, the category of acute kidney injury encompasses a range of adverse reactions, encompassing conditions like renal impairment, elevated blood creatinine levels, toxic nephropathy, instances of renal failure, and occurrences of acute kidney injury (Table 2).

Drug Interactions

Concomitant administration of Sulbactam-Durlobactam with Organic Anion Transporter 1(OAT1) inhibitors may lead to increased plasma concentrations of the drug. Therefore, concurrent use is not recommended.

Use in Specific Populations

Pregnancy

Unfortunately, there is a lack of sufficient data to thoroughly assess the potential for notable birth defects, miscarriages, or other adverse effects on both maternal and fetal health associated with the use of SUL-DUL during pregnancy.

Lactation

There is currently no information available regarding the presence of Durlobactam in human or animal milk. While small amounts of Sulbactam have been found in human milk, there is a possibility of Sulbactam being present in breast milk, with an estimated maximum daily dose for infants of 560 mcg/kg/day (which is equivalent to 1% to 2% of the dose adjusted for adult weight). However, the effects of both Sulbactam and Durlobactam on breastfeeding infants and milk production have not been established.

Pediatric Use

Patients below 18 years of age has not yet been demonstrated for safety and efficacy.

Geriatric Use

Within Trial 1, comprising 91 Sulbactam-Durlobactam-treated patients, 54% (49 individuals) were aged 65 and above, with 19% (17 patients) belonging to the 76 and older age group. However, clinical studies lacked sufficient representation of patients aged 65 and over, precluding the determination of potential age-related variations in response.

Renal Impairment

Individuals with a creatinine Clearance (CLcr) ranging from 45 to 129 mL/min: No modification of Sulbactam-Durlobactam dosage is advised.

Individuals with a creatinine Clearance (CLcr) below 45 mL/min (including those undergoing intermittent hemodialysis):

Dosing regimen adjustments are needed.

Regular monitoring of renal function is advised, and dosages should be adapted as renal function may change during therapy.

Patients Receiving Continuous Renal Replacement Therapy (CRRT)

In this context, there exists a paucity of comprehensive guidelines offering definitive dosage recommendations.

Optimal treatment strategies should be predicated upon the patient's prevailing clinical condition, accompanied by vigilant monitoring of renal function and requisite dose modifications.

Patients Exhibiting a Creatinine Clearance (CLcr) of 130 mL/min or Higher.

A modification of the dosage regimen becomes imperative in this scenario.

Monitoring of renal function should occur regularly, and dosages of Sulbactam-Durlobactam should be modified if renal function changes.

Hepatic Impairment

Pharmacokinetics of SUL-DUR remains unexplored; however, it is noteworthy that hepatic impairment is unlikely to exert a substantial impact on the elimination of Sulbactam-Durlobactam, given that both constituents undergo negligible hepatic metabolism or excretion. Consequently, no necessitation for dose modifications arises in patients with compromised hepatic impairments.

Overdosage

Regrettably, there is a lack of information pertaining to the clinical manifestations resulting from an overdose of Sulbactam-Durlobactam. It's important to note that elevated Cerebrospinal Fluid (CSF) levels of Beta-Lactams could potentially lead to neurological adverse reactions, including seizures. Notably, both Sulbactam and Durlobactam are susceptible to removal through hemodialysis. However, the clinical utility of hemodialysis as a treatment strategy for managing overdosage remains unverified due to a dearth of available clinical data.[46]

DISCUSSION

The prevalence of antimicrobial resistance, especially in CRAB infections, has led to significant challenges in managing these infections effectively. The emergence of Carbapenemase genes, particularly class D Carbapenemase genes, is a primary driver of Carbapenem resistance in *A. baumannii*. Recent clinical studies have highlighted the potential of the combination therapy of SUL-DUR as a viable treatment option for CRAB infections. SUL-DUR exhibits potent *in vitro* efficacy against Carbapenem-Resistant ABC isolates and has displayed encouraging outcomes in clinical trials. SUL-DUR, consisting of Sulbactam and Durlobactam, exhibits a favorable pharmacokinetic profile and has demonstrated efficacy and safety in treating severe infections caused by CRAB. Notably, the Phase 3 ATTACK trial established non-inferiority of SUL-DUR compared to Colistin, a commonly used treatment for CRAB infections, while also showing a lower incidence of Nephrotoxicity associated with SUL-DUR.[40] Case reports and early trial results suggest that SUL-DUR in combination with other agents like Cefiderocol might offer a potent treatment strategy.[43]

The study employs a robust interventional design, consisting of two distinct phases. Part A focuses on patients with HABP, VABP, or bacteremia caused by ABC. This segment employs an assessor-blind approach, comparing the efficacy of SUL-DUR in combination with Imipenem/Cilastatin against the active comparator Colistin plus Imipenem/Cilastatin. Part B, on the other hand, addresses infections caused by the ABC that have exhibited resistance or unresponsiveness to Colistin or polymyxin B interventions. This open-label portion evaluates the efficacy of Sulbactam-Durlobactam with Imipenem/Cilastatin in a single-group setting. The trial's focus on clinical improvement is commendable, as the APACHE II and SOFA scores are utilized to gauge the patients' baseline severity and response to treatment. This approach is in line with established criteria for assessing the severity of acute illness and predicting patient outcomes. Furthermore, the inclusion criteria for both parts of the study are well-defined, encompassing individuals with validated diagnoses of severe infections necessitating intravenous antibiotic treatment. The study introduces a novel therapeutic approach by utilizing Sulbactam-Durlobactam combination therapy. This co-packaged formulation presents a promising strategy to address CRAB infections. Sulbactam, a β-lactam antibacterial agent with β-lactamase inhibitory properties, is combined with Durlobactam, an advanced β-lactamase inhibitor, in a bid to counteract the resistance mechanisms employed by *Acinetobacter baumannii*. Literature suggests that the mechanisms of β-lactam resistance in *Acinetobacter baumannii* often involve the production of carbapenemase enzymes, rendering carbapenem antibiotics ineffective. Sulbactam's inhibition of these enzymes, coupled with Durlobactam's enhanced activity against various β-lactamases, offers a promising avenue to overcome resistance. Notably, this

trial provides valuable insights into the practical application of this novel approach, demonstrating its potential to combat infections that are unresponsive to conventional treatments. The study's findings have significant clinical implications, suggesting that Sulbactam-Durlobactam combination therapy could represent a valuable addition to the armamentarium against CRAB infections. Notably, the efficacy of this regimen is assessed against Colistin, a last-resort antibiotic often associated with significant adverse effects. The trial's design recognizes the need for alternative treatments in the face of Colistin resistance and provides a critical step forward in addressing this clinical challenge. However, certain limitations warrant consideration. The open-label masking strategy introduces potential biases, which could impact the interpretation of results. Additionally, the study's focus on short-term outcomes raises questions about the long-term effectiveness and potential development of resistance to Sulbactam-Durlobactam.[45]

The study's findings hold significant clinical implications, indicating that the combination therapy of Sulbactam-Durlobactam could be a valuable addition to combat CRAB infections. It's noteworthy that the regimen's effectiveness is evaluated against Colistin, a last-resort antibiotic with substantial adverse effects. The trial's design acknowledges the urgency for alternative treatments amid Colistin resistance, making a crucial stride in addressing this clinical challenge. Nevertheless, certain limitations necessitate consideration, as the open-label masking approach introduces potential biases that might impact result interpretation. Additionally, the study's focus on short-term outcomes raises queries about the long-term efficacy and potential resistance development to Sulbactam-Durlobactam. Sulbactam-Durlobactam introduces a novel strategy to combat *Acinetobacter baumannii*-Calcoaceticus complex infections, particularly in HABP and VABP. The innovative combination of Sulbactam and Durlobactam offers a synergistic effect against susceptible isolates, a notable advancement against multidrug-resistant infections, notably *Acinetobacter baumannii*. The dosing regimen, addressing renal function, underscores careful adjustments for impaired clearance. The meticulous infusion protocol, standardizing administration over a 3 hr interval, highlights the significance of optimizing therapeutic effectiveness through cautious administration. The prescribing information provides a comprehensive understanding of adverse reactions associated with Sulbactam-Durlobactam treatment. Notably, liver test abnormalities and acute kidney injury align with literature on β-lactam antibacterial drugs, emphasizing monitoring and timely response. Insights into specific populations underscore the need for cautious use and monitoring, with considerations for pregnancy and breastfeeding lacking comprehensive data. These findings prompt clinicians to carefully evaluate benefits and potential risks when considering Sulbactam-Durlobactam as a treatment option.[46]

To sum up, the randomized clinical trial investigating the effectiveness and safety of Intravenous Sulbactam-ETX2514 for *Acinetobacter baumannii*-Calcoaceticus Complex Infections provides important insights into addressing the management of difficult CRAB infections. The introduction of Sulbactam-Durlobactam combination therapy as an innovative strategy represents a step towards overcoming antibiotic resistance. While the trial presents promising results, further research is needed to explore the long-term effects, assess resistance development, and evaluate the treatment's role in a broader clinical context. The prescribing information for Sulbactam-Durlobactam provides a comprehensive overview of its indications, dosing guidelines, safety considerations, and limitations. By aligning with existing literature and research, this information aids healthcare professionals in making informed decisions regarding the use of this novel therapeutic option. However, the safety profile and long-term effectiveness of Sulbactam-Durlobactam require ongoing research to establish its place in the management of *Acinetobacter baumannii* infections.

CONCLUSION

In conclusion, the recent reclassification of pneumonia cases, moving away from the Healthcare-Associated Pneumonia (HCAP) framework, underlines the evolving landscape of infectious disease management. This shift reflects a growing emphasis on personalized treatment strategies, with a focus on individual patient risk factors to guide antibiotic therapy. Notably, recent research, including clinical trials such as the Phase 3 ATTACK trial, has unequivocally demonstrated the efficacy and safety of SUL-DUR in the treatment of severe infections caused by Carbapenem-Resistant *Acinetobacter baumannii* (CRAB). The escalating challenge of CRAB infections, particularly within healthcare settings, has underscored the critical need for innovative therapeutic options. SUL-DUR has emerged as a beacon of hope, showcasing its effectiveness and safety through rigorous clinical trials. This co-packaged formulation combines the strengths of Sulbactam and Durlobactam to effectively combat infections stemming from the *Acinetobacter baumannii*-Calcoaceticus complex. SUL-DUR presents a promising solution in the ongoing battle against multidrug-resistant pathogens, offering a precise and efficient treatment approach for patients grappling with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. The introduction of SUL-DUR marks a significant leap forward in addressing the formidable challenges posed by drug-resistant Gram-negative pathogens. It underscores the perpetual necessity for groundbreaking solutions in the realm of infectious diseases, heralding a future where targeted therapies provide renewed hope for patients and healthcare providers.

ACKNOWLEDGEMENT

The authors are thankful to the Vice-Chancellor, Registrar and Dean of Pharmacy, KLE Academy of Higher Education and Research, Belagavi. We would also like to thank Medical and Hospital Staff of Vivekanand General Hospital, Hubballi for providing necessary support.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ABC: *Acinetobacter baumannii*-Calcoaceticus Complex; **HABP:** Hospital Acquired Bacterial Pneumonia; **HAP:** Hospital Acquired Pneumonia; **HCAP:** Healthcare-Associated Pneumonia **VABP:** Ventilator Associated Bacterial Pneumonia; **MDR:** Multidrug-resistant **CRAB:** Carbapenem Resistant *Acinetobacter baumannii*; **SUL-DUL:** Sulbactam Durlobactam; **FDA:** Food and Drug Administration; **IDSA:** Infectious Diseases Society of America.

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Cite this article: Nyamagoud SB, Swamy AHV, Abhishek BJ, Varghese LE, Bhoomika SK. Sulbactam and Durlobactam Combination as a Newer Antibiotic for Carbapenem-Resistant *Acinetobacter baumannii* Infections. Int. J. Pharm. Investigation. 2024;14(2):289-98.