Journal of Antibiotics Research
Volume 8 | Issue 1
ISSN: 2574-5980

Research Article Open Access

Ceftobiprole Medocaril

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Citation: Ahlam Ayyad, Kyra Thompson (2024) Ceftobiprole Medocaril, J Antibioti Res 7(1): 102

Received Date: July 26, 2024 **Accepted Date:** August 26, 2024 **Published Date:** August 31, 2024

Abstract

Ceftobiprole Medocaril is a fifth-generations cephalosporin indicated for the treatment of adult patients with Staphylococcus aureus bacteremia (SAB), adult patients with bacterial skin and skin structure infections (ABSSI), and adults and pediatric patients with community-acquired bacterial pneumonia (CABP). It provides a feasible and efficient alternative for empiric therapy.

Keywords: Ceftobiprole Medocaril; Bacteremia; Skin; Soft Tissue Infections; Pneumonia

Introduction

Bacterial infections present a global health challenge, impacting millions of individuals each year. According to the 2019 National Ambulatory Medical Care Survey, US residents visited the physician office 10.2 million times for infectious and parasitic disease [1]. The high occurrence has caused the frequent prescription of antibiotics, as empiric therapy, to effectively treat these conditions. Prior to susceptibility testing, individuals are often treated based on the site of infection, the organisms most known to colonize that site, patient history, and local bacterial resistance patterns [2]. Due to common antibiotics having limited coverage, empiric therapy usually involves the use of two or more drugs to ensure a broad range of pathogens covered. The importance of broad-spectrum antibiotics that can target a variety of pathogens is crucial for optimizing treatment outcomes. Given the frequency of antibiotic prescriptions, it is important to assess the strategies used for common conditions such as Staphylococcus aureus bacteremia (SAB), acute bacterial skin and skin structure infections (ABSSSI), and community-acquired bacterial pneumonia (CABP).

Bacteremia is defined as the presence of bacteria in the bloodstream and has been associated with high morbidity and mortality, emphasizing the need for thorough evaluation and appropriate empiric therapy when suspected. Risk factors for bacteremia include advanced age, use of immunosuppressant agents, chronic liver disease, chronic renal failure, hematologic malignancies, HIV infection, IV catheters, parenteral nutrition, neutropenia, and malnutrition [3]. The appropriate selection of empiric therapy for bacteremia is a complex decision [3]. Once a pathogen has been confirmed, therapy can be adjusted to target the offend-

ing agent. Confirming bloodstream infections often poses a challenge as blood culture specimens are frequently contaminated [3]. These contaminations may be due to improper techniques or colonization from where the blood is obtained. However, factors indicative of true bacteremia includes clinical or physical findings, presence of risk factors, body temperature, leukocyte counts, and the type of pathogens found [3]. Bacteria such as staphylococcus aureus found in the blood should always be considered true bacteremia [4]. Determining the source of SAB and if metastatic spread has occurred is extremely crucial [5]. All patients who are diagnosed with SAB require an echocardiography to assess for endocarditis [4]. SAB is classified into uncomplicated and complicated. Uncomplicated is composed of cases with no implanted prosthetic devices, endocarditis excluded with a TEE, follow-up blood cultures negative for S.

Aureus, patient defervesce within 72 hours of initiating therapy, no evidence of metastatic staphylococcal infection, or ndividuals with MSSA [5]. Complicated cases are defined as patients with positive blood cultures who don't meet all the criteria for uncomplicated SAB [4, 6]. ABSSSI are a common cause of morbidity in the healthcare setting [7]. These infections present as lesions with a minimum surface of 75 cm^2 and include wound infections, cellulitis/erysipelas, and major cutaneous abscesses [8, 9]. Studies have shown an increasing number of patients seeking care due to skin and skin structure infections [8]. While the causative agent of these infections is not always identified, S. aureus remains to be the most common pathogen [10]. Since the 1990s, the emergence of community-associated methicillin-resistant staphylococcus aureus (MRSA) has presented the United States with higher rates of hospitalizations, recurrence, complications, and treatment failures [9, 11]. Although gram-positive bacteria tend be the most common cause of ABSSSI, gram negative bacteria such as streptococci, enterococci, and other gram-negative bacteria may also be involved in ABSSSI [7]. Gram-negative infections have shown to be more difficult to treat as recent antibiotic coverage has focused on gram positive organisms [9, 10]. Empiric therapy for infections should be guided by infection type and epidemiological patterns. Effective management of ABSSSI is critical and involves prompt diagnosis, appropriate treatment, and sometimes surgical intervention.

Community acquired pneumonia refers to an infection of the pulmonary parenchyma primarily caused by bacterial or viral pathogens that have been acquired outside of the hospital [12]. The clinical presentation of CAP varies but can range from fever and productive cough to respiratory distress and sepsis [12]. While pathogens are not detected in many cases, streptococcus pneumoniae remains the most common identified cause [12,13]. Other causative organisms of CAP include mycoplasma pneumoniae, chlamydia pneumoniae, haemophilus influenza, moraxella catarrhalis, and respiratory viruses [14]. The diagnosis of CAP usually requires findings of an infiltrate on chest imaging and clinical findings suggestive of CAP (10,14).It remains a prevalent and serious infection with one in every five patients being hospitalized in order to receive treatment [15]. Patients who are hospitalized are further categorized into non-severe and severe, with severe CAP being defined as the presence of respiratory failure or symptoms of sepsis [14]. For individuals treated in the outpatientsetting, it is not recommended to obtain routine sputum cultures. However, sputum cultures should be obtained for patients that are hospitalized with severe CAP.

Treatment

When treating SAB, it is crucial that source control is obtained. This can be done by removing hardware and debridement of any abscesses. The use of penicillin for serious infections is discouraged since the susceptibility is questionable without proper sensitivity testing [5]. While some strains of staphylococcus aureus may be susceptible to penicillins, methicillin-resistant staphylococcus aureus (MRSA) has become more prevalent [5]. However, Methicillin-sensitive staphylococcus aureus (MSSA), should be treated with penicillins susceptible to S. Aureus such as oxacillin or nafcillin [5]. Non-life-threatening penicillin allergies should be treated with cefazolin [5]. Patients with Type 1 penicillin allergies who are not able to tolerate cephalosporins, should be considered for oxacillin/nafcillin desensitization [5]. Vancomycin is considered the first line treatment for patients with MRSA or patients with life-threatening penicillin allergies [6]. On the other hand, daptomycin should be considered in patients with vancomycin associated renal toxicity or when the vancomycin MIC is greater than 1.5 mcg/mL [6]. Gentamicin and

rifampin are recommended as adjunct therapy for individuals with prosthetic valve endocarditis [6]. However, the addition of gentamicin is not recommended for S. Aureus bacteremia or native valve endocarditis as it has been associated with nephrotoxicity [4]. Additionally, rifampin should not be used without the recommendation from an infectious disease specialist as it has been associated with increased drug interactions and toxicity [4]. Blood cultures should be performed every 24-48 hours until it is confirmed and documented that gram-positive bacteria has been cleared from the bloodstream [6]. Duration of therapy should be calculated beginning from the day of the first negative blood culture or obtainment of source control. It is crucial that patients are treated for the correct amount of time as it has been shown that

individuals with inadequate amount of treatment have had increased rates of relapse [4]. Uncomplicated SAB is treated for 14 days while complicated SAB is treated for 28-42 days 6,4]. Individuals with osteomyelitis typically undergo treatment for a minimum of 42 days [6]. For patients with right-sided endocarditis, the duration of treatment ranges from 28 to 42 days [6]. However, injecting drug users with MSSA and minimal comorbidities are treated for 14 days [6]. Lastly, individuals with left-sided endocarditis are treated for a minimum of 42 days [6].

In 2014, the Infectious Diseases Society of America (IDSA) issued guidelines for diagnosing and treating ABSSSI [16]. These guidelines were established before the FDA approved newer antibiotics such as dalbavancin, omadacyclin, oritavancin, tedizolid, and delafloxacin [9, 20]. The guidelines differentiate between purulent and nonpurulent ABSSSI, labeling cellulitis and erysipelas as nonpurulent and abscesses as purulent.[16] Nonpurulent and purulent are further categorized into mild, moderate, and severe. While ABSSSI is a common cause of hospital admission, a majority of patients are able to be treated outpatient with oral antibiotics [7]. First line therapy for severe nonpurulent infections include vancomycin plus zosyn. Moderate nonpurulent infections are treated intravenously with penicillin, ceftriaxone, cefazolin, or clindamycin while mild infections are treated with oral antibiotics such as penicillin VK, cephalosporins, dicloxacillin, or clindamycin [16]. All purulent infections are treated with incision and drainage. When managing severe purulent infections, vancomycin, linezolid, tigecycline, daptomycin, ceftaroline, and telavancin are considered suitable antimicrobial agents [16]. For moderate purulent infections, trimethoprim-sulfamethoxazole and doxycycline are recommended [16]. In cases of methicillin-susceptible S. aureus (MSSA), severe infections are treated with nafcillin, cefazolin, or clindamycin, while moderate infections are treated with dicloxacillin or cephalexin. [16]. Although is there is lack of data to support the optimal duration of treatment, the guidelines suggest that treatment last 7 to 10 days [9, 16].

Following the diagnosis of pneumonia, treatment is dependent on the level of care a patient needs [17]. In addition to clinical judgement, doctors utilize tools such as the Pneumonia Severity Index or CURB-65 to determine the need for hospitalization in patients presenting with CAP [18]. The choice of antibiotic is individualized based on risks and benefits, patient characteristics, and local antibiotic sensitivity data [18]. Treatment with antibiotics that cover the possible pathogens associated with CAP should be started within hours, as it has been shown that delays in antibiotic treatment exceeding four hours increase mortality risk [12, 15]. All patients should be treated for a minimum of 5 days, except for those with confirmed MRSA or Pseudomonas infections, who require a minimum of 7 days of treatment [14]. Empiric therapy for previously healthy individuals being treated in the outpatient setting includes doxycycline or amoxicillin [14]. For outpatients who have taken antibiotics within the past three months or have underlying health conditions, it's recommended to treat them with either an respiratory fluoroquinolone or a combination of a beta-lactam with either a macrolide or doxycycline [17]. Outpatient therapy differs slightly from inpatient therapy, as those being treated in the hospital should receive coverage for drug-resistant S. Pneumoniae in order to rapidly achieve adequate therapy to patients [17]. For non-severe CAP, treatment should also include either an antipneumococcal fluoroquinolone or a beta-lactam paired with a macrolide [19]. Vancomycin or Zosyn may be added to this regimen, depending on prior culture results and patient history [14]. In cases of severe CAP, treatment consist of a beta-lactam with a macrolide or an antipneumococcal fluoroquinolone, with MRSA and P. Aeruginosa coverage added as necessary, considering recent hospitalizations and culture findings [19]. Patients should remain afebrile for a minimum of 48 hours prior to the discontinuation of

antibiotics [14]. Since the 2019 release of the CABP diagnosis and treatment guidelines, the FDA has approved newer antibiotics including omadacycline, delafloxacin, and lefamulin [19,20].

As antibiotic resistance continues to increase, the need for broad-spectrum drugs for empiric therapy have become crucial. Newer medications such as ceftobiprole medocaril have demonstrated promising in vitro results, proving it to be a safe and effective option for treating infections such as SAB, ABSSSI, and CABP. Healthy adults being treated with Ceftobiprole Medocaril for SAB should be treated for a maximum of 42 days, while those being treating for CABP or ABSSSI should be treated for 5 to 14 days [21]. This drug is effective against both gram-positive and gram-negative pathogens, notably including the difficult--to-treat MRSA. Ceftobiprole Medocaril offers a significant practical advantage over older antibiotics such as vancomycin as it does not require constant monitoring of trough levels, simplifying administration and convenience for healthcare providers [10]. In order to maintain the efficacy of Ceftobiprole Medocaril and to further reduce the development of drug-resistant bacteria, it should be reserved to treat or prevent infections that are proven or suspected to be caused by susceptible bacteria [21]. Susceptibility can be proven by culture or susceptibility information; however local epidemiology and susceptibility patterns should be used in the absence of that data. Ceftobiprole Medocaril's broad-spectrum efficacy and safety profile has made it a valuable asset in the fight against bacterial infections.

Ceftobiprole Medocaril: Background

Ceftobiprole Medocaril is a fifth generation extended-spectrum cephalosporin with proven in vitro activity against both gram--positive and gram-negative pathogens, including MRSA [13]. Clinical and in vitro antibacterial activity has been shown against Staphylococcus aureus, Streptococcus pyrogenes, Klebsiella pneumonia, Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae, and Haemophilus parainfluenzae [21]. It was developed by Basilea Pharmaceutica and has shown to be efficacious in treating Staphylococcus aureus bloodstream infections, including right-sided infective endocarditis, acute bacterial skin and skin structure infections, and community-acquired bacterial infections [21]. Ceftobiprole medocaril's antibacterial activity is exerted by inhibiting bacterial cell wall synthesis, a process important for bacterial growth and replication. Phase III trials have established Ceftobiprole Medocaril's therapeutic efficacy and safety profile, making it advantageous when treating infectious diseases.

Ceftobiprole Medocaril: Chemistry [21]

Ceftobiprole medocaril contains sodium salt of ceftobiprole medocaril, a, semisynthetic, cephalosporin antibacterial, for intravenous use. Its molecular weight is 690.6 g/mol. The empirical formula is $C_{26}H_{25}N_8NaO_{11}S_2$ [Figure 1].

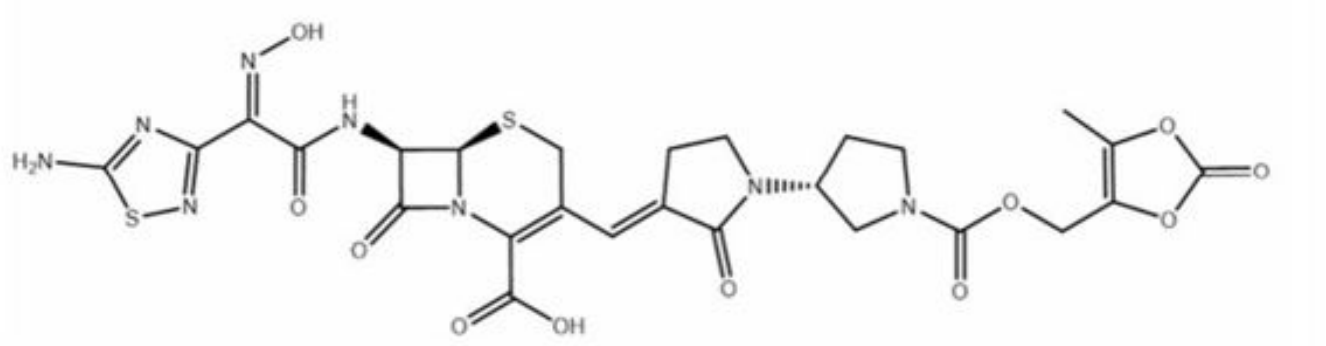

Figure 1

Ceftobiprole Medocaril: Mechanism of Action [20-21]

Ceftobiprole Medocaril once converted to its active form, has bactericidal activity that inhibits bacterial cell wall synthesis through binding to one or more of the penicillin-binding proteins (PBPs) and inhibiting their transpeptidase activity. Ceftobiprole specifically inhibits PBP2a in methicillin-resistant staphylococcus aureus (MRSA) and PBP2b and PBP2x in penicillin- resistant staphylococcus pneumoniae.

Ceftobiprole Medocaril: Pharmacokinetics [21]

Ceftobiprole medocaril is the prodrug of ceftobiprole that is metabolized by plasma esterase to its active metabolite, Ceftobiprole. It is not absorbed in the gastrointestinal tract; therefore it is administered intravenously. It exhibits linear and time-independent pharmacokinetics, and the major route of elimination is through renal excretion with 83% of it excreted unchanged in the urine.

No clinically significant differences in the pharmacokinetics of ceftobiprole were observed in adults based on age, gender, or race/ethnicity. The effect of hepatic impairment on pharmacokinetics is unknown. However, with moderate renal impairment in a creatinine clearance of 30 <50ml/min, the area under the curve increased by 2.5-fold and 3.3-fold in severe renal impairment in a creatinine clearance of <30ml/min. The effect of any degree of renal impairment in pediatric patients less than 2 years of age or in pediatric patients with creatinine clearance of < 15 mL/min/1.73 m2 on ceftobiprole pharmacokinetics is unknown. In patients with end-stage renal disease (ESRD) requiring dialysis, no clinically significant difference in the pharmacokinetics of ceftobiprole were observed in adult patients with ESRD defined as a creatinine clearance of <15ml/min. It was demonstrated to be removed by hemodialysis. A clinically significant reduction in ceftobiprole exposure is predicted in patients with augmented renal clearance (>150ml/min). It is imperative to assess renal clearance to ensure appropriate dosing prior to initiation of Ceftobiprole.

In vitro studies Ceftobiprole does inhibit or induce CYP450 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Additionally, it is an inhibitor of OATP1B1, OATP1B3, MRP2 and BSEP but is not an inhibitor of P-glycoprotein, BCRP, OAT1, OAT3, OCT1, OCT2, or MATE1. Assessing drug interactions with other medications is recommended.

Ceftobiprole Medocaril: Clinical Trials (ref. 21,13,22)

These 3 trials granted approval for the use of Ceftobiprole Medocaril in bacteremia, skin and soft tissue infections, and pneumonia [Table 1]. The first and most recent trial by Holland T et al, focused on the overall success in patients with SAB. This was a multi center phase 3, double blind, double-dummy noninferior trial. A total of 132 of 189 patients (69.8%) in the ceftobiprole group and 136 of 198 patients (68.7%) in the daptomycin group had overall treatment success (adjusted difference, 2.0 percentage points; 95% confidence interval [CI], -7.1 to 11.1). The second trial by Overcash J et al, focused on ceftobiprole in acute bacterial skin and skin structure infections. This was a multicenter phase 3, randomized double blind, active-controlled, parallel-group, noninferiority study. 679 patients were randomized to ceftobiprole (n = 335) or vancomycin/aztreonam (n = 344). Early clinical success rates were 91.3% and 88.1% in the ceftobiprole and vancomycin/aztreonam groups, respectively, and noninferiority was demonstrated (adjusted difference: 3.3%; 95% CI: -1.2, 7.8).Lastly, in the third trial by Nicholson S et al, this was a multicenter, double-blind study in which 706 patients with severe CAP requiring hospitalization were randomized to ceftobiprole or to an expert-recommended course of ceftriaxone ± linezolid (comparator group). Clinical and microbiological outcomes were determined 7-14 days after completion of therapy (test-of-cure visit). For the 469 clinically evaluable patients, cure rates were 86.6% vs. 87.4% for ceftobiprole and comparator, respectively [95% confidence interval (CI) of the difference, -6.9% to 5.3%]; in the intention-to- treat (ITT) analysis of 638 CAP patients, these cure rates were 76.4% vs. 79.3%, respectively (95% CI of the difference, -9.3% to 3.6%).

Table 1: Summary of Clinical Trials Granting Approval of Ceftobiprole Medocaril for Specific Indications

Study Number of participants	Intervention	Comparator	Result
Holland T et al. (2023)N = 390	Ceftobiprole 500mg intravenously every 6 hours for 8 days and every 8 hours thereafter	Daptomycin 6 to 10 mg per kilogram of body weight intravenously every 24 hours plus optional aztreonam (at the discretion of the trial-siteinvestigators)	Ceftobiprole was noninferior to daptomycin with respect to overall treatment success in patients with complicated *S. aureus* bacteremia.
Overcash J et al. (2021)N=679	Ceftobiprole 500mg was administered every 8 hours as a 2-hour IV infusion	Vancomycin was administered as a 2- hour 1000 mg (or 15 mg/kg) IVinfusion every 12 hours (q12h; decision regarding fixed or weight- based dose was made by the investigator on the basis of the site's standard of care), and aztreonam was administered as a 0.5-hour 1000 mgIV infusion q12h.	Ceftobiprole is noninferior to vancomycin/aztreonam in the treatment of ABSSSIs, in terms of early clinical response and investigator- assessed clinical success at the test of cure visit.
Nicholoson S et al. (2012)N=706	Ceftobiprole	Ceftriaxone + Linezolid	Ceftobiprole was non- inferior to the comparator (ceftriaxone ± linezolid) in all clinical and microbiological analyses conducted, suggesting thatceftobiprole has a potentialrole in treating hospitalizedpatients with CAP.

Ceftobiprole Medocaril: Tolerability and Pharmacovigilance

First Trial: [22] Adverse events were reported in 121 of 191 patients (63.4%) who received ceftobiprole and 117 of 198 patients (59.1%) who received daptomycin; serious adverse events were reported in 36 patients (18.8%) and 45 patients (22.7%), respectively. Gastrointestinal adverse events (primarily mild nausea) were more frequent with ceftobiprole [Table 2].

Second Trial: [10] Treatment-emergent AEs were reported in an overall higher proportion of patients in the ceftobiprole group (44.3%) compared with the vancomycin/aztreonam group (38.6%). The majority of AEs were mild or moderate, with a smaller proportion of patients experiencing severe AEs in the ceftobiprole group compared with the vancomycin/aztreonam group (2.7% vs 7.0%). The proportion of treatment-related AEs was similar in the 2 groups (19.8% and 18.1% in the ceftobiprole and vancomycin/aztreonam groups, respectively) [Table 3].

Third Trial: [13] Ceftobiprole Medocaril was generally well tolerated with only a minority of patients discontinuing their treatment courses prematurely due to adverse effects. 18 out of 310 (6%) in the ceftobiprole group and12 out of 322 (4%) in the comparator group. The difference of treatment-related adverse effects was 36% in the treatment group and 26% in the comparator group. The overall incidence of treatment-related adverse events was higher in the ceftobiprole group, primarily owing to differences in rates of nausea (7% vs. 2%) and vomiting (5% vs. 2%) [Table 4].

Table 2: Select Adverse Reactions Occurring in > 5% of SAB Adult patients receiving Ceftobiprole Medocaril

Adverse Reaction	**Ceftobiprole Medocaril N = 191**	**Daptomycin ± Aztreonam N = 198**
Anemia	12%	13%
Nausea	10%	4%
Hypokalemia	9%	3%
Vomiting	8%	2%
Hepatic Enzyme & Bilirubin Increased	8%	10%
Diarrhea	7%	3%
Blood Creatinine Increased	7%	5%
Hypertension	5%	2%

Table 3: Select Adverse Reactions Occurring in > 5% of ABSSSI Adult patients receiving Ceftobiprfole Medocaril

Adverse Reaction	Ceftobiprfole Medocaril N = 334	Vancomycin + Aztreonam N = 342
Nausea	11%	6%
Diarrhea	6%	5%
Headache	6%	7%

Table 4: Select Adverse Reactions Occurring in > 5% of CABP Adult patients receiving Ceftobiprole Medocaril

Adverse Reaction	Ceftobiprole Medocaril N = 310	Ceftriaxone† ± linezolid N = 322
Nausea	10%	4%
Hepatic Enzyme Increased	10%	11%
Vomiting	9%	3%
Diarrhea	7%	9%
Headache	7%	7%
Rash	5%	2%
Insomnia	5%	4%

Conclusions

In April 2024, the US FDA approved Ceftobiprole Medocaril, a fifth-generation cephalosporin for the treatment of adult patients with SAB, including those with right-sided endocarditis, adult patients with ABSSSI, and adults and pediatric patients with ABP. Ceftobiprole Medocaril's use is limited to infections caused by susceptible pathogens, however it's broad-spectrum activity offers a simpler and more effective solution for empiric therapy. [21]. Data from three phase 3 trials- ERADICATE, TARGET, and a randomized double-blind trial were used to prove the efficacy, safety, and tolerability of Ceftobiprole. Collectively, these trials support Ceftobiprole Medocaril as a dependable antibiotic choice for treating severe bacterial infections and when initiating empiric therapy. While Ceftobiprole has not been approved for other indications in the United States, the broad-spectrum activity of this antibiotic suggests that it could be further studied for the use in infections that are increasingly difficult to treat such as hospital-acquired pneumonia (HAP). The potential use of Ceftobiprole emphasizes it's role as an effective option in the treatment of bacterial infections including those caused by resistant pathogens.

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