***Case study***

# Safety and efficacy profile of CSE-1034 as a prolonged de-escalation therapy in prosthetic joint infection: A case report


## Abstract

### Background

Although rare, infection is considered to be most dreadful of the prosthetic related complications resulting in repeated surgical intervention, extended hospitalization or sometimes in loss of implant or permanent disability if not treated promptly. Poor treatment outcome associated with prosthetic joint infections (PJIs) could be partly attributed to rise in anti-microbial resistance among the causative agents.

### Case presentation

This is a first reported case of ceftriaxone + sulbactam + ethylenediaminetetraacetic acid (CSE 1034) being used as an de-escalation therapy for more than 24 days with good safety and efficacy outcome in a 78 year male patient with PJI associated with hip replacement surgery, treated initially with meropenem and colistin followed by prolonged de-escalation therapy (24 days).

### Conclusions

In clinically complicated cases of deep infections where prolonged use of last resort antibiotics is used, CSE-1034 can be considered as a safe, efficacious and economical de-escalating antibiotic to complete the treatment course and prevent recurrence of infection, especially in PJI.

## Introduction

The number of hip replacement surgeries has rapidly increased in recent years. The joint prosthesis is recognized as one of the most successful surgical interventions in medicine and provides significant reduction in pain, improves joint function and minimizes disability[1]. The worldwide literature survey has shown infection rates for primary total hip revision to be 1-2% and higher in cases undergoing revised total hip surgeries [2][3]. Although rare, infections following joint replacement surgery are the most devastating prosthetic-related complications and challenging to treat[3].

Prevention of prosthetic joint infections is of utmost importance, and success in treating these infections depends on extensive debridement, removal of dead and extraneous tissue and most importantly effective antibiotic therapy[4]. Antibiotics form an important part of current medical care and effective antibiotic prophylaxis constitutes an important part in the treatment of bacterial infections. Although infections following joint prosthetic surgeries are rare, however with emerging bacterial resistance, its occurrence can be increasingly difficult to eradicate [5][6] PJIs with drug resistant pathogens may require prolonged medical management resulting in extended and expensive hospital stays, repeated surgical intervention and sometimes can end up in definitive loss of implant [5]. The failure of first choice of antibiotic used in empirical therapy requires the treatment with second or third choice drugs that could be more expensive, less effective and indeed more toxic. Here, we present a case of post-surgical infection treated initially with a combination of meropenem and colistin followed by de-escalation therapy of CSE-1034.

## Case presentation

A 78 year old male was admitted to our department with chief complain of oozing at operation site. He also complained of pain in left hip joint with instability while walking.

The patient's medical history showed that he was operated for total left hip replacement (THR) recently. He also had a history of diabetes, hypertension and ischemic heart disease. Moreover, the patient had also undergone coronary artery bypass grafting (CABG) about 8 years

ago. After recently performed hip replacement surgery, the patient complained of occasional pain. PBH X-ray had shown femur splinting in proximal medial aspect and the patient was re-operated for tension wiring of implant and started with meropenem. On the post operation third day patient had an episode of rigor, the patient was transferred from surgery ward to our department, for further treatment management. Physical examination revealed the patient to be afebrile with all his vitals normal, temperature: 98.4˚F, blood pressure: 120/90, pulse: 78/min. Systemic examination of central nervous system showed the patient was conscious and oriented, cardiovascular examination revealed S1 and S2 within normal limits, per abdomen was soft and non-tender and respiratory system was clear. Hematology tests done revealed deranged TLC count (18500/cu-mm) with neutrophil count on higher side ($6.58x10^3$cells/cu-mm), normal hemoglobin (11.8g/dl); raised ESR (45mm/hr) and hs-CRP(10.4mg/dL) levels. Venous Doppler of both lower limbs showed normal flow in both lower limbs veins with no deep vein thrombosis. Mild sub-cutaneous edema was observed in left leg on both sides and continuous discharge from the operation site was noticed. Because of continuous discharge from wound; surgical site wash, wound exploration and debridement of all deep infected tissues above fascia and below deep fascia were performed. In the process, pulse lavage of the wound was done with 3-4 liters of normal saline. After wound cleansing, closure was done in layers followed by dressing. Wound discharge was forwarded to laboratory for culture and sensitivity testing Based on Musculoskeletal Infection Society criteria, a provisional diagnosis of PJI was arrived at, and the patient was re-shifted to ICU and started immediately with intravenous (IV) dose of antibiotics (meropenem + colistin) and other supportive treatment. The antibiotic choice was based on the hospital antibiogram data and the patient's hematological parameters. Laboratory culture and sensitivity report didn't reveal any pathogenic growth. After 48h of ongoing antibiotic treatment, the patient was observed to respond to treatment and the exudates from the surgical site started decreasing. The patient continued to receive same IV treatment with antibiotics for 7 days. Repeat hematological tests and other parameters confirmed patient's improvement. On $8^{th}$ day of admission, the patient was shifted to de-escalation therapy of CSE-1034 (3gm/12h), considering its broad-spectrum activity in targeting various resistant mechanisms of pathogens. The patients responded well to the de-escalation treatment and was thus continued with CSE-1034. After 10 days of treatment, the patient was hemodynamically stable and shifted to ward. He was discharged on $18^{th}$ day of admission and advised to continue

CSE-1034 1.5gm/12h via IV and other basic supportive medicine for 2 weeks. The patient was advised for follow-up and to report immediately in case of fever, pain at operation site, convulsions, headache, chest pain and breathlessness and loss of consciousness. On regular follow-ups and clinical examination, it was observed that the patient didn't show any sign and symptoms of recurrence or superinfection and was hemodynamically stable.

## Discussion

Despite the high success rate, joint prosthetic surgeries are not without complications. Of all prosthetic related complications, infection is probably the most threatening one. Although rare, prosthetic infections after total hip replacement surgeries require prolonged surgical and medical management. The costs of treating an infection after THR are reported to a minimum amount of 50,000US dollars per patient. Moreover, the steep rise in the number of operations for implanting these prostheses in past few years, has been simultaneously accompanied by number of PJIs [7]. Although, the recent technical advances in the field of medicine accompanied by use of laminar air flow, exhaust systems, antibiotic-loaded acrylic bone cement and antibiotics have all contributed to reduced infection rate, however PJIs still occur in 1-3% of patients[7].

Frequently, the organisms implicated in infected prosthetic joints are usually relatively benign organisms or simple contaminants. These microorganisms may penetrate wound during surgical procedures from both endogenous and exogenous sources including patient's external microbiota, microbiota of surrounding surgical team, hospital environment, surgical instruments and even contaminated implants. PJIs that develop during first year after prosthetic implant are considered to be SSIs and are usually treated using broad spectrum antibiotics. Though broad spectrum, anti-microbial therapy at the time of induction is given, that helps to cut the risk of infection at the surgical site[8]. These benign microorganisms tend to become pathogenic taking advantage of suppressed immune system, associated co-morbidities along with sterile surgical sites making certain individuals more vulnerable to infections.

Here, we present a case report of PJI treated successfully with initial therapy of meropenem + colistin, and de-escalation therapy of CSE-1034. The patient responded well to the treatment and was discharged on $18^{th}$ day of admission with the advice to continue CSE-1034 for 2 weeks. Hence the present report highlights the importance of CSE-1034 in deep infections

usually treated with only last resort antibiotics. The normal course of antibiotic treatment for PJIs extends from 4-6 weeks. Moreover, drug induced thrombocytopenia is reported in patients undergoing meropenem treatment for more than 10 days[9]. Thus, in deep infection cases where carbapenems are used empirically and the treatment duration extends from 4-6 weeks, CSE-1034 can be used as deescalating antibiotic to complete the treatment course and cure the infection without observing any side effects associated with prolonged meropenem therapy and compromising the safety of patients. In support of our outcome, various studies in the past have documented CSE-1034 as an effective treatment for MDR bacterial infections alone or as combination therapy with colistin[10][11]. This unique case study highlights the safety and efficacy profile in prolonged duration treatment modules along with dramatic reduction in treatment-related costs, if CSE-1034 is used in de-escalation therapy in treating PJI.

**References**


1. Lima ALL, Oliveira PR, Carvalho VC, Saconi ES, Cabrita HB, Rodrigues MB. Periprosthetic Joint Infections. Interdiscip Perspect Infect Dis 2013; 2013:.

2. Kunutsor SK, Beswick AD, Peters TJ, Gooberman-Hill R, Whitehouse MR, Blom AW, Moore AJ. Health Care Needs and Support for Patients Undergoing Treatment for Prosthetic Joint Infection following Hip or Knee Arthroplasty: A Systematic Review. PloS One 2017; 12:e0169068.

3. Masters JPM, Smith NA, Foguet P, Reed M, Parsons H, Sprowson AP. A systematic review of the evidence for single stage and two stage revision of infected knee replacement. BMC Musculoskelet Disord 2013; 14:222.

4. Minassian AM, Osmon DR, Berendt AR. Clinical guidelines in the management of prosthetic joint infection. J Antimicrob Chemother 2014; 69 Suppl 1:i29-35.

5. de Sanctis J, Teixeira L, van Duin D, Odio C, Hall G, Tomford JW, Perez F, Rudin SD, Bonomo RA, Barsoum WK, Joyce M, Krebs V, Schmitt S. Complex prosthetic joint infections due to carbapenemase-producing Klebsiella pneumoniae: a unique challenge in the era of untreatable infections. Int J Infect Dis IJID Off Publ Int Soc Infect Dis 2014; 25:73–78.

6. Legout L, Senneville E. Periprosthetic Joint Infections: Clinical and Bench Research. Sci World J 2013; 2013:.

7. Tande AJ, Patel R. Prosthetic joint infection. Clin Microbiol Rev 2014; 27:302–345.

8. Prokuski L. Prophylactic antibiotics in orthopaedic surgery. J Am Acad Orthop Surg 2008; 16:283–293.

9. Huang R, Cai G-Q, Zhang J-H, Liu F-X, Ma J-Q, Liu H, Nie X-M, Gui R. Meropenem-induced immune thrombocytopenia and the diagnostic process of laboratory testing. Transfusion (Paris) 2017; .

10. Chaudhary M, Mir MA, Ayub SG. Safety and efficacy of a novel drug elores (ceftriaxone + sulbactam + disodium edetate) in the management of multi-drug resistant bacterial infections in tertiary care centers: a post-marketing surveillance study. Braz J Infect Dis 2017; 21:408–417.

11. Sathe P, Maddani S, Kulkarni S, Munshi N. Management of ventilator associated pneumonia with a new antibiotic adjuvant entity (ceftriaxone + sulbactam + disodium edetate) - A novel approach to spare carbapenems. J Crit Care 2017; 41:145–149.

161

162

163