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Research Paper

Antibiotic Adjuvant Therapy in Diabetic Patients with Cellulitis Induced Pan Drug Resistance Infection in Lower-Limb Amputation Patient: a Case Study

Medical Science

KEYWORDS : Amputation, Cellulitis, Elores, Pandrug resistance.

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ABSTRACT

Rising complications in diabetic patient suffering with cellulitis is a serious concern. Diabetic patients with cellulitis have an increased chance of bacterial infection and are associated with high incidence of amputation. Diabetic patient flora gives an ideal environment to Gram positive and Gram negative bacterial growth. Increased morbidity and mortality is noted in antimicrobial resistant Gram-negative bacterial infections, especially in diabetic patients undergone amputation. Here we discuss a case of cellulitis with pandrug resistant infections in post lower-limb amputation treated successfully with newer antibiotic adjuvant entity: Elores (ceftriaxone+sulbactam+ adjuvant disodium edetate).

INTRODUCTION

Cellulitis is an inflammatory condition of the skin and subcutaneous tissue, occurring on any body site, mainly lower limbs are affected in up to 70% of cases (Björnsdóttir et al., 2005). Frequency of cellulitis in the diabetic lower limb is nine times higher compared to non-diabetics (Jain, 2014). Even after wound healing, recurrence of infection and lower extremity amputation rates are increasing remarkably among diabetic patients (Xavier et al., 2014). The possible predisposing factors for cellulitis in hospitalized patients are diabetes mellitus, history of cellulitis, bacterial colonization, multidrug resistance, peripheral vascular disease, overweight and lymphedema (Koutkia et al., 1999).

Infections in diabetes have higher chances of amputation compared with patients without diabetes (Richard et al., 2011). Lower limb amputation is common and associated with significant morbidity, increasing hospital stay and higher rate of secondary postoperative complications (Coulston et al., 2012; McIntosh and Earnshaw, 2009).

The local complication post-amputation are mainly due to wound contamination by pathogenic bacteria. Microbiological profile of infections in the lower limbs is vital in the provision of appropriate management (McIntosh and Earnshaw, 2009). Studies report diabetic patients wound cultures to be polymicrobial in nature, due to the patients immunocompromised state with decreased ability to combat invasive bacterial infections. In recent years, microbiological profile of pathogenic bacteria in diabetic wounds changed from Gram-positive to Gram-negative bacilli in India (Ramakant et al., 2011). *E.coli, K. pneumoniae, E. faecalis, P. mirabilis and A. baumannii* were predominant noted in patients who underwent above or below knee amputations (Xavier et al., 2014).

Patients with diabetic infections are often exposed to multiple courses of antibiotics. Previous inappropriate antibiotic exposure can have a substantial influence on anticipated antimicrobial resistance (Matsuura and Barg, 2013). It has been estimated that at least 50% of all deaths caused by diabetes are the result of infections that are untreatable due to antibiotic resistance. Furthermore, colonization of resistant bacteria in chronic ulcers is associated with delayed healing. Antibiotics tackling multi drugs resistance mechanisms are used to eliminate resistant bacteria from colonized wounds (Chhibber et al., 2013).

Here we are presenting a case of diabetic patient with cellulitis infected with multi drug resistant *E.coli*, failed to respond initial Meropenem therapy turned to pandrug-resistant bacteria after major lower-limb amputation, which was successfully treated with antibiotic adjuvant therapy ceftriaxone+ sulbactam+ adjuvant disodium edetate(Elores)

Case presentation

This case is of a 65 year male patient admitted to our hospital with chief complaints of pain, swelling, redness in left medial side of thigh since two months after coronary angiography. Patient is a known case of diabetes mellitus on regular medication. Past history of bilateral (B/L) aortofemoral bypass graft surgery 4 months back post percutaneous transluminal coronary angiography (PTCA) was reported.

On general examination, patient was showing blood pressure of 150/80mmHg, pulse 80/min, respiratory rate of 14 breaths per minute, with no signs of pallor, icterus, oedema and normal jugular venous pressure (JVP). Systemic examination was unremarkable. Local examination of left leg revealed redness, raised temperature, swollen and tenderness with regional lymphadenopathy and pus pockets. Few violaceous bullae, minor cutaneous haemorrhages were seen with skin sloughing. On palpation, patient had severe pain on left leg, showing clear signs of cellulitis of left leg.

Patient was shifted to the cardio thoracic vascular surgery (CTVS) ward and advised routine hematological tests and, pus culture and sensitivity (C/S) investigations. Hematological tests were deranged, showing Hb 10.1 grams per deciliter, increased total leukocyte count (TLC) 16,300/cumm, differential leukocyte count showed increase polymorphs 88 % while lymphocytes, monocytes, eosinophils and basophil were within normal limit. Platelet counts were raised to 5.04 lacs/cumm. Random blood sugar level was within normal range, under anti-diabetic medication. Renal function test, urine test and prothrombin test were within normal limits. Pus C/S revealed *Escherichia coli,* sensitive to carbapenems and BL+BLI combinations. Based on the signs and symptoms, physical examination and lab reports, patient was given the provisional diagnosis of infected cellulitis with diabetes mellitus. Patient was started with a broad spectrum antibiotic Meropenem and other support therapy for five days. But considering the deteriorating condition and cellulitis of the left leg, the patient underwent amputation of left leg under spinal anesthesia, with meropenem coverage.

Two days post operative, wound samples were sent for C/S testing. Sensitivity tests were performed by Kirby-Bauer disc diffusion method. Test revealed pan drug resistance *E.coli* (aminoglycosides, carbapenem, β-lactam/β-lactamase inhibitors, Polymyxins, fluoroquinolones) and only sensitivity to newer antibiotic adjuvant entity: Elores. Thus, meropenem was stopped and Elores 1.5 g *bid* dose was started with 90 minutes infusions. Considering the condition of wound and positive patient response, Elores was continued till seventeen days. Suddenly patients started having pyrexia and chills. Hematological and urine sample were sent for routine investigation and C/S testing. Urine

culture reports were positive for *Candida* and *Enterococcus species,* showing sensitivity to nitrofurantoin, tetracycline, linezolid and vancomycin. Along with the broad spectrum antibiotic, patient was put on anti-fungal tablet fluconazole and Gram positive coverage with linezolid. Post antibiotic therapy for five days, patients condition improved and in urine cultures no organism was detected.

Patient was shifted to ward with Elores 1.5 g coverage, regular dressing and supportive therapy. Patient was discharged from hospital with improvement in wound and was advised for followup. Patient arrived at the out patient department with International Normalized Ratio (INR) for standardized prothrombin time report, which was within normal range. Wound healing was markedly improved, so was the condition of the patient.

Discussion

Patients with diabetic infections and their sequel amputations can lead to devastating complications and long-term morbidity (Matsuura and Barg, 2013). The incidence of mortality associated with lower limb amputation is reported to be as high as 30 to 54% within 1 month to 1 year respectively. Initial appropriate antibiotic therapy play a vital role in the management of diabetic infections. An incorrect or delayed initial diagnosis may increase the risk of serious complications, including permanent disability and amputations. Patients with diabetes have a 30-fold higher risk of lower-extremity amputation due to infection, compared to patients without diabetes (Sumpio, 2012).

Diabetic patients are more prone to infections, the main pathogenic mechanisms involved are hyperglycemic environment favors the virulence of some pathogens; lower production of interleukins in response to infection; reduced chemotaxis and phagocytic activity, immobilization of polymorphonuclear leukocytes; glycosuria, gastrointestinal and urinary dysmotility (Casqueiro et al., 2012).

In the present case, patient was having cellulitis in the left leg caused by *E. coli*, similar to this case *E.coli* pathogens in diabetic infections have been reported in many studies (Xavier et al., 2014); Matsuura and Barg, 2013; Shanmugam and Susan, 2013). Patients with diabetic infections are often exposed to multiple courses of antibiotics. Previous antibiotic exposure can have a substantial influence on anticipated antimicrobial resistance. It has been reported that patients with previous treatment with penicillin-based therapy had higher rates of *E. coli* resistance (Matsuura and Barg, 2013). Similar to this, in the present case patient was treated with Meropenem, but his condition was deteriorated and led to amputation, post-amputation wound samples showed pan-drug resistance *E.coli* which was resistance to previously exposed Meropenem (Magiorakos et al., 2012). Pan-drug resistance in the current case defined as per Centers for Disease Control and Prevention (CDC) criteria as *E.coli* resistant to all major class of antibiotics (aminoglycosides, carbapenem, β-lactam/β-lactamase inhibitors, polymyxins, fluoroquinolones etc.).

The condition of diabetic infections worsens further if the infection caused by harboring multi–drug-resistant organisms is not treated timely with appropriate antibiotic therapy. In recent years, there has been an increase in the incidence and the prevalence of MDR Gram-negative bacilli pathogens were observed in lower limb wounds of patients with diabetes ((Xavier et al., 2014; Ramakant et al., 2011; Shanmugam and Susan, 2013)). In the present case, bacteria acquired multiple resistant mechanisms after initial exposure to Meropenem and lead to pan-drug resistance. This might be a case of false susceptibility to Meropenem earlier reported by Babay et al., (2009). The possible drug-resistance in the present case may be due to one or multiple resistance mechanism acquired by bacteria during course of improper antibiotic exposure such as production of Extended-spectrum β-lactamases (ESBLs), over expression of efflux pump activation or decreased membrane permeability (Xavier et al., 2014; Chaudhary and Payasi, 2012; Chaudhary and Payasi, 2012; Chaudhary et al., 2013). *E.coli* has been reported as the second highest ESBL producer in diabetic infections (Shanmugam and Susan, 2013). Hence, selection of initial antibiotic therapy is critical in treating PDR pathogens as it associated with higher mortality, longer hospital stays and increased healthcare costs (Rello, 2007).

Current evidence from case study shows, improper use of antibiotics can often be attributed to the amputation of infected organ and provide opportunity to bacteria to acquire multiple drug resistant mechanisms. The new antibiotic adjuvant Elores was the only drug sensitive to post amputation wound samples in the current study. This is because of its unique mechanisms of actions in tackling contemporary resistance mechanisms produced by the bacteria. In the present case patient developed Urinary tract infection (UTI) due to *Candida* and Gram- positive *Enterococcus species* as UTI is common in diabetic patients. Patient was managed with anti-fungal and Gram -positive coverage with Linezolid (Aswani et al., 2014).

Elores has established evidences against multidrug resistance mechanisms produced by bacteria. In an *In vitro* study by Chaudhary et al. (2012), on efflux pump over expressed *E.coli* strains, Elores showed significant reduction in efflux pump expression and higher susceptibility. This could be due to decreased mRNA expression of AcrAB-Tolc with Elores (Babby et al., 2009). Similarly in a study done on biofilm positive *E.coli* strain, Elores eradicated the biofilms efficiently, by removal of divalent ions present in lipopolysaccharide layer of biofilms (Chaudhary et al., 2013). Elores is also active against ESBL and MBL producing pathogens. Similarly, in a rare case study by Singh (2015), Elores was used to treat patient UTI caused by ESBL producing MDR *E.coli* .

In a study done on ESBL producing clinical isolates of *E.coli* collected from North Indian hospitals, Elores exhibited good invitro activity. The enhanced susceptibility in those pathogens is due to synergistic activity of ceftriaxone+sulbactam+ adjuvant disodium edetate and chelation of divalent ions in the Metallo β-lactamase enzymes. Elores also enhances the susceptibility by altering the bacterial outer membrane permeability, which in turn increased penetration of drugs inside the bacterial cells (Chaudhary and Payasi, 2012).

In a retrospective, comparative clinical study (n=95), Elores and Meropenem showed 94.5%, 86.5% sensitivity to *E.coli* respectively (Bhatia, 2015). Similarly phase-III clinical studies published on Elores showed 80.3% clinical cure rates in patients include skin and skin structure infections (SSSIs) (Chaudhary and Payasi 2013). Hence, above sited evidences substantiated the use of Elores in the current study.

Conclusion

Diabetic patients are more susceptible to infections, thereby warranting a need for an appropriate broad spectrum antibiotic therapy acting on various bacterial mechanisms of resistance, especially when treating Pan drug-resistant pathogens. The current pan drug resistant case was successfully treated with a newer antibiotic adjuvant entity Elores having novel modes of action in tackling resistant pathogens, could be considered as a safe and effective therapy

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