



(CASE REPORT)



OUTPATIENT MANAGEMENT OF CARBAPENEM-RESISTANT *Escherichia coli* DIABETIC FOOT INFECTION WITH ORAL MINOCYCLINE: A CASE REPORT FROM KING HUSSEIN MEDICAL CENTER

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ABSTRACT

Background: Diabetic foot infections (DFIs) are a significant clinical problem especially in patients with long-standing diabetes and multiple comorbidities. Carbapenem-resistant *Escherichia coli* (CREC) has emerged as a concerning pathogen in diabetic foot infections (DFIs) that historically have necessitated hospitalization for intravenous (IV) therapy with agents like colistin, tigecycline, or combination regimens. Hospitalization is associated with the risk of nosocomial infection, venous access problems, functional decline, and high healthcare costs, particularly in elderly patients with multiple comorbidities. In this context, oral agents with good bioavailability and activity against Gram-negative pathogens such as minocycline are still underinvestigated. We report a case of a novel approach to management of CREC diabetic foot osteomyelitis in a high-risk elderly patient with oral minocycline as an alternative to injectable colistin.

Case Presentation: We present a 63-year-old man with a 15-year history of type 2 diabetes mellitus (T2DM), hypertension, chronic kidney disease (CKD) stage 3, peripheral vascular disease (PVD), and prior myocardial infarction (age-adjusted Charlson Comorbidity Index [CCI] of 8) who presented with a non-healing right foot plantar ulcer. Clinical examination revealed a 4.5 × 3.0 cm ulcer extending to bone (probe-to-bone positive), with surrounding erythema and purulent drainage. There were no systemic signs of sepsis. Deep tissue cultures obtained during surgical debridement grew carbapenem-resistant *E. coli* (non-susceptible to meropenem, ertapenem, ceftriaxone, ciprofloxacin, and trimethoprim-sulfamethoxazole) that was susceptible to minocycline (MIC ≤4 µg/mL). Given the patient's clinical stability, adequate perfusion (ankle-brachial index [ABI] = 0.98), successful source control, and preference to avoid hospitalization, he was initiated on outpatient oral minocycline 100 mg twice daily for 6 weeks, combined with total contact casting (TCC) for offloading and weekly multidisciplinary wound care.

Outcomes: The person took minocycline by mouth for 6 weeks and had no bad effects from it. The wound was checked several times and it healed slowly but surely and by week 10 the epithelium was fully covered. The level of inflammatory markers went back to normal (CRP went from 48 mg/L to 6 mg/L). The renal function stayed the same (creatinine 1.4–1.5 mg/dL). No one had to go to the hospital during the treatment. There were no signs of recurrence at the 3-month follow-up.

Conclusions: This case highlights that selected patients with CREC diabetic foot infections can be successfully managed in the outpatient setting with oral minocycline as an alternative to injectable colistin. This method might cut healthcare expenses, prevent the use of intravenous antibiotics in hospitals on patients and avoid nephrotoxicity related to colistin in fragile patients. More research is needed to define the best ways to manage it.

Keywords: Diabetic Foot Infection, Carbapenem-Resistant *Escherichia Coli*, Minocycline, Outpatient Management, Colistin, Antimicrobial Stewardship, Charlson Comorbidity Index

1 INTRODUCTION

One of the most challenging complications in people with diabetes is diabetic foot infections (DFIs). 15-25% of patients will experience a DFI at some point in their lifetime and there are more hospitalizations from DFIs than any other diabetic complication (Lipsky et al., 2020). Chronic diseases are a major burden on the health care systems in Jordan where more than 20% of the population are diabetic with significant consequences for morbidity, mortality and health care utilization (Ajlouni et al., 2020). In patients with long-standing diabetes, multiple comorbidities, or peripheral vascular disease (PVD), management of DFI can be particularly challenging as these factors independently increase the risk of treatment failure, amputation and death.

Carbapenem-resistant Enterobacteriaceae (CRE) are complicating the management of DFIs. Carbapenem-resistant *Escherichia coli* (CREC) is emerging in healthcare settings worldwide including Jordan, making treatment paradigms more difficult and often requiring intravenous (IV) agents such as colistin (polymyxin E), tigecycline, or combination therapy (Tumbarello et al., 2021). These agents typically are reserved for hospitalized patients because of the need for IV access, close monitoring, and potential adverse effects. In particular, colistin is highly associated with nephrotoxicity which is a concern in patients with chronic kidney disease (CKD) (Sorlí et al., 2019).

Current recommendations for CREC DFIs complicated by osteomyelitis are hospitalization, surgical debridement, 4-6 weeks of IV antibiotics and close monitoring (Lipsky et al., 2020). However, hospitalization carries many potential risks including nosocomial infections, venous thromboembolism, functional decline, delirium in elderly patients, and high cost (Lavizzo-Mourey, 2020). The CCI for this patient is 8, indicating a high risk for hospitalization. For patients with multiple comorbidities, the risk of hospitalization may outweigh the benefit, particularly for less invasive outpatient alternatives.

Minocycline, a tetracycline antibiotic, has properties that make it a potentially attractive option for outpatient DFI management. It is highly orally bioavailable (90-100%), penetrates bone well, is active against many carbapenem-resistant Enterobacteriaceae, and is safe in patients with renal impairment (Saivin & Houin, 1988). Minocycline has these desirable features but, because of limited clinical experience and the past practice of using IV therapy for these infections, it is not routinely recommended for CREC DFIs. This case report describes a new strategy for the treatment of CREC diabetic foot osteomyelitis in a high-risk elderly patient with oral minocycline as an alternative to IV colistin, and demonstrates that well-selected patients may be safely and effectively treated without hospitalization.

2 CASE REPORT

2.1 Patient Demographics and Medical History

A 63-year-old Jordanian male was referred to Surgical Clinic, King Hussein Medical Center, with a non-healing ulcer on the plantar surface of his right foot. The patient was diagnosed with type 2 diabetes mellitus (T2DM) 15 years ago, with poor glycemic control (glycated hemoglobin [HbA1c] 8.4% at presentation). His past medical history was significant for hypertension (12 years), CKD stage 3 (baseline creatinine 1.4 mg/dL, estimated glomerular filtration rate [eGFR] 52 mL/min), PVD, and myocardial infarction 4 years ago. He was on metformin 1000 mg twice a day, glimepiride 4 mg a day, lisinopril 10 mg a day, atorvastatin 40 mg a day, and aspirin 81 mg a day. He has no known drug allergies.

The patient's age-adjusted CCI was calculated to be 8 points, which corresponds to an estimated 10-year mortality risk of >50%. The patient was functionally independent, living with his wife and ambulating with a walking aid, despite a high comorbidity burden.

2.2 Clinical Presentation

The ulcer had been present for about 6 weeks, starting as a small callus that increased in size despite conservative care at a primary care clinic. The patient denied fever, chills or systemic symptoms. Physical examination showed an ulcer measuring 4.5 × 3.0 cm on the plantar surface of the right foot over the second metatarsal head. The ulcer probed to bone (probe to bone positive) with surrounding erythema approximately 2 cm from the ulcer margin. Moderate

seropurulent exudate with noted purulent drainage. There was mild edema of the foot, but no ascending cellulitis or lymphangitis.

Vital signs: Temperature 36.8°C, blood pressure 138/82 mmHg, heart rate 88 beats per minute, respiratory rate 16 breaths per minute. Peripheral pulses were 2+ bilaterally dorsalis pedis with an ankle-brachial index (ABI) of 0.98. Monofilament testing (5.07 monofilament) showed decreased sensation consistent with peripheral neuropathy. There was no systemic evidence of sepsis.

2.3 Imaging and Laboratory Findings

Laboratory investigations revealed leukocytosis (white blood cell [WBC] count 12,800/ μ L, 82% neutrophils), elevated C-reactive protein (CRP; 48 mg/L), and erythrocyte sedimentation rate (ESR; 68 mm/hr). Baseline creatinine 1.4 mg/dL, eGFR 52 mL/min. HbA1c was 8.4% reflecting poor glycemic control. Plain radiographs of the right foot showed soft tissue swelling and irregularity of the second metatarsal head suggestive of osteomyelitis. Magnetic resonance imaging (MRI) was not performed for patient refusal and clear clinical and microbiological evidence of bone involvement.

2.4 Microbiological Findings

Deep tissue samples were obtained during surgical debridement in the operating room and submitted for aerobic and anaerobic culture with antimicrobial susceptibility testing. Microbiological analysis identified *Escherichia coli* with the following susceptibility profile:

Table 1: Antimicrobial Susceptibility Profile of the Carbapenem-Resistant *Escherichia coli* Isolate

Antimicrobial Agent	Susceptibility	MIC (μ g/mL)
Ampicillin	Resistant	—
Ceftriaxone	Resistant	—
Ciprofloxacin	Resistant	—
Trimethoprim-sulfamethoxazole	Resistant	—
Ertapenem	Resistant	—
Meropenem	Resistant	—
Amikacin	Susceptible	—
Colistin	Susceptible	≤ 2
Tigecycline	Susceptible	≤ 1
Minocycline	Susceptible	≤ 4

Abbreviations: MIC, minimum inhibitory concentration; —, not determined.

Carbapenemase screening was done by the modified carbapenem inactivation method (mCIM) which was positive and confirmed the organism as a carbapenemase producing, carbapenem resistant *E. coli* (CREC).

2.5 Plan of Management

The patient was clinically stable with adequate perfusion, successful source control after debridement, a high burden of comorbidities (making hospitalization a higher risk option), and a strong preference to avoid admission. These factors led the multidisciplinary team (general surgery, infectious disease consultation, and wound care) to pursue outpatient management.

Source Control: Surgical debridement was complete with removal of all necrotic tissue and all infected bone.

Antimicrobial Therapy: The patient was initiated on oral minocycline 100 mg twice daily for 6 weeks based on the susceptibility results.

Offloading The involved foot was offloaded using total contact casting (TCC).

Wound Care: Weekly multidisciplinary wound care was provided with serial debridement's as indicated and dressing changes.

Monitoring: The patient was monitored weekly with clinical assessment, inflammatory markers (CRP, ESR), renal function tests and wound measurements.

3 RESULTS

The patient was able to tolerate a six-week course of oral minocycline without any adverse effects. Serial wound assessments revealed progressive healing with complete epithelialization by 10 weeks (Fig. 1). CRP improved from 48 mg/L at baseline to 6 mg/L at the end of treatment with normalization of inflammatory markers. Renal function remained stable during the course of treatment with creatinine values between 1.4 and 1.5 mg/dL.

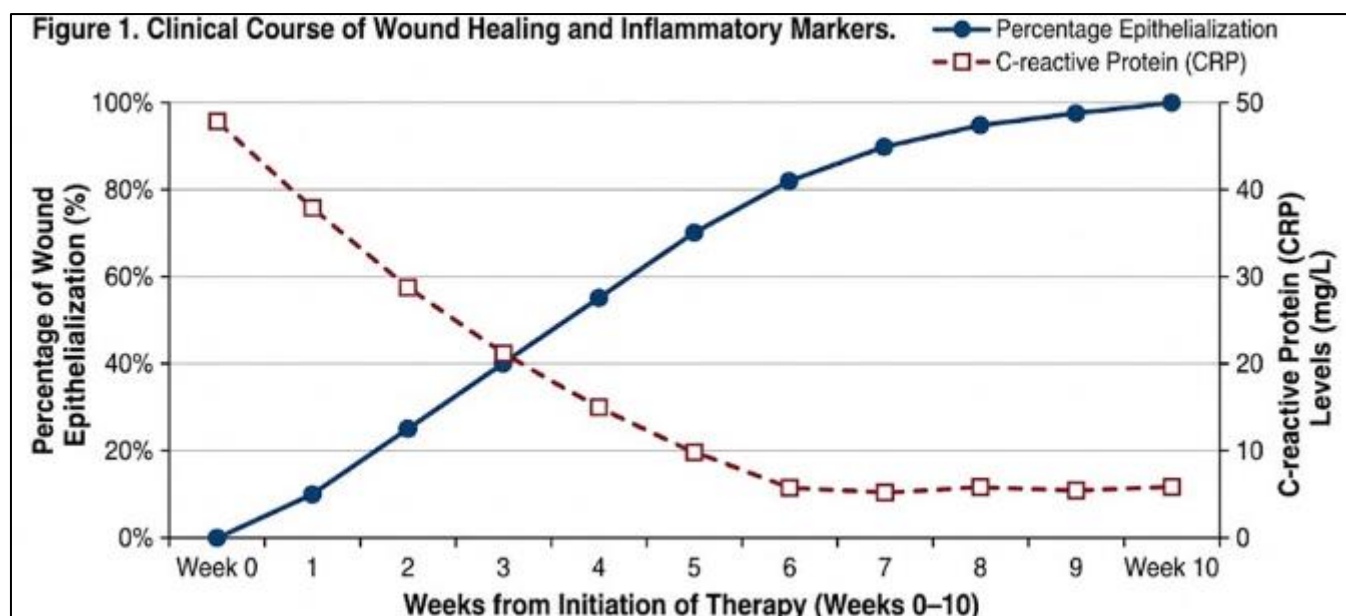


Figure 1: Clinical Course of Wound Healing and Inflammatory Markers

Line graph depicting the course of wound healing (as % epithelialization) and C-reactive protein (CRP) levels during the 10-week treatment period. The x-axis represents weeks from initiation of therapy (Weeks 0–10). The left y-axis represents percentage of wound epithelialization (0–100%). The right y-axis represents CRP levels in mg/L (0–50). Wound healing was progressive with complete epithelialization (100%) by Week 10. CRP levels declined from 48 mg/L at baseline to 6 mg/L by Week 6, remaining within normal limits thereafter.

3.1 Abbreviations: CRP, C-reactive protein.

There were no hospital admissions during the treatment period. At 3-month follow-up, there was no evidence of recurrence, and the patient remained ambulatory with his walking aid.

4 DISCUSSIONS

This case highlights the successful use of oral minocycline in a high-risk elderly patient with multiple comorbidities and diabetic foot infection with osteomyelitis due to carbapenem resistant E.coli. Several key variables contributed to the successful outcome, and these factors warrant careful consideration.

4.1 Criteria for Patient Selection

Outpatient management was successful in this case, but depended on careful patient selection. Several conditions were met that allowed for the provision of safe outpatient care:

- **Clinical Stability:** The patient was afebrile, hemodynamically stable, and without evidence of sepsis or systemic inflammatory response syndrome (SIRS). Patients who meet SIRS or sepsis criteria should not be candidates for outpatient management (Lipsky et al., 2020).
- **Adequate perfusion:** ABI 0.98 suggested preservation of the macrovascular circulation. Wounds require adequate perfusion to heal (Forsythe & Hinchliffe, 2020), and antibiotics require adequate blood flow to reach infected tissues. Revascularization is usually required in patients with severe peripheral arterial disease (ABI <0.7) before they can be managed on an outpatient basis.

- **Effective Source Control:** Surgical debridement removed all necrotic tissue and infected bone. The most common cause of treatment failure in DFIs is inadequate source control (Lavery et al., 2019). The complete debridement during the first visit enabled this patient to move to outpatient care.
- **Minocycline is a good oral antibiotic option** because of its excellent oral bioavailability and bone penetration and in vitro activity against the CREC isolate. Otherwise, I would have needed IV therapy.
- **Patient preference and social support:** The patient strongly preferred outpatient care and had enough social support at home to follow the treatment plan.

4.2 Minocycline as a Treatment for CREC DFIs

Minocycline has several advantages that make it a good choice for outpatient management of DFI:

- **Oral Bioavailability:** Minocycline has a 90-100% oral bioavailability, the highest of any oral antibiotic, providing serum concentrations comparable to IV administration (Saivin & Houin, 1988). This property of the drug's pharmacokinetics allows for an easier switch from IV to oral therapy or, in this case, to avoid hospitalization altogether.
- **Bone Penetration:** Minocycline has bone-to-serum concentration ratios >1 , achieving adequate concentrations in bone tissue for the treatment of osteomyelitis (Bassetti et al., 2021). This is compared to many other oral agents which achieve only low concentrations in bone.
- **Activity Against CRE** Minocycline has activity against carbapenem-resistant Enterobacteriaceae with lower resistance rates than other tetracyclines (Zhanel et al., 2018).
- **Renal Safety** Minocycline is generally safe in patients with renal impairment with low risk of nephrotoxicity. Conversely, colistin is associated with nephrotoxicity in 30-60% of treated patients and requires dose adjustment in renal impairment (Sorlí et al., 2019). This was especially critical in our case of CKD stage 3 as colistin would have greatly increased the risk of renal deterioration.

4.3 Implications for antimicrobial stewardship

The avoidance of IV colistin in this patient had several advantages:

- **Nephrotoxicity Prevention** Colistin-related nephrotoxicity is reported in up to 50% of treated patients and is often dose-limiting (Sorlí et al., 2019). The patient's baseline renal function was preserved with minocycline.
- **Avoidance of IV Access:** If central access is needed, prolonged peripheral IV access may lead to phlebitis, thrombosis, and central line associated bloodstream infections.
- **Antibiotic Stewardship:** The fundamental principle of antimicrobial stewardship is to use colistin only in patients with no alternative. Colistin is generally a "last-line" drug for multidrug-resistant Gram-negative infections and should be avoided if alternatives are available (Tumbarello et al., 2021).
- **Resource Utilization:** Outpatient management reduces healthcare costs and frees up hospital beds for patients who need specialized care. It also prevents patients from exposure to hospital-acquired infections and other nosocomial risks.

4.4 Comparison with traditional management.

In the past, patients with CREC DFI and osteomyelitis have been hospitalized for 4-6 weeks for IV colistin or tigecycline (Lipsky et al., 2020). This strategy required prolonged hospitalization and central venous access for daily observation, with the estimated healthcare costs of \$20,000–\$50,000 per episode in many healthcare systems (Hicks et al., 2021). Outpatient therapy with oral minocycline requires closer outpatient monitoring but results in a substantial reduction of direct medical costs and avoids the risks of hospitalization.

Outpatient antibiotic therapy for DFIs has been validated in several studies, although few are specific to carbapenem-resistant organisms. In the OVIVA trial, oral antibiotic therapy was shown to be non-inferior to IV therapy in bone and joint infections, including diabetic foot osteomyelitis, supporting the shift to oral therapy in stable patients (Li et al., 2019). Our case extends this concept by demonstrating that carefully selected patients can be managed entirely in the outpatient setting without the need for initial hospitalization.

Limitations and Cautions

Several limitations should be noted:

- **Generalizability:** This is a single case report, and the findings may not be generalizable to all patients with CREC DFIs.
- **Patient-Specific Factors:** Not all cases have favorable patient anatomy (intact vascular supply, ability to achieve complete debridement).

- Susceptibility Testing: Minocycline is not universally active against all CRE and susceptibility testing is necessary.
- Adherence: The patient showed good adherence to the treatment plan, which may not be possible in all outpatient settings.
- Duration of follow-up: Longer term follow-up is required to monitor for late recurrence.

4.5 Future Directions

The present case points to several possibilities for future research:

- Oral minocycline for CREC DFIs: prospective studies
- Development of risk-stratification tools to identify patients who can be treated in an outpatient setting
- Cost-effectiveness of oral vs IV strategies for outpatient and inpatient management
- Study of Minocycline in Combination with Other Oral Agents Against Carbapenem-resistant Pathogens

5 CONCLUSION

This case demonstrates that selected patients with carbapenem-resistant *E. coli* diabetic foot infections may be successfully treated in the outpatient setting with oral minocycline as an alternative to intravenous colistin. This approach was successful in a patient with multiple co-morbidities (Charlson index >8) and longstanding diabetes. Inclusion criteria include clinical stability, adequate perfusion, source control and reliable oral antibiotic options. This approach may reduce healthcare costs, reserve intravenous antibiotics for inpatients, avoid colistin-associated nephrotoxicity, and spare the patients from risks associated with hospitalization. Further research and clinical experience are needed before definite conclusions can be reached.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of Conflict of Interest

The authors declare no conflicts of interest regarding this manuscript. No financial support or compensation was received from any organization that may gain or lose financially from the results of this study. The authors have no relevant financial or non-financial interests to disclose.

Statement of Informed Consent

Informed consent was obtained from all individual participants included in the study. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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