



Use of Doxycycline in a Renal Impaired Patient with Enterococcal Sepsis

**Anthony A. Iwuafor¹, Bode Akashie Abraka², Patrick Ntui Mbu³,
Christian Ide², Princewill Chinedu Erengwa²
and Bassey Ewa Ekeng^{2*}**

¹Department of Medical Microbiology and Parasitology, University of Calabar, Calabar, Nigeria.

²Department of Medical Microbiology and Parasitology, University of Calabar Teaching Hospital,
Calabar, Nigeria.

³Department of Internal Medicine, University of Calabar Teaching Hospital, Calabar, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. Author AAI conceptualized and reviewed the manuscript. Authors BAA and PCE did a literature review and wrote the section on introduction. Authors PNM and CI wrote the case presentation. Author BEE drafted the initial manuscript, wrote the section on discussion, reviewed manuscript and edited English. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aim: This report highlights the use of doxycycline therapy other than the more standard regimen that includes an aminoglycoside in the management of enterococcal infection in patients with renal impairment without causing further damages to the kidney due to aminoglycoside therapy.

Presentation of Case: A case of enterococcal septicemia in a 29-year-old woman who was admitted on account of acute kidney injury secondary to pregnancy induced hypertension in the setting of pre-eclampsia. She was referred from another centre where she had emergency caesarean section done on account of severe pre-eclampsia at 36 weeks gestational age. Blood culture yielded *Enterococcus species*. When other antibiotic regimen failed, she was started on doxycycline. Patient had good clinical response and was discharged 7 days after commencement of doxycycline.

*Corresponding author: E-mail: basseyewaekeng@gmail.com;

Discussion: *Enterococci* have emerged as important agent of human disease largely because of their resistance to antimicrobial agents. They are important nosocomial pathogens capable of causing serious and potentially life-threatening infections, including sepsis. The incidence of enterococcal infections, mainly hospital-acquired, has increased over the past 2 decades and isolates with novel mechanism of resistance to antimicrobial agents are more and more frequent. Furthermore, they have great capacity for transmitting these resistances to other species and even to other genera.

Conclusion: Doxycycline is a safe and effective alternative antibiotic for the treatment of enterococcal sepsis in patients with impaired renal status.

Keywords: *Enterococcus*; enterococcal infections; sepsis; doxycycline; renal impairment.

1. INTRODUCTION

Enterococci are the third most common nosocomial blood stream pathogens and frequently are the causative pathogens of intra-abdominal, genitourinary, surgical wound, endovascular, or other serious infections. Nosocomial enterococcal blood stream infection occur at a rate of 2-4 per 10000 hospital discharge and are responsible for 10% of all infections acquired in the hospital [1]. Beta lactam antibiotics lack bactericidal activity against *enterococci* when used as monotherapy, making treatment of systemic infections particularly challenging [2]. Although *E. faecalis* are often susceptible to ampicillin, treatment failure of 60%, and lack of bactericidal activity of the cell-wall active agents prompted effort to identify combination therapies (beta-lactams/glycopeptides and aminoglycosides) that would yield a bactericidal effect in severe infections [2]. High level resistance to aminoglycosides has become increasingly prevalent, particularly among strains of *Enterococcus faecium* indicating the need for alternative therapy. To underscore the problem of aminoglycoside resistance, 24% of *enterococci* collected in 1988-89 at several tertiary care facilities in the USA displayed high-level aminoglycoside resistance [3]. Another challenge with the use of combination therapy is the accumulation of gentamicin and vancomycin in renal impaired patients leading to toxic side effects especially when drug levels are not monitored or dosage modified depending on the degree of renal failure [4,5]. Doxycycline has several advantages over other tetracycline analogues; absorption is almost complete (90-95%), tissue penetration even if modified by inflammation, is facile, elimination is slower, necessitating only one dose of 100 mg daily, and urine concentration are higher, yielding good result in the therapy of urinary tract infection [6-8]. Although 30%-50% of administered

doxycycline is excreted unchanged in the urine, it does not accumulate in cases of renal insufficiency and has been extensively used in patient suffering from various degree of renal insufficiency and also in anuric patients [6-8].

2. PRESENTATION OF CASE

A 29-year-old woman admitted in the month of December, 2018 into the intensive care unit (ICU) of the University of Calabar Teaching Hospital (UCTH), Calabar, Nigeria, with complaints of breathlessness, yellowness of the eye, abdominal pain and swelling. She was referred from Nigerian Navy hospital, Calabar, to UCTH where she had emergency Cesarean section done on account of severe pre-eclampsia at 36 weeks gestational age. She received 5 units of fresh whole blood prior to referral and was receiving intravenous (IV) Ceftriaxone and IV Metronidazole. Patient was acutely ill looking, dyspneic, afebrile, pale, icteric and dehydrated with bilateral pitting oedema up to the mid leg. She was receiving oxygen by face mask and also had urinary catheter insitu. Respiratory rate =48 c/min, SPO2=83% in room air, with widespread coarse crepitations. Abdomen was distended with generalized tenderness. A working diagnosis of oliguric acute kidney injury secondary to pregnancy induced hypertension in the setting of pre-eclampsia with HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelet) syndrome precipitated by sepsis was made. After her admission into the emergency unit of obstetrics and gynecology department, she also received another one unit of fresh whole blood and was then transferred to the intensive care unit (ICU).

Breathlessness was initially mild but as the days progressed it became worse at rest. Yellowness of the eye was also noticed at about the same time as the abdominal swelling. Abdominal pain was of gradual onset and generalized, sharp in

character, non-radiating, constant with no alleviating or relieving factor. Oliguria was noticed 12 hours prior to her presentation with approximately 300mls of urine made in 12 hours. While on admission patient was continued on IV Ceftriaxone and IV Metronidazole. Emergency exploratory laparotomy was done on day 2 of admission on account of hemoperitoneum which developed following previous caesarean section done prior to presentation. However, on the 3rd day of admission patient developed high grade fever, which was continuous and was not relieved by taking analgesics. Leg swelling and abdominal swelling progressively worsened. Due to persistent fever, antibiotics were changed on day 5 from IV Ceftriaxone to IV Meropenem. 5 days after commencement of IV Meropenem, patient became afebrile and had temperature readings within reference interval for about 5 days. Blood culture result retrieved on day 10 yielded *Enterococcus species*, however her antibiotics regimen was not changed to first line antimicrobial agents (gentamicin and vancomycin) used in management of enterococcal septicemia because the patient manifested signs of acute renal failure with elevated potassium and creatinine levels (K-6.6mmol/l, Creatinine-416.4mmol/l) and was dialyzed on day 4 and 5. Urine culture yielded *Candida albicans* which resolved after patient's catheter was changed. On day 16, antibiotics were changed from IV Meropenem to IV Ampicillin because patient was unable to afford IV Meropenem. Twenty-four hours after the commencement of IV Ampicillin, patient developed a second episode of high-grade continuous fever which persisted for 6 days. Doxycycline was introduced on day 22, at a dose of 200mg twice for the first day, followed by 100mg twice daily. Four (4) days after commencement of doxycycline, Patient became afebrile with complete resolution of abdominal swelling, pedal edema and jaundice. She was discharged three (3) days later. Patient was reviewed at two weeks, at 3 months and at 6 months after discharge. she was clinically stable with no signs and symptoms and renal functions fully restored.

3. DISCUSSION

Here we present the case of a 29-year-old woman who was admitted on account of oliguric acute kidney injury secondary to pregnancy induced hypertension with enterococcal septicemia confirmed by blood culture using BD Bactec Culture system. *Enterococci species* are

Gram-positive cocci that are normal inhabitants of gastrointestinal tract, oral cavity and female genital tracts in both humans and animals. However, they can also be significant pathogens responsible for serious nosocomial blood stream infections particularly in intensive care units [1]. Identification of enterococcus in this case report was however not done to the species level, due to lack of diagnostic tools which is not unusual in many health facilities in low- and middle-income countries. Deciding on the appropriate antibiotic therapy for this patient was indeed a difficult task considering that the patient's renal functions was impaired having undergone two sessions of dialysis and also not making adequate urine as at the time blood culture result was received. Patient relatives at this time were also unable to procure prescribed antibiotics (meropenem) due to lack of funds. First line drugs; Vancomycin and gentamicin, used in the treatment of enterococcal septicemia could not be used due to side effect of renal toxicity. High doses of IV ampicillin were not also helpful as fever was seen to persist. This posed a huge challenge to the management of the patient. Alternative drugs like Linezolid and quinupristin-dalfopristin were not readily available. Chloramphenicol could not be used due to the fact that the patient was immunocompromised and the possibility of developing a side effect of bone marrow suppression. Patient was eventually given doxycycline which resulted in marked clinical improvement. Temperature began to settle with resolution of other symptoms and patient was eventually discharged. A study done by Mahon WA et. al on the absorption and distribution of doxycycline in normal patients and in patients with severely impaired renal function showed insignificant difference in the rate of doxycycline clearance from the plasma of patients with normal renal function compared with patients with severely impaired renal function [9]. Doxycycline has been considered a safe broad-spectrum antibiotic for patients with impaired renal function. Toxic blood levels usually do not occur because of the drug's unique extra renal route of excretion [9].

4. CONCLUSION

This case report highlights the benefits of doxycycline in the management of enterococcal septicemia in patients with impaired renal function as a good alternative where first line drugs cannot be used due to their renal toxic side effects and also in resource limited settings where financial constraints are a major limitation

to health care. Doxycycline is cheap and readily available with good bioavailability, and should be considered in the treatment of enterococcal infections especially in renal impaired patients, with the aim of decreasing mortality in this group of patients.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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