SCIENTIFIC CULTURE

www.sci-cult.com

SCIENTIFIC CULTURE, Vol. 11, No. 3.2, (2025), pp. 784-791
Open Access. Online & Print

DOI: 10.5281/zenodo.11322557

EFFECTIVE REPRESENTATION OF A PATIENT WITH AUGMENTED RENAL CLEARANCE CRITERIA: PROMOTING AWARENESS AND OPTIMIZING MANAGEMENT PROCEDURES

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Received: 27/07/2025
Accepted: 27/08/2025

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ABSTRACT

Augmented Renal Clearance (ARC), defined as creatinine clearance exceeding 130 mL/min/1.73 m², is prevalent in critically ill patients, leading to accelerated clearance of renally eliminated antibiotics and potential treatment failure. This case report examines ARC's impact on antibiotic therapy in a young trauma patient with sepsis, emphasizing the need for tailored management strategies. A 17-year-old male patient was admitted to the intensive care unit (ICU) due to a road traffic accident that resulted in traumatic brain injury, spinal trauma, and multiple rib fractures. During ICU stay, the patient's condition deteriorated, such as high-grade fever with high abnormal white blood cells (WBCs) count, leading to a suspicion of sepsis, and so the initiation of antibiotics was warranted. Despite appropriate antibiotic coverage, unimproved sepsis in the presence of multiple criteria raises the concern that the patient may not benefit from the prescribed antibiotics due to augmented renal clearance. Different strategies, such as dose and/or administration time maximization, switching between different antibiotics, use of combination antibiotic therapy, daily therapeutic drug monitoring, and daily renal function and microbiology follow-up, were applied to optimize antibiotic use during the ARC state. The case underlines ARC's effects on antibiotic treatment in critically ill patients. ARC caused suboptimal drug levels despite optimal antibiotics use resulting in treatment failure. The prompt identification of ARC through an ARCTIC score and routine TDM is crucial for optimizing antibiotic use in critically ill sepsis patients.

KEYWORDS: Augmented Renal Clearance, Critically Ill Patients, Antibiotic Therapy, Sepsis, Therapeutic Drug Monitoring.

1. INTRODUCTION

Augmented Renal Clearance (ARC) is defined by an increased renal clearance (creatinine clearance (CrCl) higher than 130 mL/min/1.73 m²) in critically ill patients, leading to an increased excretion of renally cleared drugs [1]. The condition is especially paradigmatic in highly ill patients since it can lead to subtherapeutic drug levels and diminished therapeutic effect [1]. In critically ill patients, the ARC prevalence shows variability. Rates of ARCs in neurocritical care units have been reported to reach as much as 55-87% [2], although other studies have reported that ARCs can be as high as 86% [3]. Likewise, the ARC incidence in trauma ICU ranges between 28-67 % [4].

The pathophysiology of ARC is multifactorial. The increased cardiac output and systemic vasodilation result in a hyperdynamic circulatory state that improves blood flow to the kidneys and the glomerular filtration rate (GFR) [5]. This increased perfusion is typically the result of systemic inflammation caused by diseases such as sepsis, trauma, or burns [5].

Moreover, the functional reserve of the kidney, enabling GFR to increase beyond basal levels, is a factor that aids in the enhanced elimination of substances [6]. Younger age and male sex are also associated with higher ARC risk, possibly reflecting higher baseline renal function and reserve capacity [2].

ARC also affects antibiotics, mainly excreted by the kidney, such as vancomycin and beta-lactams [7]. In patients with ARC, many beta-lactam class antibiotics, such as piperacillin/tazobactam and meropenem, demonstrate shortened time above the MIC, which is essential to time-dependent bactericidal activity [8].

Research suggests that typical dosing frequently does not meet optimal pharmacokinetics/pharmacodynamics goals, including ensuring that drug levels remain above the MIC throughout the dosing period (100% f T >MIC). Extended or continuous infusions are advisable to achieve adequate concentrations [9].

Another antibiotic affected by ARC is vancomycin, which is glycopeptide. A positive correlation exists between vancomycin clearance and creatinine clearance, leading to a reduced serum concentration and a decreased area under the curve (AUC) [10].

Inadequate dose adjustment in individuals with ARC can result in sub-therapeutic antibiotic levels in the blood, leading to treatment failure, prolonged infections, and the development of resistant microbial strains [1, 8].

The gold standard method for diagnosing ARC is by CrCl measurement over 8-24 hours of urine collection. It is a direct standardized estimate of renal function and is more accurate than eGFR formulae in critically ill patients [11].

Moreover, several predictive models were developed, including the Augmented Renal Clearance in Trauma Intensive Care (ARCTIC) score. This scoring system comprises age, sex, serum creatinine, and Sequential Organ Failure Assessment (SOFA) scores, which can be used to predict the probability of ARC [12].

Therapeutic drug monitoring (TDM) during ARC may be utilized in the monitoring of therapeutic drug levels, specifically with the antibiotics, including vancomycin and β-lactams, to prevent adverse effects of the drug [13].

High initial doses or extensive/continuous infusions are recommended to optimize the pharmacokinetics of beta-lactams (percentage of time above minimum inhibitory concentration: %fT > MIC) [13]. This case report of a young trauma patient with sepsis demonstrates the importance of raising awareness concerning the specialized treatment of ARC.

2. CASE PRESENTATION

A 17-year-old male patient was admitted to the intensive care unit for polytrauma and convulsions following a road traffic accident. The injuries were traumatic brain injury, spinal trauma, and multiple chest rib fractures with severe right lung contusion, hemothorax, and pneumothorax. The SOFA score was 12 upon ICU admission. The patient underwent mechanical ventilation protocols, vasopressors (noradrenaline), pneumatic stocking application, and insertion of an intercostal drain (ICD), a peripheral line, a central line, and a urine catheter. Laboratory follow-up included daily complete blood counts (CBCs), electrolytes, renal function tests (RFTs), hepatic function tests (LFTs), cardiac enzymes, arterial blood gases (ABGs), and coagulation tests.

Medications, other than those assigned for mechanical ventilation and life support, were stress ulcer prophylaxis (Omeprazole, intravenous), intravenous fluids, prophylactic antibiotic for ICD insertion (Cefazolin, intravenous), and a seizure control drug (Phenytoin, intravenous).

Five days later (Figure 1, D-5), the patient developed a high-grade fever with a noticeable elevation in white blood cells (WBCs) count (13.2 × 10^9/L) (Table 1). Blood, sputum, and urine cultures were collected for further microbiological

investigations. Intravenous paracetamol 1g PRN and empirical ceftriaxone 1g IV every 12 hours, plus metronidazole 500 mg IV every 8 hours, were initiated. However, there has been no improvement in WBCs count yet (13.5 x 10^9/L) (Table 1). After two days (Figure 1, D-7), the urine culture revealed no growth, the blood culture was still pending, but the sputum culture revealed a positive result for Pseudomonas aeruginosa, which was susceptible to amikacin, ceftazidime, ceftazidime/avibactam, ciprofloxacin, imipenem, meropenem, and piperacillin/tazobactam. After careful assessment, ventilator-acquired pneumonia was confirmed by the treating physician, and he decided to discontinue ceftriaxone and metronidazole and to start a combination therapy with piperacillin/tazobactam 4.5 g every 6 hours and ciprofloxacin IV 400 mg q 12 hr.

Three more days (Figure 1, D-10) after the new antibiotic regimen, the patient did not show clinical improvement and WBCs continued to rise (25.7 x 10^9/L) (Table 1).A new sputum culture was requested to assess the antibacterial effects of piperacillin/tazobactam and ciprofloxacin. Later that same day, the previously requested blood culture result came up, indicating a positive Enterococcus faecalis susceptible to ampicillin, gentamicin, levofloxacin, linezolid, and vancomycin.

Following ward team discussion, vancomycin IV for Enterococcus faecalis dose of 750 mg every 12 hours (15 mg/kg every 12 hours) was decided to be added to the previous antibiotics plan, taking into account replacing all intravascular devices with a new one and collecting a 2nd blood culture sample before vancomycin initiation for further E. fecalis confirmation.

Two days after vancomycin initiation and five days following the initiation of piperacillin/tazobactam and intravenous ciprofloxacin (Figure 1, D-12), WBCs still did not show significant improvement (28.6 x 10^9/L) (Table 1), and the last sputum culture revealed the presence of positive Pseudomonas aeruginosa. The ICU team member, the clinical pharmacist, was assigned to investigate the suspected reasons behind the ineffectiveness of antibiotics.

He started by requesting a trough level for vancomycin, which revealed a significant subtherapeutic level (3.5 mcg/mL, reference range: 15–20 mcg/mL) (Table 1). When the current antibiotic regimen did not yield the expected clinical outcomes, the clinical pharmacist conducted a special pharmacokinetic study to assess the patient's current state.

After a thorough case evaluation, it was highly suspected that the patient might develop Augmented Renal Clearance (ARC), a condition that may be the reason behind ABx ineffectiveness. To determine if the patient is prone to the ARC state, the risk factors that tend to push the patient's clinical condition into the ARC state were identified and assessed. The noticeable risk factors were critical illness, younger age < 50 years old, traumatic brain injury, and "sepsis". Also, other indicators raising concern that the patient might develop an ARC state were an estimated creatinine clearance close to 200 mL/min (Table 1), recurrent positive sputum pseudomonas aeruginosa despite appropriate antibiotics coverage, significant subtherapeutic vancomycin trough level, and no significant drug interaction which may alter the therapeutic effect of the current antibiotics.

After discussions with ICU physicians, the concept of the relationship between the ARC phenomenon and extensive antibiotic excretion, as well as treatment failure, was widely accepted. **So, the antibiotics plan was adjusted as follows**

- To collect a 3rd blood culture sample before vancomycin dosage adjustment, then to reload vancomycin dose at 1500 mg once (25 mg/kg), followed after 8 hours by a maximum maintenance dose of 1000 mg every 8 hours (20 mg/kg every 8 hours)
- To start extended infusion of meropenem as 2 g over 3 hours infusion every 8 hours instead of piperacillin/tazobactam due to its safer kidney profile as a combination with vancomycin and its familiarity among ICU ward personnel when a broad-spectrum antibiotic preparation & administration as extended infusion is required. Moreover, the latest hospital antibiogram shows no superiority of piperacillin/tazobactam activity over meropenem activity against Pseudomonas aeruginosa.
- Ciprofloxacin IV dose kept the same until further evaluation to avoid undesirable fluoroquinolone adverse reactions.
- To collect body fluid from ICD drains for further microbiology investigation, which was presumed as an additional source of infection that might contain non-susceptible microorganisms, which might hinder patient response to current antibiotics.

Then (Figure 1, D-14), the new vancomycin trough level was requested 30 minutes before the 4th dose of the new regimen. Again, another trough level revealed as a sub-therapeutic level (4.9 mcg/ml) despite dose maximization (table 1).

Table 1: Laboratories of Concern during the Days of Sepsis Management and Augmented Renal Clearance.

	WBCs Ref: 4.5 to 11 x 10^9/L	SCr Ref: 59 - 104 μmol/L	SCr Ref: 0.7 -1.2 mg/dL	CrCl (CG formula, ABW= 56 kg)	Vancomycin level Ref: 15-20 mcg/ml
Day 4	11.3	93	1.05	91	
Day 5	13.2	82.2	0.93	103	
Day 6	13.5	67.5	0.76	125	
Day 7	14	67.7	0.77	125	
Day 8	13.7	59.9	0.68	141	
Day 9	19.4	51.3	0.58	165	
Day 10	25.7	50	0.57	169	
Day 11	25	50.3	0.57	168	
Day 12	28.6	44	0.5	192	3.5
Day 13	22.1	43	0.49	197	
Day 14	17.8	38.8	0.44	218	1st sample: 4.9 2nd sample: 6.8
Day 15	18.5	32.8	0.37	258	
Day 16	17.3	48.6	0.55	174	34.6
Day 17	18.5	44.1	0.5	192	1.1
Day 18	18.2	32.3	0.37	262	4.46
Day 19	18.6	37.2	0.42	227	
Day 20	18.4	28	0.32	302	
Day 21	16.2	40	0.45	211	
Day 22	15.9	50	0.57	169	
Day 23	12	51	0.58	165	

WBCs: White Blood Cells, SCr: Serum Creatinine, CrCl: Creatinine Clearance, CG: Cockroft-Gault, ABW: Actual Body Weight, Kg: Kilogram, Ref: Reference range

Another blood sample was collected before the next dose to confirm the later vancomycin trough level. The new sample also revealed another sub-therapeutic level (6.8 mcg/ml) (Table 1). **So, multiple options were set under team assessment as follow**

- To keep the vancomycin current dose the same with intensive clinical evaluation for signs and symptoms of bacteremia, especially any indicator for persistent fever, chills, and hypotension. Also, frequent follow-up for RFTs and vancomycin trough levels was considered.
- To follow the pending blood cultures for further Enterococcus faecalis confirmation: the 2nd blood culture, which was sampled earlier post intravascular devices replacement and before vancomycin initiation, and the 3rd blood culture sample, which was collected before vancomycin dose maximization.
- To change the method of administration for vancomycin from intermittent infusion into 3000 mg continuous infusion over 24 hours, versus switching vancomycin to another comparable alternative less affected by ARC.

Due to unfamiliarity with vancomycin as large dose continues infusion over 24 hr among ward personnel and the physician's strong tendency to relate the patient's current sepsis with ventilator-acquired pneumonia rather than bacteremia, the decision was made to keep the vancomycin dose the same with daily RFTs and vancomycin trough 3 times weekly until receiving blood culture results.

Additionally, as the respiratory clinical picture still showed unsatisfactory progress, characterized by progressive infiltrates on the chest x-ray, increased purulent sputum production, and difficult extubation, another intervention was implemented to improve the ciprofloxacin IV dose to 400 mg every 8 hours, among other procedures.

Two days later (figure 1, D-16), the ICD drain culture came back negative. Additionally, the second blood culture was negative for Enterococcus faecalis. As this negative blood culture might be a strong indicator to discontinue vancomycin, the decision was made to wait until the third blood culture sample confirmation . So, vancomycin trough level was followed as ordered, but this time the monitoring revealed an unexpected result. Surprisingly, the vancomycin trough level jumped to 34.6 mcg/mL (Table 1), a higher undesirable therapy indicator. Multiple investigations were conducted to assess the proper execution of vancomycin sampling protocols by ward nurses; however, the apparent evidence suggests that the sampling was performed before vancomycin dose as per protocols. Therefore, vancomycin was withheld for 24 hour until further post-24-hour level investigation .

Later (Figure 1, D-17), the vancomycin level at 24 hours post-holding revealed a significant sub-therapeutic level of 1.1 mcg/mL (Table 1). This drop

occurs just 24 hours after discontinuation, strongly supporting the patient ARC state phenomenon. Vancomycin was resumed at 1 g every 8 hours again. After one day of resuming the vancomycin dose (Figure 1, D-18), the trough level was slightly elevated to 4.46 mcg/mL (Table 1). Additionally, the 3rd blood culture result, obtained on the same day, yielded another "no growth" result. So, vancomycin was discontinued.

Meropenem and ciprofloxacin IV were continued with further daily clinical evaluation. A new sputum culture was requested on day 7, counting from the day of ciprofloxacin IV dose maximization as the last optimized antibiotic for ARC (Figure 1, D-21). The newly collected sputum culture revealed no pathogen (Figure 1, D-23). Moreover, other parameters, such as the daily trend of WBCs towards normalization (Table 1), acceptable ABG, less thick mucus secretions, and an acceptable x-ray, were also considered indicators of a satisfied patient's clinical condition outcomes. So, both antibiotics were finally discontinued at nearly 10 days of dose and/or administration maximization (Figure 1, D-23).

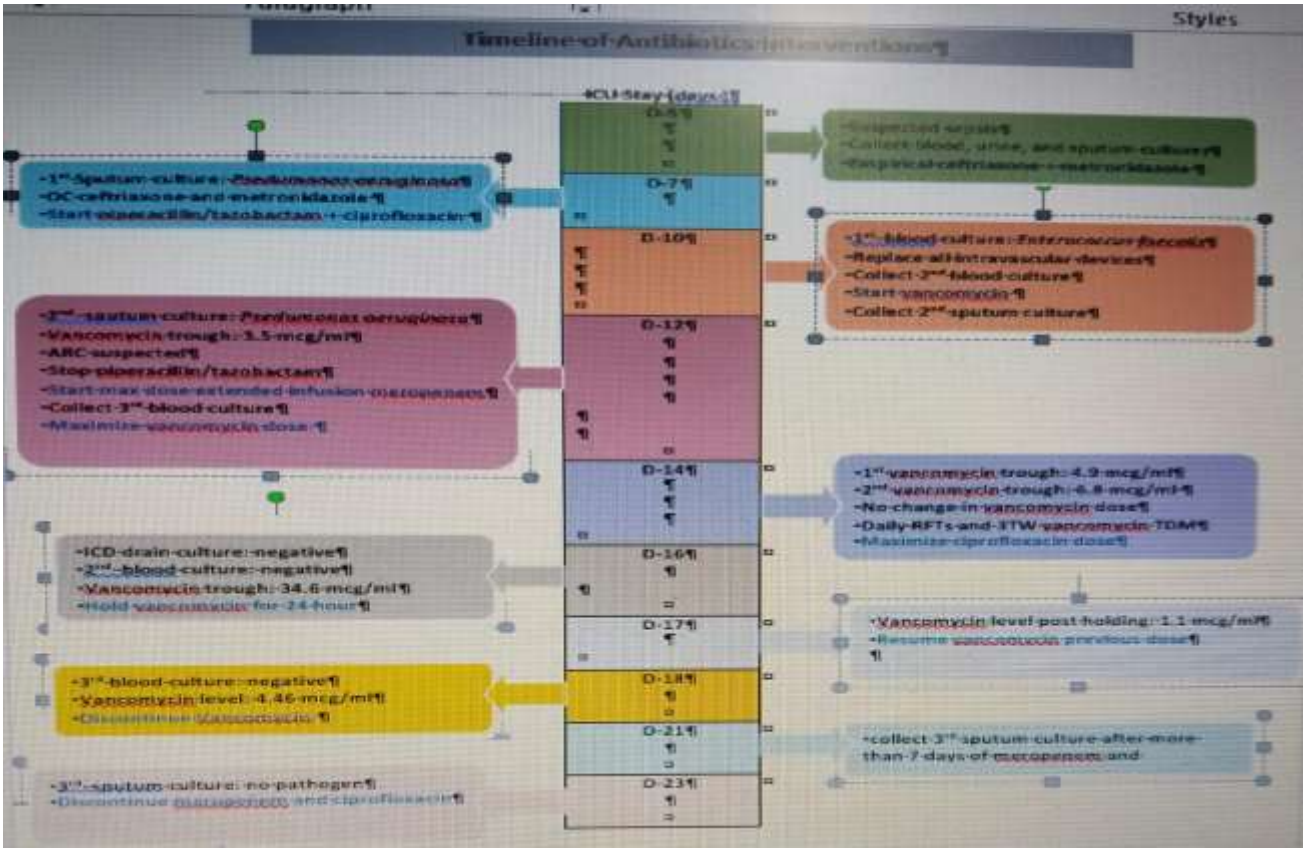

Figure 1: Timeline Illustrating Empirical and Culture-guided Antibiotic therapy before and after the onset of augmented renal Clearance.

Antibiotics doses:

ceftriaxoneIV: 1 g every 12 hour

Metronidazole IV: 500 mg every 8 hours

Piperacillin/tazobactam: 4.5 g every 6 hours

Meropenem: 2 g extended infusion over 3 hours every 8 hours

Ciprofloxacin IV: 200 mg every 12 hour maximized later into 200 mg every 8 hours

Vancomycin IV: 750 mg every 12 hours (15 mg/kg q 12 hr) maximized later into 1 g every 8 hours (20 mg/kg q 8 hr)

Abbreviations:

D-: Day

DC: Discontinue

ARC: Augmented Renal Clearance

RFTs: Renal Function Test

3TW: Three Times Weekly

TDM: Therapeutic Drug Monitoring

ICD: Intercostal Drain

IV: Intravenous

3. DISCUSSION

This case of a 17-year-old male trauma patient with sepsis highlights the critical need for awareness and tailored management in ARC. Numerous studies report the prevalence of ARC among critically ill

patients. For example, Luo et al. (2021) demonstrated that ARC was observed in 57.7% of patients with sepsis and multi-trauma, with a weak correlation between cardiac index and creatinine clearance [14]. Conversely, Zhao et al. (2022) reported a higher prevalence of poor vancomycin PK-PD targets in Chinese patients, with a prevalence of 21.3 percent among adults [15]. The patient in the presented case had ARC characteristics that are associated with high creatinine clearance rates, traumatic brain injury, sepsis, and positive sputum cultures, even when the patient had optimal antibiotic coverage. The current findings are consistent with the existing body of literature, which also describes young age, trauma, and sepsis as the significant risk factors associated with ARC [16].

The clinical relevance of ARC is that the pharmacokinetics of renally excreted antibiotics are affected, including beta-lactams (meropenem, piperacillin/tazobactam), aminoglycosides, and glycopeptides (vancomycin). Enhanced clearance lowers the plasma drug level, which can result in subtherapeutic concentrations, failure of therapy, and the development of antimicrobial resistance [17]. For vancomycin, efficacy against severe infections, such as bacteremia, has been shown to be dependent on an AUC to MIC ratio of 400-600 or trough levels of 15-20 mcg/mL [18]. As in this case, initial vancomycin trough levels were significantly subtherapeutic at 3.5 mcg/mL, indicating the effect of ARC on drug clearance. Research studies, such as those by Zhao et al., indicate that inadequate vancomycin trough levels can be observed in 21.3% of patients with ARC despite receiving standard doses [15]. Another study, conducted by Sahraei et al. (2022), showed that a dose of vancomycin 15 mg/kg every 8 hours was more effective in achieving pharmacokinetic attainment in ARC patients compared to standard dosing regimens [19]. Similarly, beta-lactams such as meropenem depend on their ability to achieve sufficient concentrations above the MIC and maintain them over time (e.g., 100% fT>MIC) to achieve and maintain bactericidal effects [20].

ARC should be managed using individualized dosing regimens to overcome the high drug clearance. TDM is a guiding principle that enables clinicians to optimize doses based on drug levels [14]. For instance, follow-up for the targeted AUC to MIC ratio of 400-600, targeted trough level of 15-20 mcg/mL, above, or below these targets for vancomycin by TDM, it has been proven a valuable tool for vancomycin monitoring and hence dose escalating, keeping, or de-escalating during ARC state. In critically ill patients with an increased renal clearance (CrCl >130 mL/min), the recommended dosing regimen for vancomycin includes a daily continuous infusion of 3,500-4,500 mg to ensure adequate therapeutic exposure, as reported by Vu et al. (2019) [21]. With increased doses of vancomycin to 1000 mg every 8 hours (3000 mg/day), therapeutic levels were never achieved in the present case, and subsequent measurements fluctuated between 4.9 mcg/mL and a surprisingly high supratherapeutic level of 34.6 mcg/mL. This variability is likely a representation of changing dynamic renal functions, which is widespread among severely ill patients, suggesting the importance of frequent TDM determined by combining local and/or international TDM protocols with physician or pharmacist expertise [22]. For beta-lactams, extended (e.g., 3-hour) or continuous infusions improve the time above MIC, enhancing efficacy [20]. The switch to extended meropenem infusion (2 g over 3 hours every 8 hours) in this case aligns with recommendations, as recent meta-analyses have shown that prolonged infusions reduce mortality and improve clinical cure rates in critically ill patients with sepsis [23, 24]. However, the decision not to use continuous vancomycin infusion due to staff unfamiliarity highlights practical barriers to implementing evidence-based strategies.

Several cases in the literature mirror the challenges observed in this case. Goboova et al. (2015) described a 16-year-old male with polytrauma and sepsis who developed ARC (CrCl 138–340 mL/min/1.73 m^2), requiring vancomycin doses up to 6 g/day (2 g every 8 hours) to achieve therapeutic troughs of 15–19 mg/L [25]. This case closely resembles ours, with a similar patient profile and the need for significant vancomycin dose escalation. Another relevant case involved a 34-year-old male with an intracranial infection caused by Streptococcus intermedius, where ARC led to subtherapeutic vancomycin and meropenem concentrations [26]. Only after escalating meropenem to 16 g/day and vancomycin to 1.5 g four times daily were therapeutic levels achieved, leading to recovery [26].

The case also raises considerations about antibiotic selection in ARC. Meropenem's favorable renal safety profile and familiarity in the ICU made it a suitable choice over piperacillin/tazobactam. However, the persistence of P. aeruginosa in sputum cultures despite the use of appropriate antibiotics suggests possible additional infection sources or resistance mechanisms, although intercostal drain cultures were negative. This aligns with the

literature, indicating that ARC can exacerbate treatment challenges in multidrug-resistant infections [27].

Diagnosing ARC presents challenges, as standard serum creatinine-based estimates (e.g., Cockcroft-Gault, MDRD) often underestimate CrCl in critically ill patients. Measured CrCl via 8- to 24-hour urine collection is the gold standard to confirm ARC [11]. However, in this case, ARC was suspected based on an estimated CrCl exceeding 200 mL/min, in conjunction with clinical indicators such as young age, traumatic brain injury, sepsis, and persistent subtherapeutic vancomycin levels. Scoring systems, such as the ARCTIC score, have been developed to predict ARC in trauma patients, with a score of ≥6 indicating a high likelihood of ARC [12].

4. CONCLUSION

This case highlights the critical impact of ARC on antibiotic therapy in critically ill trauma patients with sepsis. Future management of ARC should prioritize early recognition upon admission using tools like the ARCTIC score, and further follow-up of CrCl via 8- to 24-hour urine collection later during hospital stay. The patient's subtherapeutic vancomycin levels and persistent infection despite escalated dosing, as in this case, highlight ARC's role in treatment failure. This may necessitate daily TDM for vancomycin and beta-lactams that could be de-escalated later to thrice, twice, or once weekly following attainment of a steady drug therapeutic level and patient clinical improvement. Research is needed to standardize dosing regimens and explore rapid TDM assays for beta-lactams. Other strategies like using extended or continuous antibiotic infusions, such as meropenem in this case, may be warranted in the future as first line when sepsis is suspected or confirmed in critical illness. The eventual resolution of infections after vancomycin discontinuation and continued meropenem and ciprofloxacin therapy emphasizes the importance of dynamic clinical evaluation. Additionally, addressing practical barriers, such as staff training on continuous infusion protocols, will enhance the adoption of evidence-based practices, thereby improving outcomes in patients with ARC.

Acknowledgements: We are deeply grateful to our colleagues for their valuable support and constructive input throughout the development of this article.

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