Impact of Hypoalbuminemia on Ceftriaxone Treatment Failure in Patients with *Enterobacterales* Bacteremia

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Introduction

Ceftriaxone is one of the most commonly utilized antibiotics in hospitalized patients due to its convenient once-daily dosing and robust Gram-negative activity.[1] Ceftriaxone's pharmacokinetic profile displays high protein binding (83-96%) which contributes to reduced elimination rate of free drug allowing for convenient, once daily dosing for most indications.[2]

In patients with hypoalbuminemia, however, the proportion of free drug is increased which can lead to increased ceftriaxone clearance and suboptimal time above the minimum inhibitory concentration for target pathogens.[3,4] Furthermore, decreased ceftriaxone exposure may lead to increased rates of treatment failure in the setting of hypoalbuminemia especially in patients who are critically ill.[5]

Despite ubiquitous use of ceftriaxone in hospitalized patients and pharmacokinetic studies suggesting suboptimal target attainment, data assessing clinical outcomes with ceftriaxone treatment in patients with hypoalbuminemia is limited.

Objectives

To determine the impact of hypoalbuminemia on clinical outcomes among patients with *Enterobacterales* bacteremia treated with ceftriaxone

Methods

This study was approved by the Houston Methodist Institutional Review Board.

Study Design

- Retrospective, multicenter, observational cohort study

Study Period

- Admission May 1, 2016 – April 30, 2021

Inclusion Criteria

- Ceftriaxone-susceptible *Enterobacterales* from blood
- Age ≥ 18 years
- Ceftriaxone for > 72 hours beginning within 48 hours of index culture collection

Exclusion Criteria

- Polymicrobial bacteremia at baseline
- Other antibiotic therapy for > 48 hours
- Concomitant CNS infection
- Ceftriaxone dosing interval ≠ every 24 hours
- No baseline plasma albumin
- Pregnancy

Statistical Analysis

- Propensity-matched outcomes analysis
- Continuous variables
  - Welch's t-test or Mann-Whitney U test
- Categorical variables
  - Pearson's chi-squared or Fisher's exact test

Results

Figure 1. Patient Selection Flow Diagram

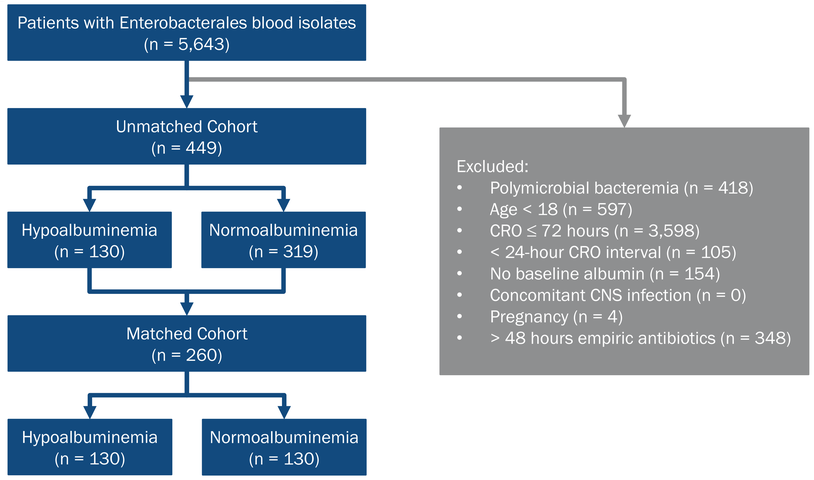


Table 1. Baseline Characteristics

Variable n (%), median [IQR]	Hypoalbuminemia (n = 130)	Normoalbuminemia (n = 130)	*P* value
Age, years	65.2 [56.0–80.6]	70.3 [56.4–82.5]	0.34
Sex, female	78 (60.0)	77 (59.2)	0.90
BMI, kg/m^2	25.9 [21.9–31.3]	28.0 [24.0–33.7]	0.09
Plasma albumin, g/dL	2.2 [2.0–2.4]	3.2 [2.8–3.5]	<0.01
ICU admission	41 (31.5)	41 (31.5)	1.00
SOFA score	4 [2.0–6.0]	4 [2.0–6.0]	0.57
Comorbidities			
Immunosuppressed	18 (13.8)	18 (13.8)	1.00
Cirrhosis	14 (10.8)	7 (5.4)	0.11
Malignancy	17 (13.1)	13 (10.0)	0.44
Average ceftriaxone dose, g/day	1.6 [1.0–1.9]	1.6 [1.0–1.8]	0.60
Time to ceftriaxone initiation, hours	5.2 [1.4–32.6]	2.1 [0.5–8.6]	<0.01
Time to first effective antibiotic, hours	1.6 [0.7–2.9]	1.1 [0.3–2.6]	0.06
Infection source			
IV catheter	5 (3.8)	1 (0.8)	0.10
Intra-abdominal	19 (14.6)	13 (10.0)	0.44
LVAD driveline	0 (0.0)	1 (0.8)	1.00
Skin and soft tissue	1 (0.8)	1 (0.8)	1.00
Urinary	87 (66.9)	99 (76.1)	0.10
Unknown	18 (13.8)	15 (11.5)	0.58

Table 2. Index Blood Culture Results

Organism n (%)	Hypoalbuminemia (n = 130)	Normoalbuminemia (n = 130)
Escherichia coli	94 (72.3)	94 (72.3)
Klebsiella pneumoniae	24 (18.5)	16 (12.3)
Proteus mirabilis	6 (4.6)	8 (6.2)
Other	6 (4.6)	12 (9.2)

Results

Figure 2. Primary Outcome Among Propensity-Matched Cohort (n = 260)

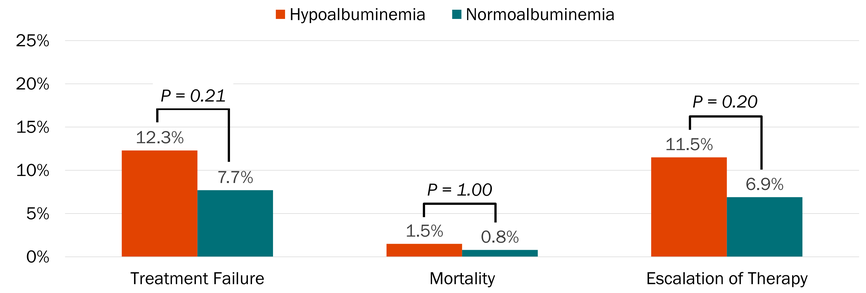
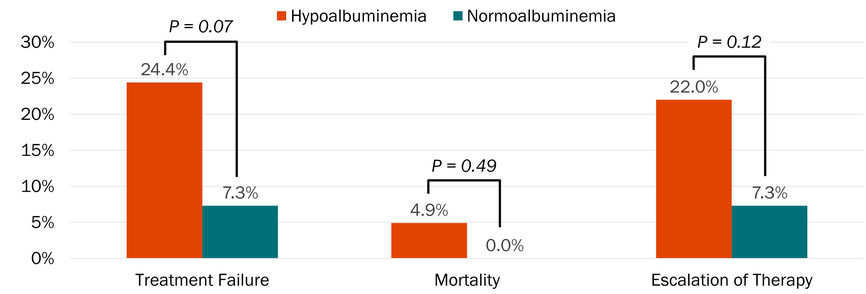


Table 3. Secondary Outcomes Among Propensity-Matched Cohort

Outcome n (%), median [IQR]	Hypoalbuminemia (n = 130)	Normoalbuminemia (n = 130)	*P* value
Length of stay, days	6.8 [5.2–9.6]	6.4 [5.0–9.3]	0.34
Duration of antibiotic therapy, days	5.4 [4.1–8.1]	5.7 [4.0–8.0]	0.93
Time to infection resolution, days	1.0 [0.5–2.2]	0.9 [0.2–2.5]	0.36

Figure 3. Primary Outcome Among ICU Subgroup (n = 82)



Discussion

Patients with hypoalbuminemia experienced numerically greater rates of treatment failure than patients with normoalbuminemia. However, the difference in the primary outcome was small and did not reach the prespecified threshold for statistical significance. Other secondary outcomes among the overall cohort occurred at similar rates between groups. Among the subgroup of critically ill patients, the difference in treatment failure was more pronounced likely due to additional alterations in pharmacokinetic parameters that are more common in this population. More aggressive ceftriaxone dosing strategies or selection of alternative agents may be preferred in these patients.

References

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Disclosures

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