JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

A proposed management pathway for community-acquired Gram-negative sepsis in Chinese older adults

Liling Jing[1], Weiwei Zhang[1], Yunlong Liu[2]

[1] Changhai Hospital, Navy Military Medical University (Second Military Medical University), Shanghai, China
[2] Shanghai Baoshan Hospital of Integrated Traditional Chinese and Western Medicine (Baoshan Hospital, Shanghai University of Traditional Chinese Medicine), Shanghai 201999, China

Abstract

Introduction: Sepsis epidemiology varies regionally. We aimed to characterise community-acquired sepsis in Chinese older adults and develop an evidence-based, cost-effective empirical therapeutic pathway tailored to local antimicrobial-resistance patterns.

Methods: This single-centre, retrospective observational cohort study conducted at a tertiary hospital in Shanghai, China, enrolled 122 consecutive older adults (age ≥ 65 years) meeting Sepsis-3 criteria between June 2021 and May 2023. Microbiological data, antimicrobial-susceptibility profiles, clinical characteristics, and 28-day all-cause mortality were analysed. Multivariate logistic regression was used to identify independent risk factors for mortality.

Results: Gram-negative bacteria predominated (54.9%) and showed high susceptibility to cefoperazone-sulbactam (85.0%). The 28-day mortality rate was 37.7%. Multivariate analysis identified increasing age (adjusted odds ratio [aOR] = 1.10 per year), need for intensive care unit admission (aOR = 6.65), mechanical ventilation (aOR = 5.78), and dialysis (aOR = 3.62) as independent predictors of mortality. Notably, adequate empirical antimicrobial therapy was not an independent protective factor in the adjusted model. A cost-effective clinical pathway with cefoperazone-sulbactam as the first-line empirical therapy and escalation based on clinical response was developed for use in resource-limited settings.

Conclusions: The findings underscore the dominance of Gram-negative pathogens and the critical influence of host factors on survival among older adults with sepsis in China. They also provide a carbapenem-sparing, pragmatic, and sustainable management pathway for initial sepsis treatment in resource-limited settings, which can be replicated for antimicrobial stewardship in other regions with similar epidemiological profiles. The clinical effectiveness of this hypothesis-generating pathway requires validation in prospective, multicentre studies.

Key words: sepsis; older adults; Gram-negative bacterial infections; cefoperazone-sulbactam; mortality; antimicrobial stewardship.

J Infect Dev Ctries 2026; 20(8):1161-1170. doi:10.3855/jidc.22560

(Received 29 October 2025 – Accepted 30 January 2026)

Introduction

Sepsis is a life-threatening form of organ dysfunction caused by dysregulated host responses to infection and diagnosed by a Sequential Organ Failure Assessment (SOFA) score ≥ 2 [1,2]. Global mortality rates are > 10%, increasing to > 40% in cases involving septic shock. Notably, sepsis accounts for over 20% of all global deaths annually [3]. In Chinese intensive care units (ICUs), the incidence of sepsis ranges from 20.6% to 50.8%, with an in-hospital mortality rate of 33% [4].

The ageing of the global population has intensified the geriatric sepsis burden, since older adults with sepsis face distinct challenges [5]. In these patients, immunosenescence impairs the functioning of neutrophil extracellular traps (NETs) and macrophages, while comorbidities (e.g. diabetes and organ insufficiency) increase susceptibility and complexity [6]. Previous studies have identified notable interregional differences in the characteristics of sepsis: while Western cohorts showed Gram-positive predominance (e.g., *Staphylococcus aureus*: ~37%, $p < 0.05$ vs. Asian data), Asian cohorts exhibited higher Gram-negative prevalence (70.1%, $p < 0.001$ against Western baselines) [7,8].

The SOFA and quick SOFA (qSOFA) scores have inherent limitations: as organ dysfunction scores, they cannot reflect pathogen characteristics or immune dysregulation states, and their reliance on laboratory parameters limits their utility in emergency department assessments [9]. In this context, biomarkers have shown promise: (1) Procalcitonin (PCT) has shown superior discriminatory power to C-reactive protein (CRP; area under the curve [AUC]: 0.85 vs. 0.77), peaking 24 - 48 hours post-infection [10,11]. (2) Similarly, monocyte distribution width (MDW), a haematological parameter, has shown early promise (AUC: 0.84) for rapid, cost-effective screening [12]. However, the applicability of biomarkers in older adults requires further validation, especially in patients with chronic inflammation, who may show false-positive results.

Therefore, to address the critical need for evidence-based empirical therapy in geriatric healthcare, this study aimed to bridge this knowledge gap. To this end, we developed and validated a novel decision pathway integrating local pathogen epidemiological characteristics, antimicrobial-resistance profiles, and clinical risk stratification. Furthermore, our findings provide robust validation for cefoperazone-sulbactam as a cost-effective empirical treatment option within this specific patient population and healthcare setting.

Methods

Study Design

This single-centre, retrospective observational cohort study was conducted at Changhai Hospital (Shanghai, China), a 2,000-bed tertiary academic medical centre. Consecutive older adults (age ≥ 65 years) meeting the Sepsis-3 criteria (suspected infection + acute increase ≥ 2 points in SOFA score) were enrolled between June 2021 and May 2023.

Antimicrobial selection: Antimicrobial selection was clinician-driven and based on the treating physician's clinical judgement, availability in the institutional antimicrobial formulary, and local empirical practice patterns at the time of admission. No formal or informal institutional protocols to guide or restrict antibiotic selection for antimicrobial therapy in geriatric sepsis were in place during the study period.

Patients who met the following criteria were included: (1) age ≥ 65 years at sepsis diagnosis; (2) community-acquired infection, defined as the absence of hospitalisation, residence in a long-term care facility, or receipt of haemodialysis/intravenous chemotherapy within 90 days prior to admission; and (3) availability of complete microbiological and outcome data. The exclusion criteria were as follows: (1) sepsis directly attributable to a recent invasive healthcare procedure or major trauma; (2) active malignancy requiring chemotherapy or radiotherapy or ongoing immunosuppressive therapy; (3) receipt of any antibiotic therapy within 90 days prior to admission; or (4) death within 24 hours of admission. Patients who died within 24 hours of admission were excluded because this subgroup typically included patients with irreversible, end-stage multi-organ failure or refractory septic shock at presentation. In these patients, mortality was almost exclusively determined by the pre-admission disease trajectory and the severity of initial organ dysfunction, rather than the effects of in-hospital interventions such as antimicrobial therapy. Thus, inclusion of this subgroup would have introduced significant bias by conflating the effects of late-stage disease with the effectiveness of the empirical antimicrobial strategies evaluated in this study. However, this exclusion may have led to a slight underestimation of the overall mortality burden of geriatric sepsis in real-world settings.

The study protocol was approved by the Ethics Committee of Baoshan Hospital. Given the retrospective design and anonymised data analysis, the requirement for informed consent was waived in compliance with the Declaration of Helsinki.

Data Collection and Definitions

Baseline demographic characteristics (age, sex), clinical parameters (blood pressure, heart rate, respiratory rate, smoking status, alcohol consumption), and comorbidities were recorded. Patients were followed up during hospitalisation and underwent post-discharge surveillance through structured telephone interviews. The primary endpoint was the 28-day all-cause mortality. The secondary endpoints were pathogen distribution, antimicrobial susceptibility, and risk factors for mortality.

Adequate empirical antimicrobial therapy was defined as intravenous administration of an antimicrobial agent within 24 hours of obtaining culture specimens, which was subsequently confirmed to be effective against the isolated pathogen(s) on the basis of in vitro susceptibility-testing results [13]. Notably, while this definition is methodologically appropriate and consistent with prior literature, its clinical relevance in older adults with advanced organ dysfunction warrants careful interpretation. In this vulnerable population, mortality is predominantly driven by host factors, including frailty, baseline organ reserve, and the severity of illness, which may diminish the observable influence of appropriate initial antimicrobial selection even with confirmed in vitro susceptibility. Additionally, altered pharmacokinetics, delayed tissue penetration, renal replacement therapy-induced changes in drug clearance, and the presence of potential undiagnosed co-infections may limit the clinical effectiveness of antibiotics classified as 'adequate' by laboratory criteria alone. Therefore, the absence of an independent protective effect of adequate empirical therapy in the multivariate analysis should not be interpreted as a failure of antimicrobial selection, but may rather reflect the dominant influence of disease severity and host vulnerability in this cohort.

Pathogen Culture and Antimicrobial-Susceptibility Testing

Clinical specimens were collected from the enrolled

patients. Blood cultures were performed using 10-mL aliquots in BacT/ALERT® FA/FN bottles (BioMérieux, France), incubated at 37°C for up to 5 days, in accordance with CLSI M47-Ed4. Positive bottles underwent isolation on Columbia blood agar and MacConkey agar (24 - 48 hours, 35°C); identification by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics); and antimicrobial-susceptibility testing (AST) using VITEK®2 GN cards (CLSI M100-Ed33 breakpoints).

The selection of antibiotics for the susceptibility-testing panels was based on the recommendations in the CLSI M100-Ed33 guideline for Enterobacterales, non-fermenting bacteria, and Gram-positive cocci. Priority was given to agents included in our hospital's formulary and to antibiotics of particular interest for this study (such as cefoperazone-sulbactam).

Statistical Analysis

All statistical analyses were performed using SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality by using the Shapiro–Wilk test. On the basis of their distribution, continuous data were presented as median with interquartile range (IQR), and categorical data were presented as frequencies and percentages (n, %).

For between-group comparisons (survivors vs. non-survivors), the Mann–Whitney U test was used for non-normally distributed continuous variables, and the Chi-square test or Fisher's exact test was applied for categorical variables, as appropriate.

To identify independent risk factors for 28-day all-cause mortality, we conducted a two-step modelling process. First, univariate logistic regression analyses were performed for all candidate variables. Variables with p values less than 0.2 in the univariate analysis were eligible for inclusion in the multivariate logistic regression model. These variables were as follows: age, presence of any comorbidity, need for ICU admission, presence of shock at diagnosis, need for renal replacement therapy (dialysis), need for mechanical ventilation, and administration of adequate empirical antimicrobial therapy.

Before building the final multivariate model, multicollinearity among the retained predictors was rigorously assessed by calculating the variance inflation factor (VIF). A VIF value ≥ 5 was set as the threshold indicating significant collinearity. This assessment revealed a high degree of collinearity between 'presence of shock at diagnosis' and 'vasopressor use' (VIF > 5). To ensure clinical relevance and to avoid over-adjustment for closely related manifestations of organ dysfunction, the variable 'vasopressor use' was retained in the final model, while 'shock at diagnosis' was excluded.

The final multivariate model was constructed using the Enter method. The handling of missing data was pre-specified: variables with fewer than 5% missing values were managed using complete-case analysis. The goodness-of-fit of the final multivariate logistic regression model was evaluated using the Hosmer–Lemeshow test, and a non-significant p value of 0.45 indicated that the model fit the data well. Results from the logistic regression analyses are presented as odds ratios (ORs) with their corresponding 95% confidence intervals (CIs). A two-tailed p value less than 0.05 was considered statistically significant.

Model Limitation Note: Although the multivariate model was methodologically appropriate, and ICU admission and mechanical ventilation were identified as independent predictors of 28-day mortality in this model, these two variables should be interpreted with caution. In clinical practice, ICU admission and mechanical ventilation are markers of underlying disease severity rather than direct causal factors of death. In older adults with sepsis, the need for these interventions reflects advanced organ dysfunction and critical illness status, which are the fundamental drivers of poor outcomes. This potential interpretive limitation should be considered when extrapolating the model's findings to clinical decision-making.

Results

Patient Characteristics and Clinical Outcomes

A total of 122 older adults with sepsis (median age: 72 years [IQR, 68–77 years]; 70.5% male) were included. Among them, 38.5% required mechanical ventilation, and 31.1% received vasopressors. The 28-day mortality rate was 37.7% (46/122). Non-survivors were significantly older than survivors (75 years [IQR, 69–81 years] vs. 71 years [IQR, 67–75 years]; p = 0.018). The two groups also showed significant differences in clinical indicators, namely, hypotension (systolic BP: 90 mmHg [69–110 mmHg] vs. 127 mmHg [110–146 mmHg]; $p < 0.001$), tachycardia (heart rate: 109 bpm [80–126 bpm] vs. 86 bpm [80–106 bpm]; p = 0.003), and tachypnoea (respiratory rate: 23/min [18–25/min] vs. 19/min [16–21/min]; p = 0.042). Non-survivors also required substantially higher intervention rates: mechanical ventilation (56.5% vs. 27.6%; p = 0.001), vasopressor use (47.8% vs. 21.1%; p = 0.002), and dialysis (34.8% vs. 14.5%; p = 0.009) (Table 1).

Pathogen Distribution and Survival Associations

Gram-negative pathogens predominated (54.9%, 67/122), with *Escherichia coli* (23.8%, 29/122) and *Klebsiella pneumoniae* (10.7%, 13/122) being the most prevalent organisms. Descriptive analysis revealed no significant differences in survival outcomes between patients infected with the two major pathogen categories: Gram-negative pathogens: 53.9% (41/76) survivors vs. 56.5% (26/46) non-survivors ($p = 0.782$); Gram-positive pathogens: 46.1% (35/76) vs. 45.7% (21/46) ($p = 0.966$).

The following observations were purely descriptive and underpowered to infer causal associations with mortality: Fastidious pathogens (those requiring specific growth conditions) were more frequently isolated from non-survivors (10.9% vs. 6.6%, $p = 0.352$), with *Campylobacter jejuni* exclusively isolated in non-survivors (4.3% vs. 0%, $p = 0.109$). The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) was higher in non-survivors (6.5% vs. 2.6%, $p = 0.352$), although the difference was not statistically significant.

Viral co-infections occurred only in non-survivors (2.2% vs. 0%, $p = 0.357$), while fungal infections showed comparable rates in non-survivors and survivors (2.2% vs. 1.3%, $p > 0.999$). No survival-related disparities were observed in the occurrence of infections caused by *Pseudomonas aeruginosa* (6.5% vs. 5.3%, $p = 0.697$) and other Gram-negative bacilli (8.7% vs. 5.3%, $p = 0.452$) (Table 2).

Antimicrobial-Susceptibility Profiles

Gram-negative isolates (n = 67) showed the highest susceptibility rates to carbapenems and β-lactam/β-lactamase inhibitor combinations. Meropenem was the most active agent (89.7%, 52/58), followed closely by

Table 1. Participants' baseline characteristics.

Parameter	Total (n = 122)	Survivors (n = 76)	Non-survivors (n = 46)	*p*
Age	72 (68-77)	71 (67-75)	75 (69-81)	0.018
Male, sex	86 (70.5%)	55 (72.4%)	31 (67.4%)	0.559
Blood pressure (mmHg)				
Systolic	124 (103-138)	127 (110-146)	90 (69-110)	< 0.001
Diastolic	70 (59-80)	74 (65-80)	58 (41-73)	0.001
Heart rate	97 (80-115)	86 (80-106)	109 (80-126)	0.003
Respiratory rate	20 (18-23)	19 (16-21)	23 (18-25)	0.042
Cardiovascular disease	19 (15.6%)	11 (14.5%)	8 (17.4%)	0.667
Chronic pulmonary disease	7 (5.7%)	4 (5.3%)	3 (6.5%)	0.772
Diabetes	15 (12.3%)	7 (9.2%)	8 (17.4%)	0.182
Any Comorbidity	41 (33.6%)	20 (26.3%)	21 (45.7%)	0.03
Smoking	61 (50%)	36 (47.4%)	25 (54.4%)	0.455
Alcohol	28 (23.0%)	16 (21.1%)	12 (26.1%)	0.522
Infection site				
Abdomen only	35 (28.7%)	22 (29.0%)	13 (28.3%)	0.935
Urinary only	30 (24.6%)	19 (25.0%)	11 (23.9%)	0.893
Thorax only	25 (20.5%)	15 (19.7%)	10 (21.7%)	0.791
≥ 2 Sites	5 (4.1%)	3 (3.9%)	2 (4.3%)	0.914
Other	27 (22.1%)	17(22.4%)	10 (21.7%)	0.939
Dialysis	27 (22.1%)	11 (14.5%)	16 (34.8%)	0.009
Mechanical ventilation	47 (38.5%)	21 (27.6%)	26 (56.5%)	0.001
Vasopressor use	38 (31.1%)	16 (21.1%)	22 (47.8%)	0.002

Age presented as median (IQR); however, it was treated as a continuous variable for logistic regression analysis.

Table 2. Pathogen Distributions Stratified by Survival.

Pathogen	Total (n = 122)	Survivors (n = 76)	Non-survivors (n = 46)	*p*
Gram-negative	67 (54.9%)	41 (53.9%)	26 (56.5%)	0.782
E. coli	29 (23.8%)	19 (25.0%)	10 (21.7%)	0.687
K. pneumoniae	13 (10.7%)	9 (11.8%)	4 (8.7%)	0.572
P. aeruginosa	7 (5.7%)	4 (5.3%)	3 (6.5%)	0.697
Fastidious	10 (8.2%)	5 (6.6%)	5 (10.9%)	0.352
L. pneumophila	5 (4.1%)	3 (3.9%)	2 (4.3%)	0.999
C. jejuni	2 (1.6%)	0	2 (4.3%)	0.109
Other GNB	8 (6.6%)	4 (5.3%)	4 (8.7%)	0.452
Gram-positive	56 (45.9%)	35 (46.1%)	21 (45.7%)	0.966
S. aureus	15 (12.3%)	9 (11.8%)	6 (13.0%)	0.845
MRSA	5 (4.1%)	2 (2.6%)	3 (6.5%)	0.352
Other pathogens	7 (5.7%)	3 (3.9%)	4 (8.7%)	0.289
Fungal	2 (1.6%)	1 (1.3%)	1 (2.2%)	0.999
Viral	1 (0.8%)	0	1 (2.2%)	0.357

GNB: Gram-negative bacilli; MRSA: methicillin-resistant *Staphylococcus aureus*.

imipenem (86.2%, 56/65). Cefoperazone-sulbactam demonstrated potent in vitro activity, and its susceptibility rate of 85.0% in the tested Gram-negative isolates was close to that of carbapenems and exceeded that of piperacillin-tazobactam (79.0%, 49/62). Susceptibility to third-generation cephalosporins was moderate (ceftriaxone: 78.1% [50/64]; ceftazidime: 74.2% [46/62]). Levofloxacin (63.9%, 39/61) and amikacin (63.8%, 37/58) demonstrated reduced activity.

Gram-positive isolates (n = 56) were highly susceptible to glycopeptide antibiotics (teicoplanin: 95.7% [45/47]; vancomycin: 92.2% [47/51]). In contrast, susceptibility was lower to ceftriaxone (68.6%, 24/35) and levofloxacin (65.2%, 30/46; tested in 82.1% of isolates). Penicillin demonstrated low activity (31.0%, 13/42).

Not all isolates were tested against all antimicrobial agents. Total tested isolates (n) for each agent are specified in Table 3.

Table 3. Drug sensitivity analysis.

Antibiotic	Total	Sensitivity
Gram-negative bacteria		
Meropenem	58	52 (89.66%)
Imipenem	65	56 (86.15%)
Cefoperazone/sulbactam	60	51 (85.00%)
Piperacillin/tazobactam	62	49 (79.03%)
Ceftriaxone	64	50 (78.12%)
Ceftazidime	62	46 (74.19%)
Levofloxacin	61	39 (63.93%)
Amikacin	58	37 (63.79%)
Gram-positive bacteria		
Teicoplanin	47	45 (95.74%)
Vancomycin	51	47 (92.16%)
Ceftriaxone	35	24 (68.57%)
Levofloxacin	46	30 (65.22%)
Penicillin	42	13 (30.95%)

Levofloxacin susceptibility testing was not performed for all Gram-positive isolates.

Risk Factors for 28-Day Mortality among Older Adults with Community-Acquired Sepsis

A total of 122 older adults with community-acquired sepsis were included in the final analysis. The 28-day all-cause mortality rate was 37.7% (n = 46), and 62.3% of the patients survived (n = 76).

The univariate analysis identified several factors significantly associated with 28-day mortality (Table 4). Non-survivors were significantly older than survivors (median [IQR]: 75 [69-81] vs. 71 [67-75] years; OR = 1.07, 95% CI: 1.01–1.13; $p = 0.021$). In addition, the presence of comorbidities (45.65% vs. 26.32%; OR = 2.35, 95% CI: 1.09–5.09; $p = 0.03$), the need for ICU admission (91.3% vs. 67.1%; OR = 5.12, 95% CI: 1.66–15.96; $p = 0.005$), the presence of shock at diagnosis (47.83% vs. 21.05%; OR = 3.44, 95% CI: 1.55–7.65; $p = 0.002$), the requirement for renal replacement therapy (dialysis) (34.78% vs. 14.47%; OR = 3.15, 95% CI: 1.31–7.61; $p = 0.011$), and the need for mechanical ventilation (56.52% vs. 27.63%; OR = 3.41, 95% CI: 1.58–7.35; $p = 0.002$) were all significant risk factors. In contrast, administration of adequate empirical antimicrobial therapy was identified as a significant protective factor (69.57% among non-survivors vs. 85.53% among survivors; OR = 0.387, 95% CI: 0.158–0.958; $p = 0.038$).

A multivariate logistic regression analysis was performed to identify independent predictors of mortality (Table 4). Four variables remained significantly and independently associated with an increased risk of 28-day death. The need for ICU admission was the strongest independent risk factor (adjusted OR = 6.65, 95% CI: 1.87–23.56; $p = 0.003$), followed closely by the need for mechanical ventilation (adjusted OR = 5.78, 95% CI: 2.24–14.91; $p < 0.001$). Furthermore, increasing age (adjusted OR = 1.1 per year, 95% CI: 1.03–1.18; $p = 0.007$) and requirement for dialysis (adjusted OR = 3.62, 95% CI: 1.25–10.46; $p = 0.017$) were also identified as independent predictors. Although significant in univariate analysis, comorbidities and adequate empirical antimicrobial therapy were not retained in the final multivariate model.

Rate of Extended-Spectrum Beta-Lactamase–Producing Isolates

A total of 42 non-duplicate clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae* were collected during the study period. Phenotypic confirmatory testing revealed that the overall extended-

Table 4. Risk factors for 28-day mortality among elderly patients with community-acquired sepsis.

Parameter	Survivors (n = 76)	Non-survivors (n = 46)	Univariate		Multivariate	
			OR (95% CI)	*p*	OR (95% CI)	*p*
Age (years)	71(67-75)	75(69-81)	1.07 (1.01–1.13)	0.021	1.1 (1.03–1.18)	0.007
Comorbidity	20 (26.32%)	21 (45.65%)	2.35 (1.09–5.09)	0.03		
ICU admission	51 (67.1%)	42 (91.3%)	5.12 (1.66–15.96)	0.005	6.65 (1.87–23.56)	0.003
Adequate empirical antimicrobial therapy	65 (85.53%)	32 (69.57%)	0.387 (0.158–0.958)	0.038		
Presence of shock at diagnosis	16 (21.05%)	22 (47.83%)	3.44 (1.55–7.65)	0.002		
Dialysis	11 (14.47%)	16 (34.78%)	3.15 (1.31–7.61)	0.011	3.62 (1.25–10.46)	0.017
Mechanical ventilation	21 (27.63%)	26 (56.52%)	3.41 (1.58–7.35)	0.002	5.78 (2.24–14.91)	< 0.001

a. Shock was excluded from the multivariable model due to its collinearity with vasopressor use. OR: odds ratio, CI: confidence interval.

spectrum beta-lactamase (ESBL) production rate was 36% (15/42). The ESBL-positivity rates were 38% (11/29) for *E. coli* and 31% (4/13) for *K. pneumoniae*. The high prevalence of ESBL-producing Enterobacterales in this cohort strongly supports the use of β-lactam/β-lactamase inhibitor combinations over third-generation cephalosporins for empirical treatment of serious infections likely caused by these pathogens.

Proposed Framework for Empirical Therapy in Older Adults with Sepsis

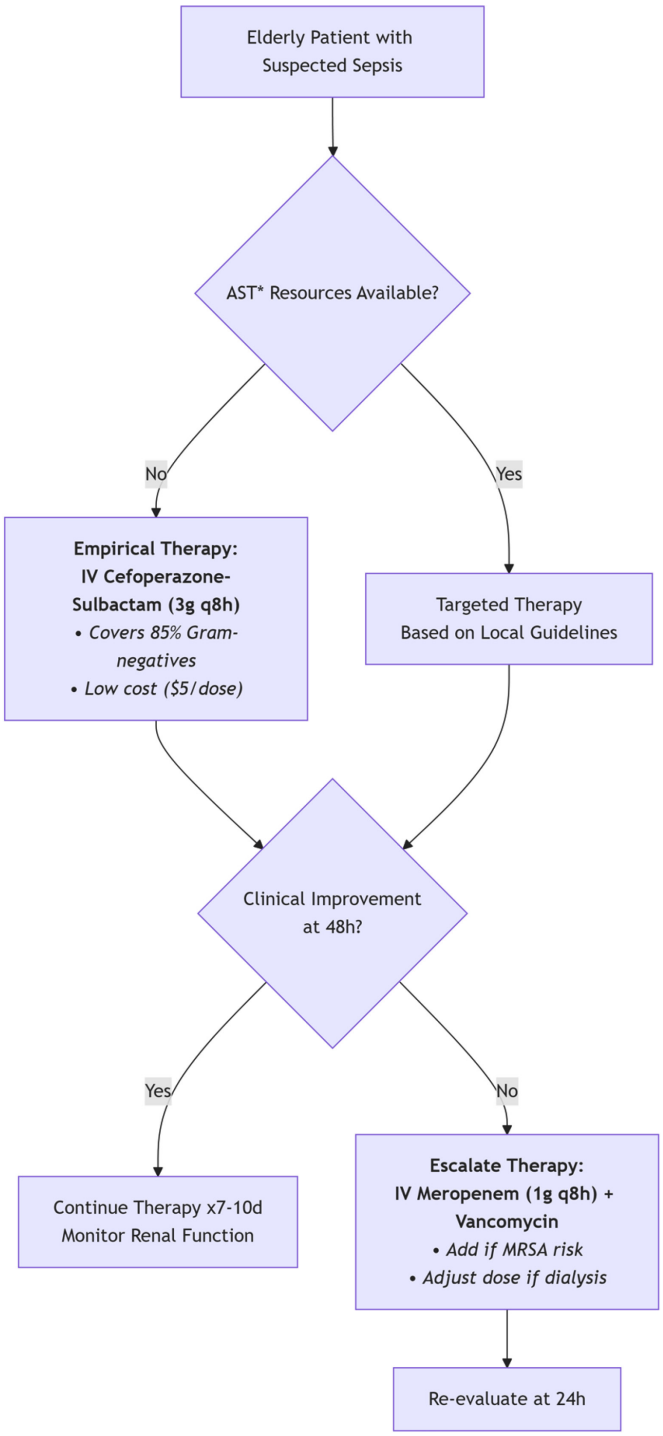
A structured proposed clinical framework was developed to guide the initial management of older adults presenting with suspected community-acquired sepsis, with the availability of AST resources serving as a key branch point (Figure 1). Notably, this framework was derived from local epidemiological and antimicrobial-susceptibility data of the study cohort and has not been validated for improvements in clinical outcomes. Thus, its application should be restricted to regions with similar pathogen distribution and resistance profiles.

For settings where AST resources were not immediately available, the framework recommended the initiation of empirical intravenous therapy with cefoperazone-sulbactam (3 g administered every 8 hours). This regimen was selected on the basis of its ability to provide coverage for approximately 85% of common Gram-negative pathogens in our clinical setting, coupled with its favourable low-cost profile (approximately USD 5 per dose). The patients were then closely monitored for a predefined period of 48 hours.

The framework specified that patients showing significant clinical improvement within this 48-hours window should be continued on the cefoperazone-sulbactam regimen for 7 to 10 days, with monitoring of renal function to guide dose adjustments. For patients demonstrating no clinical improvement after 48 hours of empirical therapy, the framework required mandatory escalation of antimicrobial coverage. This escalation involved switching to intravenous meropenem (1 g every 8 hours) to broaden Gram-negative coverage and the addition of vancomycin to cover potential MRSA infections, particularly in patients showing risk factors for this pathogen. Re-evaluation was mandated 24 hours after initiation of this escalated regimen.

In clinical environments where AST resources were readily available, the framework directed clinicians to omit broad empirical regimens in favour of initiating targeted antimicrobial therapy immediately, based on local guidelines and epidemiologic data, once appropriate cultures were obtained.

Figure 1. Proposed Empirical Therapy Framework for Sepsis in Older Adults in Resource-Limited Settings.



AST: Antimicrobial-susceptibility testing. Recommendations derived from cohort data (n = 122) showing 85% Gram-negative coverage with cefoperazone-sulbactam. Escalation to meropenem was indicated only after treatment failure or confirmation of carbapenem-susceptible pathogens. This framework is for local application only and requires prospective validation before broader implementation.

Exploratory Post-hoc Analysis

A post-hoc analysis was conducted to evaluate the potential influence of the proposed empirical antimicrobial pathway. Eight patients received initial empirical therapy that was fully aligned with the pathway recommendations (i.e., initiation with cefoperazone-sulbactam in the absence of immediate AST data availability), while a matched cohort of eight patients received alternative regimens that did not conform to the pathway.

This small-sample (n = 8 per group) comparison was for illustrative purposes only, and no statistical inference or causal conclusions can be drawn from the observed numerical trends. Although the findings were underpowered by the extremely small sample size, patients managed according to the proposed pathway showed a lower 28-day mortality rate than those who were not (25% [2/8] vs. 37.5% [3/8]). Furthermore, adherence to the pathway was associated with a marked reduction in carbapenem use. Only 25% (2/8) of the patients in the pathway-aligned group required carbapenems during their treatment course, in comparison with 50% (4/8) of those in the non-aligned group.

This analysis was explicitly exploratory; thus, the true clinical value and efficacy of this management pathway require confirmation in future prospective, adequately powered multicentre studies.

Discussion

This study provided a critical characterisation of community-acquired sepsis in older adults at a Chinese tertiary care centre. The findings revealed a distinct epidemiological profile characterised by a predominance of Gram-negative pathogens and high antimicrobial susceptibility to β-lactam/β-lactamase inhibitor combinations. In addition to the descriptive findings, our analysis yielded two key contributions. First, it validated a cost-effective empirical therapy pathway. Second, it provided crucial insights into the determinants of mortality for this vulnerable population.

The predominance of Gram-negative infections (54.9%) in our cohort aligns with the findings of Asian epidemiological studies but contrasts with the Gram-positive predominance reported in Western studies. This difference between Asian and Western studies highlights the need for region-specific clinical guidelines. The high in vitro susceptibility of Gram-negative isolates to cefoperazone-sulbactam (85.0%) confirms the viability of this combination as a carbapenem-sparing agent. A strategic reduction in carbapenem usage is the cornerstone of antimicrobial stewardship, since it can mitigate the selection of drug-resistant organisms, a goal strongly supported by IDSA guidelines. These guidelines advocate for de-escalation and preferential use of narrow-spectrum agents such as β-lactam/β-lactamase inhibitor combinations over carbapenems when appropriate [14].

Our multivariate analysis revealed a pivotal, nuanced finding. Adequate empirical antimicrobial therapy served as a protective factor in univariate analysis, but it was not an independent predictor of survival in the final model. Thus, in older adults with sepsis, the overwhelming influence of unmodifiable host factors may outweigh the benefits of optimal initial antibiotic selection [15]. These factors include advanced age, organ dysfunction requiring life support such as mechanical ventilation and dialysis, and a high comorbidity burden. Furthermore, although ICU admission and mechanical ventilation emerged as strong predictors of mortality, they likely served as proxies for underlying disease severity rather than direct mediators of death. Notably, this study did not formally assess frailty or baseline functional status, which are critical unmeasured confounders in this population. Frailty is characterised by reduced physiological reserve and impaired stress response. Pre-existing functional dependence, such as limitations in activities of daily living, is another key factor. Both frailty and functional dependence are established predictors of poor outcomes in critically ill older adults, and they often mediate the effects of both infection severity and treatment interventions. This explains why 'adequate therapy' lost its independent protective effect in the present study. The trajectory of critical illness in these frail patients was likely determined by the severity of their immunosenescence and baseline organ reserve, and antibiotics cannot rapidly reverse these underlying vulnerabilities. Furthermore, some non-significant trends in non-survivors, including a higher prevalence of MRSA, fastidious and difficult-to-culture pathogens such as *C. jejuni*, and viral co-infections, hint at an alternative explanation, i.e. the definition of 'adequate coverage' may need expansion in high-risk older adult cohorts to include pathogens not routinely targeted by first-line regimens [16].

In response to these findings, we proposed a pragmatic clinical decision pathway. This pathway diverges from the broad-spectrum recommendations in international guidelines such as the Surviving Sepsis Campaign guidelines, since those guidelines are designed for high-resource settings and prioritise global generalizability. In contrast, our algorithm offers a

tiered, resource-aware strategy. For settings without immediate access to AST, the algorithm recommends cefoperazone-sulbactam as a first-line agent. This recommendation is based on robust local susceptibility data. Escalation to broader-spectrum agents is mandated only if patients show no clinical improvement. This approach balances the urgency of sepsis treatment with the principles of antimicrobial stewardship, a consideration that may receive less attention in guidelines that prioritise universal immediate broad-spectrum coverage. Our pathway is primarily applicable to resource-limited regions or institutions where carbapenems must be reserved as last-line drugs.

The dosage of cefoperazone-sulbactam (3 g every 8 hours) was selected on the basis of its pharmacokinetic/pharmacodynamic properties. This dosage achieved effective drug exposure against common pathogens in our region, including some ESBL-producing Enterobacterales. Crucially, cefoperazone contains an *N*-methylthiotetrazole side chain. This structure is associated with vitamin K-dependent coagulopathy, which manifests as hypoprothrombinaemia and a disulfiram-like reaction (DLR). Therefore, in older adults, particularly those with hepatic dysfunction or malnutrition, monitoring prothrombin time and prophylactic vitamin K supplementation should be considered. For patients with renal impairment, dosage adjustment should be based on the manufacturer's prescribing information. These careful considerations encompassing dosing and adverse effects reinforced the practicality and safety profile of our proposed pathway in managing older adults with sepsis.

The broader relevance of this study extends beyond its immediate findings, since it provides a replicable model for other low- and middle-income countries. The model involves three key steps: (1) local surveillance to define pathogen prevalence and resistance patterns; (2) identification of affordable first-line agents with optimal coverage; and (3) embedding these data into a simple, actionable clinical pathway. This 'local data-driven' model is essential for curbing antibiotic resistance globally. It can also improve patient outcomes in a cost-effective manner [17].

Although this study provided a detailed characterisation of sepsis in older adults, several limitations require acknowledgement. First, the single-centre, retrospective design inherently limited the generalisability of our findings. The data were derived from a tertiary hospital in Shanghai, China; these data may not be directly applicable to other low- and middle-income countries with distinct epidemiological profiles, healthcare resource-availability levels, and antimicrobial-resistance patterns. Second, the exclusion of patients who died within 24 hours or lacked microbiological data may have introduced selection biases. This exclusion potentially led to underestimation of mortality. Third, the proposed empirical therapy framework has not been prospectively tested. The exploratory post-hoc analysis with a small sample size of eight patients per group only demonstrated numerical trends. It did not show statistically significant improvements in clinical outcomes. Fourth, we acknowledge that in vitro antimicrobial susceptibility does not equate to clinical efficacy in older adults with advanced organ dysfunction. The real-world effectiveness of antibiotics can be influenced by factors such as altered pharmacokinetics, delayed tissue penetration, and host immune status. This is true even when in vitro testing indicates susceptibility. Additionally, the post-hoc assessment of the clinical pathway was exploratory. Therefore, our findings reflect the local context of a Shanghai tertiary centre and should be validated in future prospective, multicentre studies.

Notwithstanding these limitations, we believe the primary relevance of our work extends beyond the specific pathogen prevalence rates reported herein. The practical, 'locally tailored' antimicrobial stewardship model provided in this study is a replicable methodological framework that can be adopted by other hospitals or healthcare systems. This approach is particularly relevant for clinicians in resource-conscious settings facing similar challenges of antimicrobial resistance. Therefore, we recommend that the development of institutional empirical therapy guidelines should be preceded by active local pathogen surveillance and AST.

Conclusions

In conclusion, this study confirmed the critical role of host factors in determining survival after sepsis in older adults. It demonstrated that effective empirical therapy need not be synonymous with the broadest-spectrum agents but must be informed by local epidemiological characteristics. The proposed pathway offers a rational, sustainable, and economically viable strategy for initial sepsis management in environments where resource constraints and antimicrobial stewardship are simultaneously relevant considerations.

Funding
This study was supported by the Banshan Key Clinical Specialty Project (BSZK-2023-A01).

Corresponding author
Yunlong Liu
Shanghai Baoshan Hospital of Integrated Traditional Chinese and Western Medicine (Baoshan Hospital, Shanghai University of Traditional Chinese Medicine)
No. 28 Tuanjie Road, Baoshan District 201999
Shanghai, China.
E-mail: iamlong329@163.com

Conflict of interest
No conflict of interest is declared.

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