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TIME TO ANTIMICROBIAL THERAPY IN SEPTIC SHOCK PATIENTS TREATED WITH AN EARLY GOAL-DIRECTED RESUSCITATION PROTOCOL: A POST-HOC ANALYSIS OF THE ARISE TRIAL

Running Title

Antimicrobial timing and outcomes in septic shock

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1742-6723.13634

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Author Contribution

SP, EB designed the study. MF, EB analysed the data. SP prepared the original draft and all authors reviewed and contributed to the final version prior to submission.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

Financial Support

Nil

Key words

Septic shock, timing anti-microbial agents, mortality

Word count

Abstract 249 words

Main text 2538 words

ABSTRACT

Objective

Intravenous antimicrobial therapy within 1 hour of the diagnosis of septic shock is recommended in international sepsis guidelines. We aimed to evaluate the association between antimicrobial timing and mortality in patients presenting to the emergency department (ED) with septic shock.

Methods

Post-hoc analysis of 1587 adult participants enrolled in the Australian Resuscitation in Sepsis Evaluation (ARISE) multicentre trial of early goal-directed therapy for whom the time of initial antimicrobial therapy was recorded. We compared participants who had initiation of antimicrobials within the first hour (early) or later (delayed) of ED presentation. A propensity score model using inverse probability of treatment weighting was constructed to account for confounding baseline covariates. The primary outcome was 90-day mortality.

Results

The median (interquartile range) time to initiating antimicrobials was 69 (39-112) minutes with 712 participants (44.9%) receiving the first dose within the first hour of ED presentation. Compared with delayed therapy, early administration was associated with increased baseline illness severity score and greater intensity of resuscitation pre-randomisation (fluid volumes, vasopressors, invasive ventilation). All-cause 90-day mortality was also higher; 22.6% versus 15.5%; unadjusted odds ratio (OR) 1.58 (95%CI 1.16-2.15), P=0.004. After inverse probability of treatment weighting, the mortality difference was non-significant; OR 1.30 (95%CI 0.95-1.76); P=0.1. Live discharge rates from ICU (OR 0.81, 95%CI 0.72-0.91; P=0.80) and hospital (OR 0.93, 95%CI 0.82-1.06; P=0.29) were also not different between groups.

Conclusion

In this post-hoc analysis of the ARISE trial, early antimicrobial therapy was associated with increased illness severity, but 90-day adjusted mortality was not reduced.

INTRODUCTION

The Surviving Sepsis Campaign (SSC) guidelines recommend intravenous antimicrobial administration within one hour of the recognition of septic shock.[1] Integral to this recommendation is the retrospective study conducted by Kumar *et al*. which reported that, for every hour delay in administration of effective antimicrobial therapy after the onset of refractory hypotension, survival to hospital discharge decreased by 7.6%.[2] A retrospective analysis of the SSC database subsequently reported increased hospital mortality when antimicrobials were initiated more than 1 hour after presentation.[3] More recently, antimicrobial administration within 3 hours of emergency department (ED) presentation, as part of a state-mandated bundle of care for septic shock, has been reported to decrease risk-adjusted hospital mortality, compared to initiation between 3 and 12 hours.[4]

Whilst prompt antimicrobial administration for septic shock has biological plausibility, the literature is conflicting as to whether early initiation is, indeed, associated with a time-dependent survival benefit.[5,6,7] Accordingly, we sought to examine the relationship between timing of initial antimicrobial therapy and 90-day mortality in patients presenting to the ED with septic shock and enrolled in the Australasian Resuscitation in Septic Shock Evaluation (ARISE) trial.[8]

METHODS

We conducted a post-hoc analysis of the ARISE trial, a multinational, randomised, clinical trial conducted in 51 tertiary and non-tertiary metropolitan and rural hospitals between 2008 and 2014. ARISE evaluated the effect of early goal-directed therapy (EGDT) versus usual care in 1600 patients presenting to the ED with septic shock. The study protocol, statistical analysis plan and trial results have been previously published.[8,9] Approval was obtained from the Human Research Ethics Committee at Monash University and at each participating site.

Participants

The ARISE inclusion criteria were ≥18 years, suspected or confirmed infection, ≥2 systemic inflammatory response criteria and either refractory hypotension (defined as systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg after an intravenous fluid challenge of ≥1000ml administered within 60 minutes) or blood lactate ≥4.0 mmol/L. Entry criteria had to be met ≤6 hours of ED presentation and commencement of the first intravenous antimicrobial dose was mandated prior to randomisation. Antimicrobial choice and timing was at the treating clinician's discretion. Participants for whom commencement time was not available were excluded from this analysis.

Pre-randomisation characteristics included demographics, co-morbidities, Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) scores and physiologic, laboratory and microbiologic variables including infection source, causative organism, antimicrobial timing (defined as the time from ED presentation to commencing administration) and time to appropriate antimicrobial administration. The antimicrobial agent was deemed appropriate when a relevant cultured organism obtained from a specimen collected within 24 hours of ED presentation was susceptible *in vitro* to the prescribed therapy.[10] For culture-negative infections, 2 independent intensive care or emergency physicians blinded to treatment allocation and patient outcome deemed antimicrobial therapy appropriate for the clinically-confirmed infection according to Australian antibiotic therapeutic guidelines.[2,11,12] Where discrepancies occurred, review by a clinical microbiologist was undertaken to achieve consensus.

We also recorded receipt of organ support (vasopressors, mechanical ventilation, acute renal replacement therapy), ED, intensive care unit (ICU) and hospital duration of stay and mortality up to day-90.

Statistical analysis

Continuous variables are reported as mean and standard deviation (SD) or median and interquartile range (IQR) and categorical variables as number (%). We compared baseline characteristics for

participants commencing the first antimicrobial dose ≤60 minutes after ED presentation (early group) versus participants receiving the first dose >60 minutes after presentation (delayed group). The 60 minute timeframe was chosen *a priori* based upon the SSC recommended time to administration.[1] Between-group comparisons were performed using Student's t-test, Mann Whitney, chi-squared tests or Fisher's exact test as appropriate. For the primary outcome (90-day mortality), the unadjusted between-group average treatment effect (ATE) was assessed using generalised estimating equation (GEE) regression, clustered by site, with outcome expressed as the odds ratio (OR) with corresponding 95% confidence intervals (CI). Hazard ratios (HR) with 95%CI were obtained using Cox proportional hazards regression. Time-to-event analysis from randomisation to day-90 is shown as a Kaplan Meier curve and between-group comparisons analysed using the log-rank test. To assess non-linearity, time to antimicrobial therapy was secondarily analysed as a continuous covariate and the relationship with 90-day mortality assessed using a restricted cubic spline with 4 knots. For most patients presenting to the ED, microbial culture results and/or infection source are not initially known. Accordingly, we also conducted a sensitivity analysis examining the relationship between time to appropriate antimicrobial therapy and 90-day mortality. For the secondary outcomes ICU and hospital length of stay, time to event analysis using competing risks regression, with death as the competing event, was performed. Live discharge rates are expressed as the sub-hazard ratio (SHR) with 95%CI. To adjust for baseline covariate imbalance between groups, a propensity score model was constructed using logistic regression to estimate the probability of receiving antimicrobials within 60 minutes. Model covariates were ICU site, after-hours recruitment, age, APACHE III score, Charlson comorbidity score groups (0, 1, 2, ≥3), temperature, heart rate, white cell count, haemoglobin, mechanical ventilation and infection site. Inverse probability of treatment weighting (IPTW) pseudo-population was used to estimate the ATE of antimicrobial timing group using a logistic regression model with robust standard errors, and additionally via a Cox proportional hazards model for time to death, censored at day-90.

All analyses were undertaken in Stata MP/15.1 and full details are presented in the Supplementary Appendix.

RESULTS

Participants

Of 1600 enrolled patients, 10 declined consent, 2 were lost to follow-up at day-90 and one participant did not have the time to antimicrobials recorded, leaving a final cohort of 1587 patients for this analysis (Supplementary Figure S1). Twenty-eight patients (1.8%) did not have the time to appropriate antimicrobial therapy recorded. The median (IQR) time from ED presentation to enrolment was 2.7 (2.0-3.9) hours with 852 (53.7%) patients fulfilling the refractory hypotension criterion, 476 (30.0%) the hypoperfusion criterion and 258 (16.3%) fulfilling both criteria. The proportion of patients with refractory hypotension was not different between the early and delayed groups (69% versus 71%; P=0.44).

Time to antimicrobial initiation

The overall median (IQR) time from ED presentation to commencing the first antimicrobial dose was 69(39-112) minutes. Details of the first agent administered are provided in Supplementary Table S1. In 712 patients (44.9%), the first dose was commenced ≤60 minutes of ED presentation. Patients in the early group and those for whom the first dose was >60 minutes (delayed group) were of similar age and gender (Table 1). However, early administration was associated with increased illness severity as indicated by higher APACHE II and SOFA scores, greater physiological and biochemical derangements, increased fluid and vasopressor administration and increased receipt of mechanical ventilation pre-randomisation. Blood, pulmonary and soft-tissue infections were also more common in patients receiving early antimicrobials. Microbial pathogens from any source were identified in 474 patients (66.6%) and 541 patients (61.8%) in the early versus delayed groups (P=0.05).

The first antimicrobial administered was deemed appropriate in 1025 of 1559 patients (65.7%) and the median time to initiation was 90(47-177) minutes (Table S2). Blood, pulmonary and neurological infections were more common in patients receiving appropriate therapy ≤60 minutes of ED presentation.

Primary outcome

The unadjusted 90-day mortality was higher in the early group, 22.6% (161 of 712 patients) versus 15.5% (136 of 875 patients) in the delayed group, P<0.001 (Table 2). This pattern persisted under the univariate GEE model with an estimated OR of 1.58(95%CI 1.16-2.15), P=0.004 (Table 3). The risk of death remained higher after multivariable analysis incorporating multiple baseline covariates; OR 1.38(95%CI 1.06-1.79), P=0.02 (Table 3). After accounting for baseline imbalance, the between-group 90-day mortality difference in the final propensity score model was no longer significant; OR 1.30(95%CI 0.95-1.76). Survival time to day-90 was also not different between groups. The unadjusted and IPTW survival distributions are shown in Figure 1. When time to first antimicrobial was analysed as a continuous variable, a non-linear, bimodal pattern was observed (Supplementary Figure S2). The highest probabilities of death by day-90 were associated with antimicrobial initiation approximately 30 and 180 minutes after ED presentation.

Sensitivity analyses according to the initiation of appropriate antimicrobials did not change the results (Supplementary Tables S3 and S4).

Secondary outcomes

Organ support was increased in the early group (Table 2). The early group also had a longer unadjusted ICU duration of stay but hospital stay was similar. Under competing risks regression, the unadjusted incident rate for live discharge was lower in the early group for both ICU and hospital stay. The effect of antimicrobial timing became non-significant in the final propensity score model adjusted

for baseline covariates (Table 3). The unweighted and weighted cumulative incidence curves are shown in Figure 2.

DISCUSSION

In this post-hoc analysis of a large randomised trial evaluating protocolised haemodynamic resuscitation for septic shock, antimicrobial therapy was initiated within one hour of ED presentation in approximately 50% of patients. Early administration was associated with a higher severity of illness and increased 90-day mortality compared to participants for whom the first antimicrobial was delayed beyond one hour. However, after propensity score-adjustment for key baseline characteristics including severity of illness score, mechanical ventilation and infection site, the association between antimicrobial timing and mortality was non-significant.

Our findings contrast with the linear relationship between antimicrobial timing and hospital mortality reported by Kumar *et al.* Importantly, in this landmark study, the time to antimicrobial initiation after the onset of hypotension was prolonged (average 13.5 hours) and, in some patients, was over 36 hours[11] In contrast, the design of the ARISE trial required antimicrobial initiation pre-randomisation and within 6 hours of ED presentation. Accordingly, the majority of our patients commenced therapy within 2 hours of presentation. Nonetheless Kumar *et al.* reported that a delay of even 30 minutes after the onset of hypotension was associated with a 5.5% decrease in survival. Our findings do not support these initial observations. Ferrer *et al.,* using data from the SSC database, similarly reported that mortality increased in the first hour after presentation compared to the second hour, followed by a progressive increase in mortality for patients receiving the first antimicrobial within 6 hours.[3] Other retrospective, observational studies have also reported a temporal relationship between antimicrobial timing and survival.[4,13] Conversely, a pre-planned analysis of a randomised trial evaluating an ED-based resuscitation protocol did not find a linear association between antimicrobial timing and hospital mortality in patients with septic shock; albeit a delay in initiation until after shock recognition was associated with decreased survival.[14] More recently, and consistent with our findings, a systematic

review of 11 observational studies examining antimicrobial timing did not find a survival benefit when antimicrobials are administered within 3 hours of ED presentation (OR 1.16; 95%CI 0.92-1.46) or within 1 hour of severe sepsis or septic shock recognition (OR 1.46; 95%CI 0.89-2.40).[15] The IPTW-related OR we report for the time to first antimicrobial (1.30; 95%CI 0.95-1.76) is consistent with this meta-analysis.

Timely antimicrobials are a cornerstone of therapy for septic shock. Whilst early administration is likely to reduce pathogen load, uncertainty exists around the definition of "timely". Randomised trials evaluating a causal relationship between timing and clinical outcomes are not feasible; accordingly recommendations supporting administration within one hour are derived from expert consensus, multicentre observational studies and healthcare databases.[2,3] It is possible, however, that the observed linear effect between timing and mortality is confounded by the overall quality of the resuscitation.[4] This confounding would explain the inability to demonstrate a treatment effect in our study and in similar studies in which the management of septic shock has included a structured resuscitation protocol.[7,14] Of note, for patients that receive antimicrobials within 1 hour in observational studies, in-hospital mortality has ranged from 21-32%.[2,3,4] Moreover, in the original report by Kumar *et al*., hospital mortality was even higher (56.2%). In contrast, in-hospital mortality in our study was only 8%.

There are several explanations for why we did not demonstrate a survival benefit with early antimicrobial administration. First, our patients all received the initial antimicrobial within 6 hours of presentation and there may be an early therapeutic window during which the exact timing of administration is unimportant. In a large, single-centre retrospective study of ED patients with septic shock and a comparable time to first antimicrobial (91 [77-58] minutes), 28-day mortality did not change with hourly delays up to 5 hours after shock recognition.[7] Pre-hospital administration by emergency services personnel has also not improved survival in a large Netherlands study of patients with sepsis randomised to in-ambulance ceftriaxone, compared to usual care administration after ED

presentation.[16] The potential benefit of early empirical, non-targeted antimicrobials may also be counterbalanced by the risk of drug-related side effects and emergence of antimicrobial resistance, particularly when the initial antimicrobial is not appropriate for the microbial pathogen. Further, Hranjec *et al.* reported that antimicrobial initiation only after objective findings of confirmed infection was associated with decreased mortality compared to a more aggressive approach that involved commencing empirical antimicrobials when infection is suspected (13% versus 27%; P=0.02).[17]

Strengths and limitations

Our study is based on a large, prospectively-collected dataset derived from a well-executed multicentre, randomised trial conducted in 51 centres across 5 countries, including large university-affiliated metropolitan hospitals and smaller regional hospitals; ensuring generalisability of the results. Moreover, data collection by trained research coordinators maintained the accuracy of antimicrobial timing with negligible missing data. We observed increased unadjusted mortality with earlier administration and used propensity score methods to account for the confounding effect of potentially unbalanced variables including age, severity of illness and co-morbidities. IPTW models yield more precise estimates than conventional logistic regression and the small E-value (1.54) suggests that the contribution of unknown or unmeasured confounders was modest. We also conducted a sensitivity analysis to account for appropriateness of the initial antimicrobial; albeit information on effectiveness, which, in addition to antimicrobial type, includes dosage and schedule was not collected in ARISE.[11] It is therefore possible that some patients, despite initially receiving an appropriate agent, received an inadequate dose. Nonetheless, earlier studies reporting a linear relationship between antimicrobial timing and mortality have likewise not included more granular data such as dose and dosing schedule.

The ARISE entry criteria excluded patients not commencing the first antimicrobial within 6 hours of ED presentation, potentially creating practice misalignment. Whilst observational studies have reported antimicrobial initiation up to 36 hours after presentation[2,3,4], delayed therapy is not usual

practice in Australia and New Zealand. A prospective, observational study of resuscitation practices in patients presenting to the ED with sepsis and hypotension in 70 Australian and New Zealand hospitals recently reported that the median time to commencing antimicrobials was 77 (IQR 42-148) minutes, consistent with the time to initiation of 69 minutes in our study. Similarly, Seymour *et al.* reported a time to administration of 57 minutes in nearly 50,000 patients across 149 New York hospitals employing a state-mandated sepsis resuscitation protocol.[4]

CONCLUSIONS

In patients with septic shock randomised to a hemodynamic resuscitation protocol, we found no association between antimicrobial timing and mortality when antimicrobials were commenced within 6 hours of ED presentation. These data do not suggest that expeditious antimicrobial therapy is not important*;* rather that a pragmatic opportunity may exist for extending the narrow timeframe recommended in international guidelines, thereby allowing more time to obtain blood cultures prior to initiation, refine antimicrobial selection and focus on urgent haemodynamic resuscitation.

ACKNOWLEDGMENTS

The ARISE trial was endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group and Australasian College for Emergency Medicine. Thank you to Alexander Vlaar for his review of the final manuscript.

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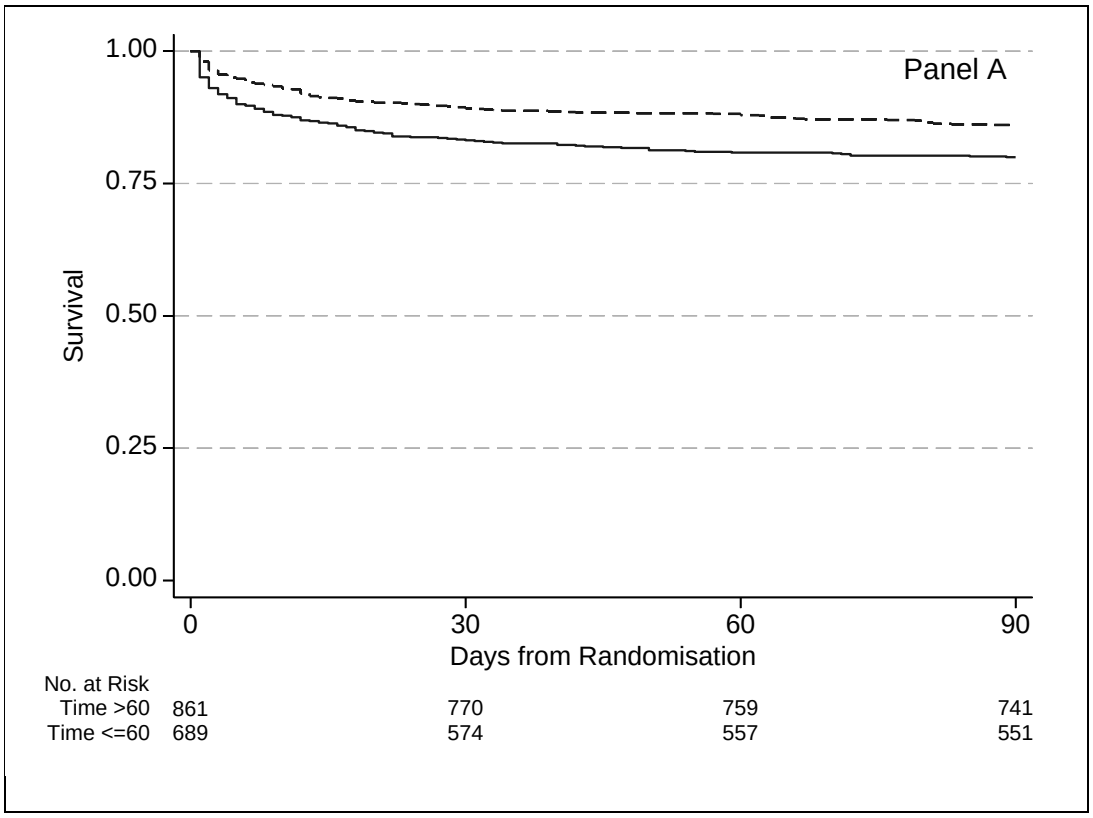
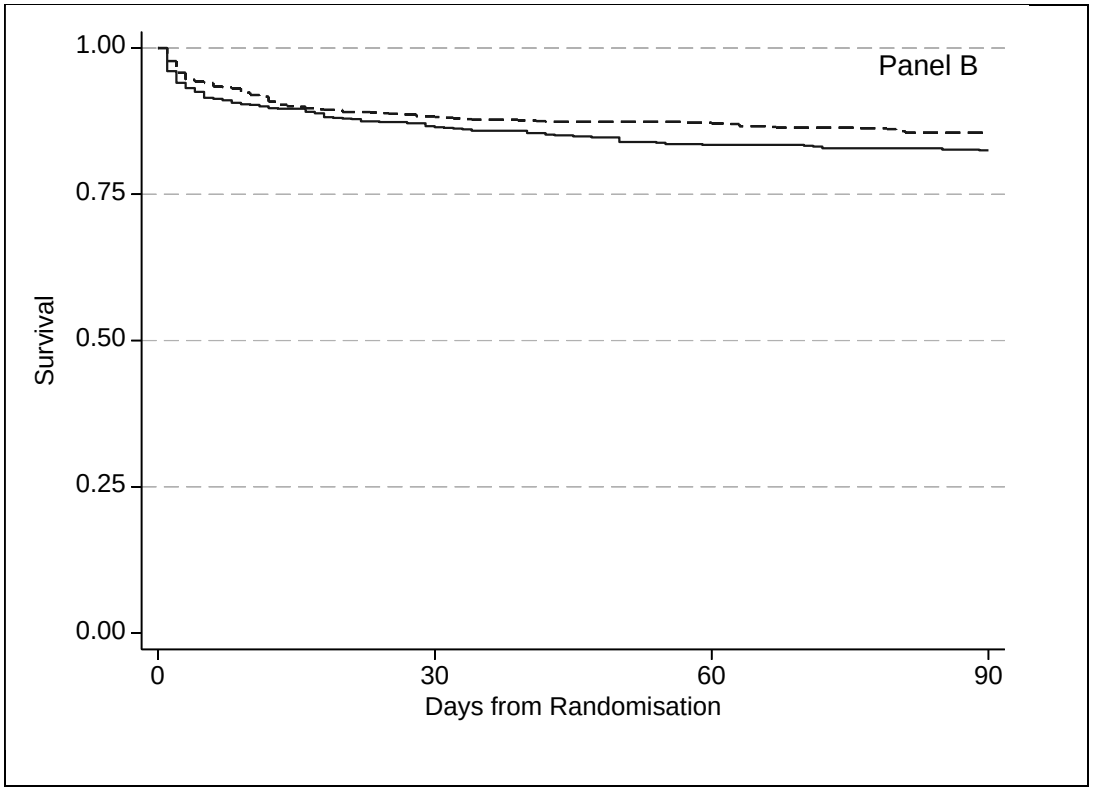
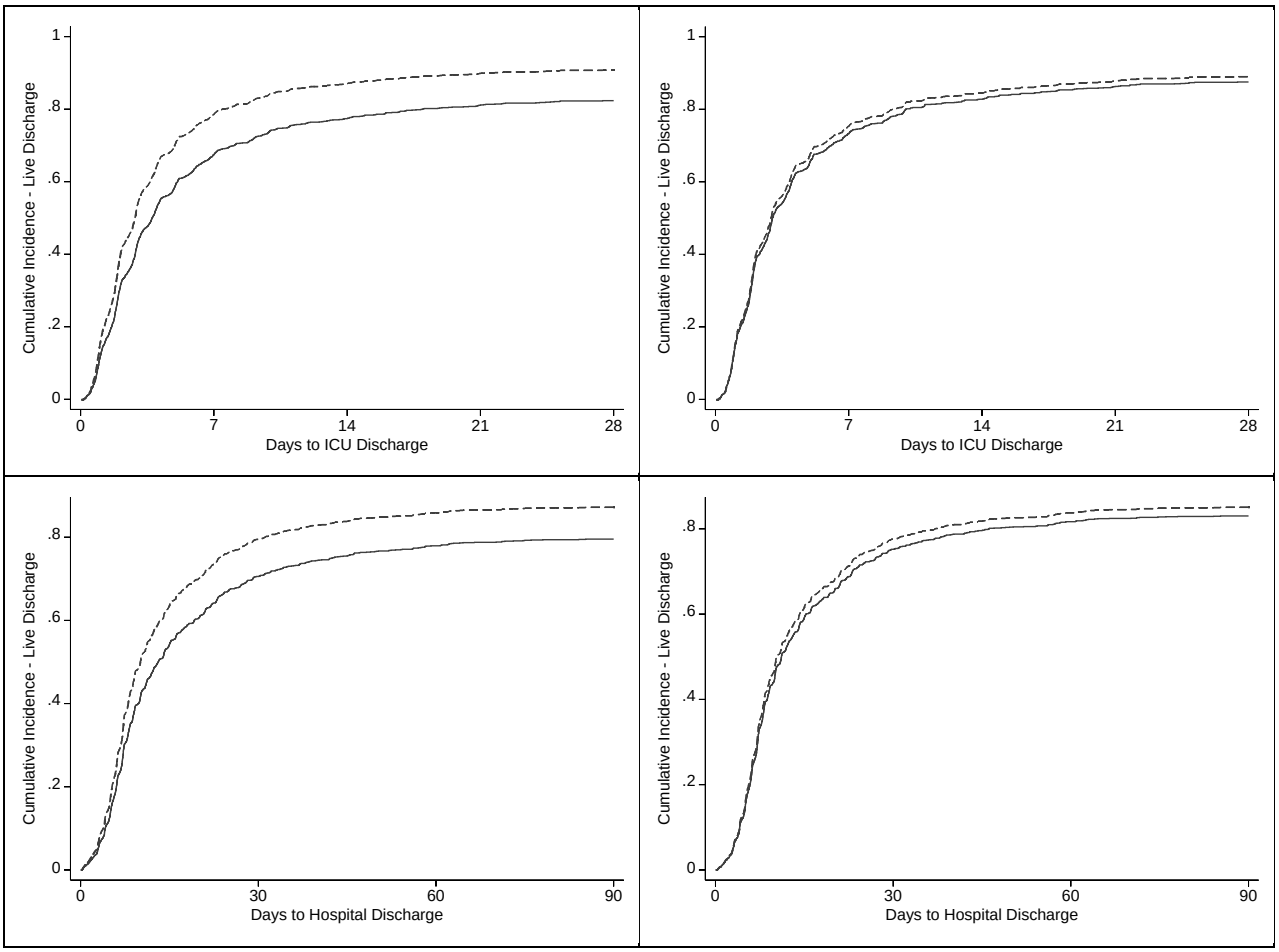
Figure 1. Survival to day-90 according to the timing of antimicrobial initiation ≤60 minutes or >60 minutes after Emergency Department presentation





i.v. denotes intravenous; ED, emergency department; HR, hazard ratio; CI, confidence intervals. Panel A shows Kaplan-Meier unadjusted estimates for probability of death from randomisation to day-90 for patients receiving the first i.v. antimicrobial dose ≤60 minutes (early group; solid line) or >60 minutes (delayed group; dashed line) after ED presentation; HR 1.48 (95%CI 1.16-1.90), log-rank P=0.002. Panel B shows the standardised inverse probability of treatment weighted probability of death at 90 days for the early (solid line) and late (dashed line) groups; HR 1.21 (95%CI 0.90-1.63), log-rank P=0.21. Baseline covariates included in the model were intensive care unit site, age, Acute Physiology and Chronic Health Evaluation III score, Charlson comorbidity index score, temperature, heart rate, white cell count, haemoglobin, invasive mechanical ventilation and infection site; n=1333

Figure 2. Unadjusted and inverse probability of treatment weighted cumulative index curves for live discharge from ICU and hospital, with death as a competing event



CIF denotes cumulative incidence function; SHR, sub-hazard ratio; CI, confidence intervals; IPTW, inverse probability of treatment weighting.

Live discharge rates are expressed as the SHR with 95%CI. The left panels show the unadjusted cumulative incidence for live discharge from ICU (top left) and hospital (bottom left). Unweighted CIF SHR for ICU 0.72 (95%CI 0.65-0.82) (P<0.001) and hospital 0.77 (95%CI 0.69-0.86) (P<0.001). The right panels show the IPTW model for live discharge from ICU (top right) and hospital (bottom right). IPTW CIF SHR for ICU 0.94 (95%CI 0.82-1.08) (P=0.40) and hospital 0.93 (95% CI 0.82-1.06)

(P=0.29). Baseline covariates included in the model were ICU site, after-hours recruitment, age, APACHE III score, Charlson comorbidity index score, temperature, heart rate, white cell count, haemoglobin, invasive mechanical ventilation and infection site; n=1384.

Table 1. Baseline characteristics according to the timing of antimicrobial initiation

Characteristic	Time to first antimicrobial		
	Early* n=712	Late* n=875	P-value
Median time to first antimicrobial, min (IQR)	36 (23-48)	105 (81-148)	
Age, years	62.3±16.3	63.4±16.6	0.17
Male sex, n (%)	433 (60.8)	516 (58.9)	0.44
Median Charlson comorbidity index score (IQR)	1 (0-2)	1 (0-2)	0.94
APACHE II score	16.7±6.6	14.7±6.3	<0.001
Median SOFA Score (IQR)	4 (2-6)	3 (2-5)	<0.001
Inclusion criterion**			
Refractory hypotension	491 (69.0)	619 (70.7)	0.44
Hypoperfusion	373 (52.4)	361 (41.3)	<0.001
Physiologic and laboratory variables#			
Temperature, ^{0}C	37.7±1.6	37.5±1.5	0.03
Heart rate, beats/min	108±23	102±21	<0.001
Systolic blood pressure, mm Hg	99±23	99±22	0.61
Respiratory rate, breaths/min	26±8	24±7	<0.001
Glasgow Coma Score	14.0±2.3	14.6±1.3	<0.001
pH	7.34±0.13	7.36±0.12	0.02
Lactate, mmol/L	4.7±3.0	4.2±3.1	0.01
Creatinine, mmol/L	181±128	166±132	0.02
White cell count, x 10^9/l	13.1±9.0	14.1±10.2	0.04

Mechanical ventilation, n (%)	135 (19.0)	83 (9.5)	<0.001
Vasopressor infusion, n (%)[##]	185 (26.0)	147 (16.8)	<0.001
Median total intravenous fluids (IQR)^			
Volume, L	2.5 (1.9-3.5)	2.3 (1.6-3.1)	0.002
Volume, ml/kg	33.3 (21.2-46.7)	31.8 (19.7-45.9)	0.10
Allocated to EGDT, n (%)	347 (48.7)	444 (50.1)	0.43
Causative site of infection, n (%)			
Lungs	257 (36.1)	293 (33.4)	0.01
Abdomen	55 (7.7)	69 (7.9)	
Urinary tract	132 (18.5)	175 (20.0)	
Skin and soft tissue	81 (11.4)	84 (9.6)	
Central nervous system	12 (1.7)	7 (0.8)	
Blood	84 (11.8)	77 (8.7)	
Other	44 (6.2)	80 (9.1)	
Unknown	47 (6.6)	91 (10.4)	
Causative organism, n (%)			
Gram-positive	178 (25.0)	232 (26.5)	0.05
Gram-negative	228 (32.0)	247 (28.2)	
Other^^	68 (9.6)	62 (7.1)	
Culture-negative	238 (33.4)	334 (38.2)	
Blood culture positive, n (%)	291 (40.9)	307 (35.1)	0.02

Data are presented as mean±standard deviation unless indicated. IQR denotes interquartile range; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; EGDT, early goal-directed therapy; ED, Emergency Department; i.v., intravenous.

* Refers to the time from ED presentation to the commencement of the first i.v. dose of any antimicrobial agent. Early defined as administration ≤ 60 minutes and delayed > 60 minutes after ED presentation.

** 258 patients (16.3%) met both the refractory hypotension and hypoperfusion criteria.

Data available for 84-100% of patients, other than pH, for which data was available for 46% of patients.

Vasopressors includes noradrenaline, adrenaline, metaraminol and vasopressin.

^ Intravenous fluids includes all fluids administered before randomisation, including fluid administered before arrival to hospital. Volume (L) n=1568 and volume (ml/kg) n=1508.

^^ Other includes fungal, parasitic and viral infectious agents.

Table 2. Unadjusted outcomes for early versus delayed antimicrobial therapy

Variable	Time to first antimicrobial*		
	Early n=712	Late n=875	P-value
Primary outcome			
Death by day 90, n (%)	161 (22.6)	136 (15.5)	<0.001
Secondary outcomes			
ICU admission, n (%)	627 (88)	757 (87)	0.36
ICU mortality, n (%)	96 (15)	68 (9)	<0.001
Hospital mortality, n (%)	139 (20)	104 (12)	<0.001
Median (IQR) duration of stay, hours**			
ED	3.8 (2.7-5.4)	5.1 (3.6-7.1)	<0.001
ICU	71 (39-143)	56 (30-110)	<0.001
Hospital	216 (124-408)	195 (118-386)	0.22
Use and duration of organ support			
Invasive mechanical ventilation, n (%)	280 (39)	208 (24)	<0.001
Median duration invasive ventilation (IQR), hours	66 (24-168)	62 (23-159)	0.97
Vasopressor support, n (%)	536 (75)	594 (68)	0.001
Median duration vasopressor support (IQR), days	35 (14-71)	28 (13-57)	0.01
RRT, n (%)[#]	118 (17)	96 (11)	0.001
Median duration RRT (IQR), days	86 (34-212)	1 (20-128)	0.05

ICU denotes intensive care unit; IQR, interquartile range; ED, Emergency Department; i.v., intravenous; RRT, renal replacement therapy.

* Refers to the time from ED presentation to the commencement of the first i.v. dose of any antimicrobial agent. Early defined as administration ≤ 60 minutes and delayed > 60 minutes after ED presentation.

** Duration of stay was calculated from the time of randomisation, except for the ICU stay, which is calculated from the time of ICU admission.

[#] Data for RRT was censored at 90 days after randomisation.

Table 3. Adjusted estimates for the effect of time to initiation of antimicrobial therapy ≤60 minutes (early) compared to >60 minutes (delayed) after ED presentation on 90-day all-cause mortality and length of stay

	Time to first antimicrobial n = 1587	P-value
Models for 90-day mortality	OR/HR (95%CI)	
GEE *		
Univariate	1.58 (1.16-2.15)	0.004
Multivariable	1.38 (1.06-1.79)	0.02
Logistic regression**		
IPTW model	1.30 (0.95-1.76)	0.10
E-value for point estimate	1.54 (1.01-1.99)	-
Cox proportional hazards		
Unadjusted[#]	1.48 (1.16-1.90)	0.002
IPTW model	1.21 (0.90-1.63)	0.21
Models for length of stay[##]	SHR (95%CI)	
ICU		
Unweighted	0.81 (0.72-0.91)	<0.001
IPTW model	0.98 (0.86-1.12)	0.80
Hospital		
Unweighted	0.77 (0.69-0.86)	<0.001
IPTW model	0.93 (0.82-1.06)	0.29

ED denotes Emergency Department; GEE, generalized estimating equation; OR, odds ratio; HR, hazard ratio; SHR, sub-hazard ratio; CI, confidence intervals, IPTW, inverse probability of treatment weighting; APACHE, Acute Physiology And Chronic Health Evaluation. An OR/HR/SHR > 1 favours initiation of antimicrobial therapy > 60 minutes after ED presentation.

* Generalised estimating equations, logit function with robust standard errors, clustered by contributing hospital site (n=1412). Baseline covariates included in multivariable model were age, APACHE III score, Charlson comorbidity index score, temperature, infection site, invasive mechanical ventilation, renal replacement therapy and temperature. Effect estimate as OR.

** Stabilised inverse probability of treatment weighted model on balanced pseudopopulation (n=1339). Baseline covariates included ICU site, age, APACHE III score, Charlson comorbidity index score, temperature, heart rate, white cell count, haemoglobin, invasive mechanical ventilation and infection site. Effect estimate as OR. The E-value represents the minimum OR a confounder would be required to have with both the outcome (90-day mortality) and group assignment (early or delayed) to explain the observed effect estimate.

Cox proportional hazards regression, with robust standard errors, clustered by contributing hospital site (n=1333). Effect estimate as HR.

Competing risks regression, with death as a competing risk. Effect estimate as sub-hazard ratio. ICU IPTW length of stay n=1188 of 1384 patients admitted to ICU; Hospital IPTW length of stay n=1363

SUPPLEMENTARY APPENDIX

TIME TO ANTIMICROBIAL THERAPY IN SEPTIC SHOCK PATIENTS TREATED WITH AN EARLY GOAL-DIRECTED RESUSCITATION PROTOCOL: A POST-HOC ANALYSIS OF THE ARISE TRIAL

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STATISTICAL ANALYSIS

Continuous variables are reported as mean and standard deviation (SD) or median and interquartile range (IQR) and categorical variables as number (%). We compared baseline characteristics for participants who commenced the first antimicrobial dose or the first appropriate dose ≤60 minutes after ED presentation (early group) versus participants receiving the first dose >60 minutes after presentation (delayed group). ED presentation was defined as the recorded triage time. The 60 minute timeframe was chosen *a priori* based upon the SSC recommended time to antimicrobial administration.[1] Between-group comparisons were performed using Student's t-test, Mann Whitney, chi-squared tests or Fisher's exact test as appropriate.

For the primary outcome (90-day all-cause mortality), the unadjusted population average effect between groups was assessed using generalised estimating equation (GEE) regression, clustered by contributing site, with outcome expressed as the odds ratio (OR) with corresponding 95% confidence intervals (CI). Contributing sites with less than 5 events were collapsed to a single category, leaving 24 of 51 ARISE sites. A multivariable GEE model was constructed, incorporating baseline covariates independently associated with the primary outcome and retained at P<0.1. Model covariates were age, APACHE III score, Charlson comorbidity index score, infection site, mechanical ventilation, renal replacement therapy and temperature. Interaction terms were not examined. No imputation was undertaken for missing data, given such data could not be considered "missing at random". Individual covariates were considered for model inclusion only when missing data constituted <10% and the final model subject numbers reported. Hazard ratios (HR) with 95% CI were obtained using Cox proportional hazards regression. Time-to-event analysis from randomisation to day 90 is shown as a Kaplan Meier curve and between-group comparisons analysed using the log-rank test. To assess non-linearity, time to antimicrobial therapy from ED presentation to 6 hours post-randomisation was secondarily analysed as a continuous covariate and the temporal relationship with 90-day mortality assessed using a restricted cubic spline with 4 knots. The SSC guidelines recommend initiating antimicrobials within the first hour of recognising septic shock.[1] However, for most patients presenting to the ED, the results of microbial cultures and/or the source of infection are not known initially. Accordingly, we also conducted a sensitivity analysis examining the relationship between time to initiation of appropriate antimicrobial therapy and 90-day mortality.

To adjust for baseline covariate imbalance between groups, a propensity score model was constructed using logistic regression to estimate the probability of receiving antimicrobials within 60 minutes. No imputation was undertaken for missing data and covariates with ≥10% missing data were omitted. Covariates were retained at P<0.1 and, irrespective of association with treatment assignment, covariates showing a strong association with outcome were retained in the propensity

score model.[2,3] Baseline covariates included in the final propensity score model included ICU site, after-hours recruitment, age, APACHE III score, Charlson comorbidity score groups (0, 1, 2, ≥3), temperature, heart rate, white cell count, haemoglobin, mechanical ventilation and infection site.

Inverse probability of treatment weighting (IPTW) was used to create a ''pseudo-population'' in which the baseline covariates were balanced, with weights stabilised.[4] Propensity score model performance was assessed by covariate standardised differences >10% between groups and propensity score overlap. The IPTW pseudo-population was used to estimate the average treatment effect (ATE) of antimicrobial therapy timing group using a logistic regression model with robust standard errors, and additionally via a Cox proportional hazards model for time to death, censored at day 90. Given the probability of significant unmeasured confounding variables, the E-value for the group ATE was calculated. The E-value represents the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain a specific treatment–outcome association, conditional on the measured covariates.[5] A small E-value indicates there is minimal unmeasured residual confounding contributing to the observed treatment effect; with 1 the smallest possible E-value.

For the secondary outcomes, ICU and hospital length of stay, time to event analysis using competing risks regression, with death as the competing event was performed. Live discharge rates are expressed as the respective sub-hazard ratio (SHR) with 95% CI. All analyses were undertaken in Stata MP/15.1.

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FIGURES

Figure S1. Participant flow

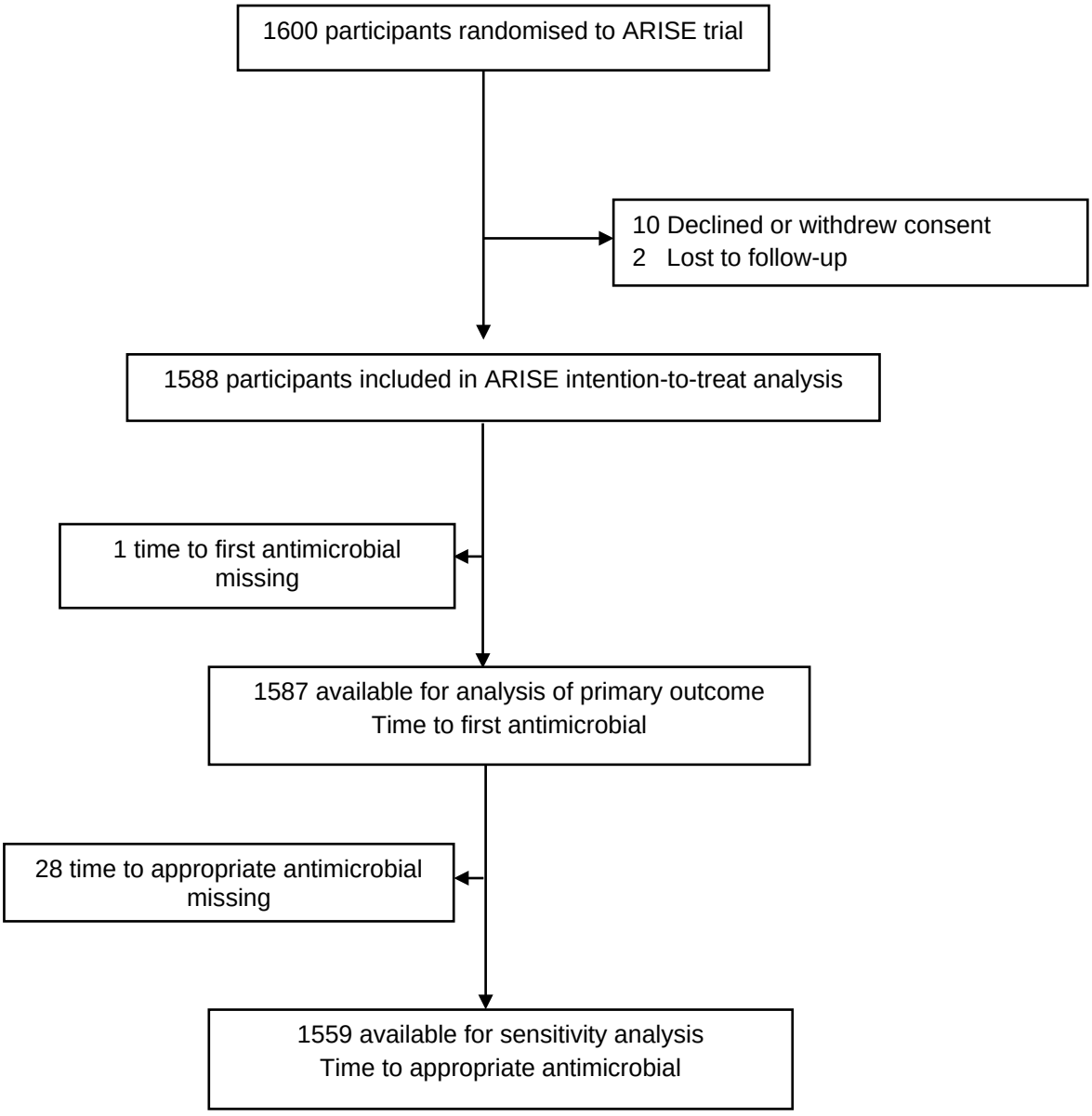
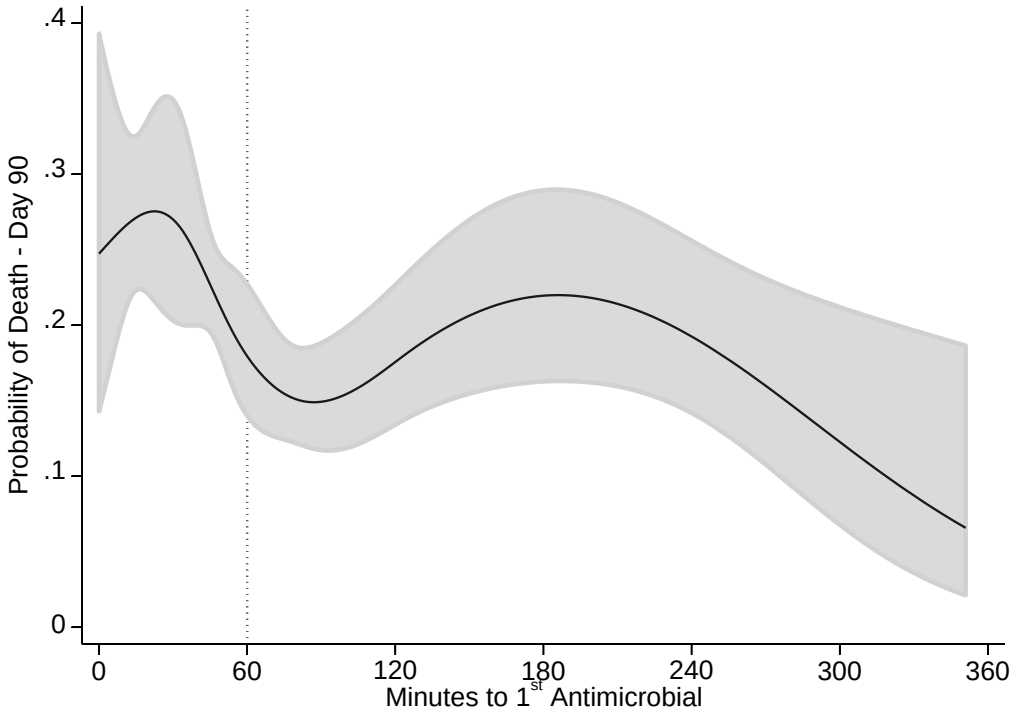


Figure S2. Time to initiation of antimicrobial therapy and probability of death at day-90 with time as a continuous variable



Probability of death modelled using generalised estimating equation regression clustered by intensive care unit site with time to initiation of the first intravenous antimicrobial dose as a continuous variable using restricted cubic splines (4 knots). The solid line represents the predicted mortality and the shaded area the 95% confidence intervals.

TABLES

Table S1. Details of the first antimicrobial agent administered after ED presentation

Antimicrobial class*	Number of patients (%)
Penicillins	385 (22.6)
Cephalosporins	814 (51.3)
Macrolides	57 (35.9)
Aminoglycosides	179 (11.3)
Carbapenems	16 (1.0)
Fluoroquinolones	18 (1.1)
Glycopeptides	53 (3.3)
Nitroimidazoles	35 (2.2)
Other	34 (2.1)

Data available for 1586 patients. *Penicillins* includes amoxycillin/ampicillin, amoxicillin/clavulanate, dicloxacillin, flucloxacillin, penicillin, piperacillin/tazobactam; *Cephalosporin*, ceftazidime, cefazolin, cefepime, cefotaxime, ceftriaxone, cefuroxime, cephalexin, cephalothin; *Macrolides*, azithromycin, erythromycin, roxithromycin; *Aminoglycosides*, amikacin, gentamicin, *Carbapenem*, meropenem; *Fluoroquinolones,* ciprofloxacin, moxifloxacin; *Glycopeptides*, vancomycin; *Nitroimidazoles,* metronidazole; *Other* includes amphotericin B, acyclovir, aztreonam, chloramphenicol, linezolid, sulfamethoxazole/trimethoprim.

715 (45.1%) patients received a second antimicrobial agent within a median 20 (interquartile range 3-60) minutes of the administration of the first antimicrobial agent, 457 (28.8%) patients received a third antimicrobial agent within 90 (42-150) minutes and 139 (8.8%) patients received a fourth antimicrobial agent within 135 (95-195) minutes.

Table S2. Baseline characteristics according to the initiation of appropriate antimicrobial initiation ≤60 minutes or >60 minutes after ED presentation

Characteristic	Appropriate antimicrobial		
	Early* n=534	Late* n=1025	P-value
Median time to appropriate antimicrobial, min (IQR)	37 (24-48)	136 (91-267)	
Age, years	61.8±16.4	63.3±16.5	0.06
Male sex, n (%)	318 (59.2)	611 (59.6)	0.87
Median Charlson comorbidity index score (IQR)	1 (0-2)	1 (0-2)	0.82
APACHE II score	16.7±6.6	15.0±6.5	<0.001
Median SOFA Score (IQR)	4 (2-6)	3 (2-5)	<0.001
Inclusion criterion**			
Refractory hypotension	368 (68.9)	742 (70.5)	0.52
Hypoperfusion	290 (54.3)	444 (42.2)	<0.001
Physiologic and laboratory variables#			
Temperature, ^{0}C	37.7±1.6	37.6±1.5	0.19
Heart rate, beats/min	108±23	103±22	<0.001
Systolic blood pressure, mm Hg	99±24	99±21	0.74
Respiratory rate, breaths/min	26±8	24±8	0.01
Glasgow Coma Score	13.9±2.4	14.5±1.4	<0.001
pH	7.33±0.13	7.36±0.12	<0.01
Lactate, mmol/L	4.1±3.0	4.7±3.2	<0.001
Creatinine, mmol/L	176±123	171±135	0.50

White cell count, x 10^9/l	13.1±9.3	13.9±9.9	0.11
Mechanical ventilation, n (%)	115 (21.5)	102 (10.0)	<0.001
Vasopressor infusion, n (%)##	147 (27.5)	181 (17.7)	<0.001
Median total intravenous fluid (IQR)^			
Volume, L	2.5 (1.9-3.5)	2.3 (1.7-.1)	0.007
Volume, ml/kg	33 (21-47)	32 (20-46)	<0.001
Allocated to EGDT, n (%)	267 (50)	509	0.90
Site of infection, n (%)			
Lungs	206 (38.6)	333 (32.7)	0.001
Abdomen	31 (5.8)	90 (8.8)	
Urinary tract	101 (18.9)	202 (19.6)	
Skin and soft tissue	52 (9.7)	109 (10.7)	
Central nervous system	12 (2.3)	7 (0.7)	
Blood	61 (11.6)	96 (9.3)	
Other	36 (6.7)	88 (8.4)	
Unknown	34 (6.4)	100 (9.9)	
Causative organism, n (%)			
Gram-positive	129 (24.2)	281 (26.7)	0.17
Gram-negative	154 (28.8)	312 (30.5)	
Other^	54 (10.1)	76 (7.2)	
Culture-negative	197 (36.9)	375 (35.6)	
Blood culture positive, n (%)	201 (37.6)	398 (38.0)	

Data are presented as mean±standard deviation unless indicated. IQR denotes interquartile range; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; EGDT, early goal-directed therapy; ED, Emergency Department; i.v., intravenous.

* Refers to the time from presentation to the ED to commencement of the first i.v. dose of an antimicrobial agent to which the relevant cultured organism obtained from a specimen within 24 hours of ED presentation is susceptible in vitro. Early defined as administration ≤ 60 minutes and delayed > 60 minutes after ED presentation. For culture-negative patients, antimicrobial therapy was deemed appropriate according to the clinically identified source of infection. The determination of appropriate antimicrobial therapy was performed by two independent intensive care and ED clinicians blinded to the EGDT treatment allocation and to the primary outcome. Where unresolved, a third review by a clinical microbiologist was undertaken and consensus achieved.

Data available for 82-98% of patients, other than pH for which data was available for 44% of patients.

Vasopressors includes noradrenaline, adrenaline, metaraminol and vasopressin.

^ Intravenous fluids includes all fluids administer before randomisation, including fluid administered before arrival to hospital. Volume (L) n=1540 and volume (ml/kg) n=1480.

^^ Other includes fungal, parasitic and viral infectious agents.

Table S3. Unadjusted outcomes for patients according to the appropriateness of the first antimicrobial administered after ED presentation

Outcome	First antimicrobial appropriate* 534	First antimicrobial inappropriate* 1025	P-value
ICU admission	465 (87.1)	864 (87.2)	0.84
Mortality, n (%)			
ICU	76 (16.3)	84 (9.4)	<0.001
Hospital	109 (20.4)	130 (12.7)	<0.001
90-day	126 (23.6)	166 (16.2)	<0.001
Organ support, n (%)			
Mechanical ventilation	211 (39.5)	273 (26.6)	<0.001
Vasopressor support	394 (73.8)	718 (70.0)	0.12
Renal replacement therapy	85 (15.9)	127 (12.4)	0.05

ICU denotes intensive care unit; ED, Emergency Department.

* Refers to the administration of the first i.v. dose of an antimicrobial agent after ED presentation. Antimicrobial therapy deemed appropriate if the relevant cultured organism obtained from a specimen within 24 hours of ED presentation is susceptible in vitro or according to the clinically identified source of infection for culture-negative patients. The determination of appropriate antimicrobial therapy was performed by two independent intensive care and ED clinicians blinded to the EGDT treatment allocation and to the primary outcome. Where unresolved, a third review by a clinical microbiologist was undertaken and consensus achieved.

Table S4. Adjusted estimates for the effect of time to initiation of appropriate antimicrobial therapy ≤60 minutes (early) compared to >60 minutes (delayed) after ED presentation on 90-day all-cause mortality

	Time to appropriate antimicrobial n=1559	P-value
Models for 90-day mortality	OR/HR (95% CI)	
GEE*		
Univariate	1.56 (1.26-.194)	<0.001
Multivariable	1.39 (1.08-1.77)	0.01
Logistic regression**		
IPTW model	1.37 (1.00-1.88)	0.05
E-value for point estimate	1.62 (1.04-2.08)	-
Cox proportional hazards		
Unadjusted[#]	1.47 (1.15-1.89)	0.002
IPTW	1.28 (0.94-1.73)	0.113

ED denotes Emergency Department; GEE, generalized estimating equation; OR, odds ratio; HR, hazard ratio; CI, confidence intervals; IPTW, inverse probability of treatment weighting; APACHE, Acute Physiology And Chronic Health Evaluation. An OR/HR > 1 favours initiation of antimicrobial therapy > 60 minutes after ED presentation.

* Generalised estimating equations, logit function with robust standard errors, clustered by contributing hospital site. Baseline covariates included in multivariable model were age, APACHE III score, Charlson comorbidity index score, temperature, infection site, invasive mechanical ventilation, renal replacement therapy and temperature. Effect estimate as OR.

** Stabilised inverse probability of treatment weighted model on balanced pseudopopulation. Baseline covariates included ICU site, age, APACHE III score, Charlson comorbidity index score, temperature, heart rate, white cell count, haemoglobin, invasive mechanical ventilation and infection site. Effect estimate as OR. The E-value represents the minimum OR a confounder would be required to have with both the outcome (90-day mortality) and group assignment (early or delayed) to explain the observed effect estimate.

Cox proportional hazards regression, with robust standard errors, clustered by contributing hospital site. Effect estimate as HR.