Antibiotics for Sepsis: Does Each Hour Really Count, or Is It Incestuous Amplification?

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- Incestuous amplification—the (extreme) reinforcement of ideas and/or beliefs that occurs when like-minded people communicate with each other
- "Each hour's delay in initiating antibiotics costs lives"
- Time Zero (when the infection starts or organ dysfunction begins) and time to presentation/recognition of sepsis is largely unknown but vary from hours to several days

NECCS

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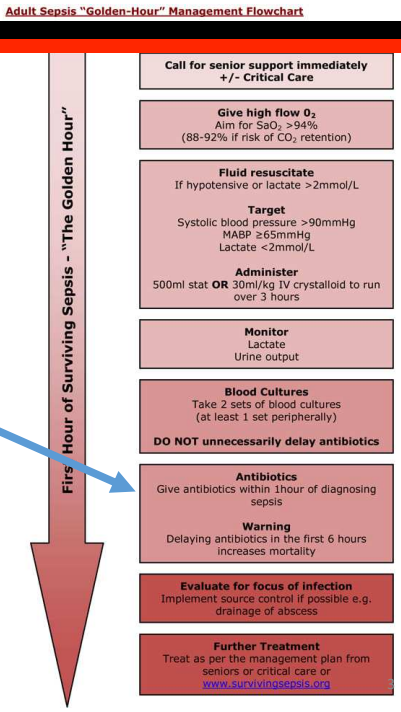
SEPSIS TREATMENT	ORGAN SUPPORT
	ANTIBIOTICS
	SOURCE CONTROL



Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes, MB BS, MD(Res) (Co-chair)[1]; Laura E. Evans, MD, MSc, FCCM (Co-chair)[2];

- We recommend the administration of IV antibiotics be initiated as soon as possible after recognition and within 1 h for sepsis and septic shock
- We recommend empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens
- We suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock

SPECIAL EDITORIAL

The Surviving Sepsis Campaign Bundle: 2018 update

Mitchell M. Levy[1*], Laura E. Evans[2] and Andrew Rhodes[3]

Table 1 Bundle elements with strength of recommendations and underpinning quality of evidence [12, 13]

From: The Surviving Sepsis Campaign Bundle: 2018 update

Bundle element	Grade of recommendation and level of evidence
Measure lactate level. Re-measure if initial lactate is > 2 mmol/L	Weak recommendation, low quality of evidence
Obtain blood cultures prior to administration of antibiotics	Best practice statement
Administer broad-spectrum antibiotics	Strong recommendation, moderate quality of evidence
Rapidly administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L	Strong recommendation, low quality of evidence
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg	Strong recommendation, moderate quality of evidence

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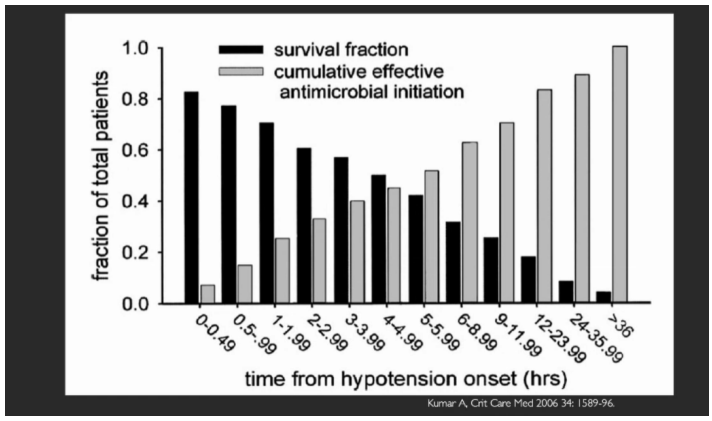
Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

Importance of timing of therapy



2154 ICU patients, hour-by hour linear relationship btw delay antibiotics and mortality

Kumar A et al. Crit Care Med 2006

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CHEST Original Research

CRITICAL CARE MEDICINE

Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock

Anand Kumar, MD; Paul Ellis, MD; Yaseen Arabi, MD, FCCP;

Objective: Our goal was to determine the impact of the initiation of inappropriate antimicrobial therapy on survival to hospital discharge of patients with septic shock.
Methods: The appropriateness of initial antimicrobial therapy, the clinical infection site, and relevant pathogens were retrospectively determined for 5,715 patients with septic shock in three countries.
Results: Therapy with appropriate antimicrobial agents was initiated in 80.1% of cases. Overall, the survival rate was 43.7%. There were marked differences in the distribution of comorbidities, clinical infections, and pathogens in patients who received appropriate and inappropriate initial antimicrobial therapy ($p < 0.0001$ for each). The survival rates after appropriate and inappropriate initial therapy were 52.0% and 10.3%, respectively (odds ratio [OR], 9.45; 95% CI, 7.74 to 11.54; $p < 0.0001$). Similar differences in survival were seen in all major epidemiologic, clinical, and organism subgroups. The decrease in survival with inappropriate initial therapy ranged from 2.3-fold for pneumococcal infection to 17.6-fold with primary bacteremia. After adjustment for acute physiology and chronic health evaluation II score, comorbidities, hospital site, and other potential risk factors, the inappropriateness of initial antimicrobial therapy remained most highly associated with risk of death (OR, 8.99; 95% CI, 6.60 to 12.23).
Conclusions: Inappropriate initial antimicrobial therapy for septic shock occurs in about 20% of patients and is associated with a fivefold reduction in survival. Efforts to increase the frequency of the appropriateness of initial antimicrobial therapy must be central to efforts to reduce the mortality of patients with septic shock. *(CHEST 2009; 136:1237–1248)*

Kumar et al. Chest 2009

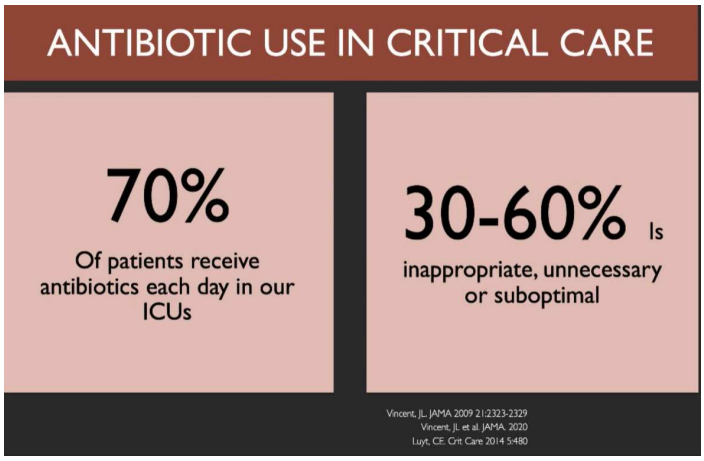
- Inappropriate initial anti microbial therapy for septic shock in 20%
- Associated with a fivefold reduction in survival (52% vs. 10.3%)

Chest 2009

EDITORIAL

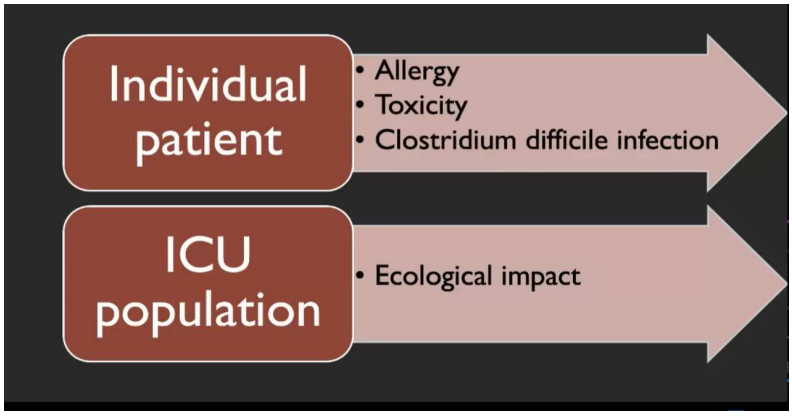
Infection, Antibiotics, and Patient Outcomes in the Intensive Care Unit

Mo Yin, MRCP; Paul Anantharajah Tambyah, MD; Eli N. Perencevich, MD, MS



JAMA 2020

Side-effects of antibiotics



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Are we sure the patient has infection?

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Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study

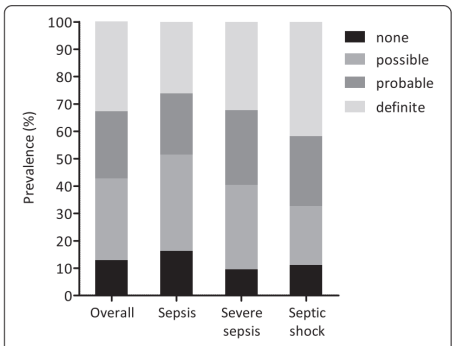


Fig. 1 Plausibility of infection stratified by clinical severity upon presentation in patients with presumed sepsis. Comparison between the clinical diagnosis of infection at the time of ICU admission and the actual presence of infection as determined by post-hoc evaluation

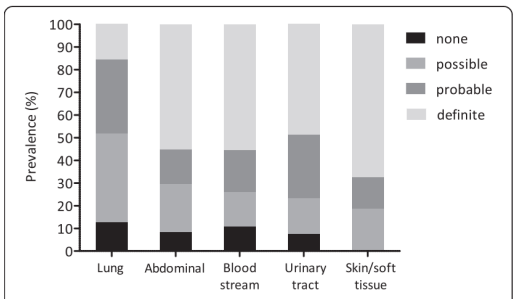
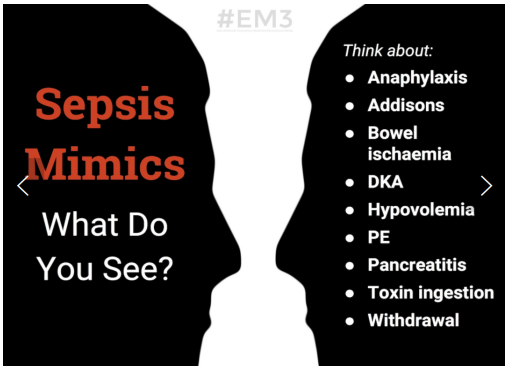


Fig. 2 Plausibility of infection in patients with presumed sepsis upon presentation for the most frequent sites of infection. Distribution of plausibility of infection for lung infections (community-acquired pneumonia and hospital-acquired pneumonia), abdominal infections (primary and secondary peritonitis), bloodstream infections (primary bloodstream infections, catheter-related bloodstream infections, and endocarditis), urinary tract infections, and skin/soft tissue infections

Klein Klowenberg Crit Care 2015



Conditions that mimic sepsis

Cardiac disease	Arrhythmias
	Heart failure
	Myocardial infarction
Pulmonary disease	Acute respiratory distress syndrome
	Aspiration pneumonitis
	Asthma exacerbation
	Bronchiectasis exacerbation
	Chronic obstructive pulmonary disease exacerbation
	Interstitial lung disease flare
	Hypersensitivity pneumonitis
	Pulmonary embolism
Gastrointestinal disease	Acute liver failure
	Bowel obstruction
	Gastrointestinal hemorrhage
	Inflammatory bowel disease
	Mesenteric ischemia
	Pancreatitis
	Volvulus
Central nervous system disease	Autonomic dysfunction
	Seizure
	Stroke/intracranial hemorrhage
Endocrine disease	Adrenal insufficiency
	Diabetic ketoacidosis
	Myxedema coma
	Thyroid storm

Hematologic/ oncologic disease	Antiphospholipid syndrome
	Malignancy
	Hemophagocytic syndrome
	Tumor lysis syndrome
Rheumatologic/ autoimmune disease	Gout
	Rheumatoid arthritis
	Still's disease
	Systemic lupus erythematosus
	Vasculitis
Drugs/toxins	Drug overdose
	Drug/alcohol withdrawal
	Hypersensitivity drug reaction
	Medication toxicity
	Malignant hyperthermia
	Neuroleptic malignant syndrome
	Serotonin syndrome
Other	Allograft rejection (solid organ transplant recipients)
	Anaphylaxis
	Compartment syndrome
	Heat stroke
	Hemorrhage
	Hypovolemia
	Postoperative period
	Severe burns
	Tissue ischemia

Challenges in EARLY antibiotic therapy

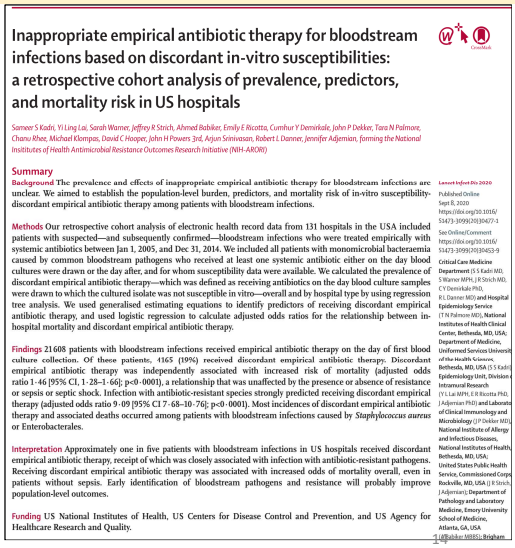
- Need for adequate source control
- Adequacy of antibiotic dosing
- Appropriate antibiotic therapy

- Exact start of an infection (time zero)

Importance of appropriate antibiotics

- 21,500 patients with BSI in US hospitals
- 20% 'discordant' therapy
- 45% sepsis, 15% septic shock
- 46% increase in mortality
- Increased odds of mortality even in patients without sepsis
- Discordant therapy driven by antibiotic-resistant pathogens.

Lancet Infec Dis 2020



Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals

Sameer S Kadri, Yi Ling Lai, Sarah Warner, Jeffrey R Strich, Ahmed Babiker, Emily E Ricotta, Cumhur Y Demirkale, John P Dekker, Tara N Palmore, Chanu Rhee, Michael Klompas, David C Hooper, John H Powers 3rd, Arjun Srinivasan, Robert L Danner, Jennifer Adjemian, forming the National Institutes of Health Antimicrobial Resistance Outcomes Research Initiative (NIH-AROR)

Summary

Background The prevalence and effects of inappropriate empirical antibiotic therapy for bloodstream infections are unclear. We aimed to establish the population-level burden, predictors, and mortality risk of in-vitro susceptibility-discordant empirical antibiotic therapy among patients with bloodstream infections.

Methods Our retrospective cohort analysis of electronic health record data from 131 hospitals in the USA included patients with suspected—and subsequently confirmed—bloodstream infections who were treated empirically with systemic antibiotics between Jan 1, 2005, and Dec 31, 2014. We included all patients with monomicrobial bacteraemia caused by common bloodstream pathogens who received at least one systemic antibiotic either on the day blood cultures were drawn or the day after, and for whom susceptibility data were available. We calculated the prevalence of discordant empirical antibiotic therapy—which was defined as receiving antibiotics on the day blood culture samples were drawn to which the cultured isolate was not susceptible in vitro—overall and by hospital type by using regression tree analysis. We used generalised estimating equations to identify predictors of receiving discordant empirical antibiotic therapy, and used logistic regression to calculate adjusted odds ratios for the relationship between in-hospital mortality and discordant empirical antibiotic therapy.

Findings 21 608 patients with bloodstream infections received empirical antibiotic therapy on the day of first blood culture collection. Of these patients, 4165 (19%) received discordant empirical antibiotic therapy. Discordant empirical antibiotic therapy was independently associated with increased risk of mortality (adjusted odds ratio 1·46 [95% CI, 1·28–1·66]; p<0·0001), a relationship that was unaffected by the presence or absence of resistance or sepsis or septic shock. Infection with antibiotic-resistant species strongly predicted receiving discordant empirical therapy (adjusted odds ratio 9·09 [95% CI 7·68–10·76]; p<0·0001). Most incidences of discordant empirical antibiotic therapy and associated deaths occurred among patients with bloodstream infections caused by *Staphylococcus aureus* or Enterobacterales.

Interpretation Approximately one in five patients with bloodstream infections in US hospitals received discordant empirical antibiotic therapy, receipt of which was closely associated with infection with antibiotic-resistant pathogens. Receiving discordant empirical antibiotic therapy was associated with increased odds of mortality overall, even in patients without sepsis. Early identification of bloodstream pathogens and resistance will probably improve population-level outcomes.

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- 44 German ICUs
- 1011 severe sepsis/septic shock
- Times to AT, source control and adequacy of AT and 28-day mortality

RESEARCH Open Access

Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study

Frank Bloos[1,2*], Daniel Thomas-Rüddel[1,2], Hendrik Rüddel[1], Christoph Engel[3], Daniel Schwarzkopf[2], John C Marshall[4], Stephan Harbarth[5], Philipp Simon[6], Reimer Riessen[7], Didier Keh[8], Karin Dey[9], Manfred Weiß[10], Susanne Toussaint[11], Dirk Schädler[12], Andreas Weyland[13], Maximillian Ragaller[14], Konrad Schwarzkopf[15], Jürgen Eiche[16], Gerhard Kuhnle[17], Heike Hoyer[18], Christiane Hartog[1,2], Udo Kaisers[6] and Konrad Reinhart[1,2] for the MEDUSA Study Group

Abstract

Introduction: Current sepsis guidelines recommend antimicrobial treatment (AT) within one hour after onset of sepsis-related organ dysfunction (OD) and surgical source control within 12 hours. The objective of this study was to explore the association between initial infection management according to sepsis treatment recommendations and patient outcome.

Methods: In a prospective observational multi-center cohort study in 44 German ICUs, we studied 1,011 patients with severe sepsis or septic shock regarding times to AT, source control, and adequacy of AT. Primary outcome was 28-day mortality.

Results: Median time to AT was 2.1 (IQR 0.8 – 6.0) hours and 3 hours (-0.1 – 13.7) to surgical source control. Only 370 (36.6%) patients received AT within one hour after OD in compliance with recommendation. Among 422 patients receiving surgical or interventional source control, those who received source control later than 6 hours after onset of OD had a significantly higher 28-day mortality than patients with earlier source control (42.9% versus 26.7%, P <0.001). Time to AT was significantly longer in ICU and hospital non-survivors; no linear relationship was found between time to AT and 28-day mortality. Regardless of timing, 28-day mortality rate was lower in patients with adequate than non-adequate AT (30.3% versus 40.9%, P < 0.001).

Conclusions: A delay in source control beyond 6 hours may have a major impact on patient mortality. Adequate AT is associated with improved patient outcome but compliance with guideline recommendation requires improvement. There was only indirect evidence about the impact of timing of AT on sepsis mortality.

Critical care 2014

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Timing of Antibiotic Therapy (AT)

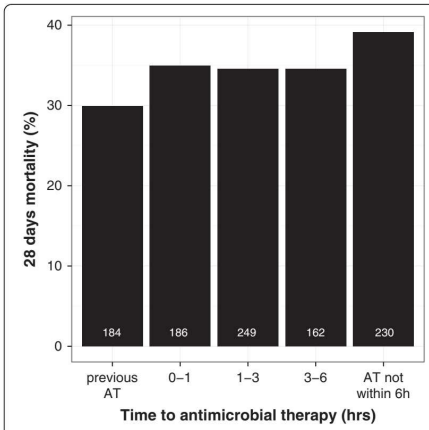

Figure 1 Twenty-eight-day mortality according to time to antimicrobial therapy. Numbers in the bars represent number of patients in this group. Previous AT, patients who received antimicrobial therapy (AT) before onset of infection-related organ dysfunction.

Table 3 Time to antimicrobial therapy and source control according to survival

	Survivors	Nonsurvivors	*P* value
Time to antimicrobial therapy (hours)			
28-day survival	2.0 (0.6 to 5.6) (n = 659)	2.5 (1.0 to 6.6) (n = 352)	0.112
ICU survival	2.0 (0.7 to 5.4) (n = 667)	2.8 (0.9 to 7.0) (n = 329)	0.023
Hospital survival	2.0 (0.6 to 5.1) (n = 581)	2.8 (0.9 to 7.0) (n = 329)	0.020
Time to source control (hours)			
28-day survival	2.0 (−0.5 to 10.1) (n = 286)	5.7 (0.4 to 18.0) (n = 139)	0.004
ICU survival	2.0 (−0.6 to 9.1) (n = 286)	6.0 (0.5 to 19.9) (n = 132)	<0.001
Hospital survival	2.0 (−0.5 to 9.3) (n = 249)	5.5 (0.4 to 18.9) (n = 166)	0.001

Data are shown as median and interquartile range.

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Time to Antibiotic Therapy

Table 5 Multivariate logistic regression model for the impact of patient-related factors on 28-day mortality

Variable	Odds ratios (95% CI)	*P* value
All patients ($n = 725$)[a]		
Time to antimicrobial therapy >1 hour[b]	0.81 (0.54 to 1.23)	0.323
Initial SOFA score[c]	1.19 (1.13 to 1.26)	<0.001
Age[d]	1.04 (1.03 o 1.06)	<0.001
Maximum lactate (day 1)[e]	1.09 (1.04 to 1.14)	<0.001
Intra-abdominal focus	1.08 (0.75 to 1.57)	0.670
Urogenital focus	0.65 (0.36 to 1.14)	0.143
Unknown focus	1.26 (0.57 to 2.78)	0.574
Community-acquired infection	0.89 (0.65 to 1.22)	0.484
Inadequate empiric antimicrobial therapy	1.44 (1.05 to 1.99)	0.026
No de-escalation of antimicrobials within 5 days	1.17 (0.66 to 2.14)	0.597
Time to source control >6 hours	2.36 (1.22 to 4.71)	0.012

Bloos et al. Crit Care 2014

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Narrative Review

Impact of time to antibiotic therapy on clinical outcome in patients with bacterial infections in the emergency department: implications for antimicrobial stewardship

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Sepsis
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Skin infection
Urinary tract infection

ABSTRACT

Background: Rapid initiation of antibiotic treatment is considered crucial in patients with severe infections such as septic shock and bacterial meningitis, but may not be as important for other infectious syndromes. A better understanding of which patients can tolerate a delay in start of therapy is important for antibiotic stewardship purposes.
Objectives: To explore the existing evidence on the impact of time to antibiotics on clinical outcomes in patients presenting to the emergency department (ED) with bacterial infections of different severity of illness and source of infection.
Sources: A literature search was performed in the PubMed/MEDLINE database using combined search terms for various infectious syndromes (sepsis/septic shock, bacterial meningitis, lower respiratory tract infections, urinary tract infections, intra-abdominal infections and skin and soft tissue infections), time to antibiotic treatment, and clinical outcome.
Content: The literature search generated 8828 hits. After screening titles and abstracts and assessing potentially relevant full-text papers, 60 original articles (four randomized controlled trials, 43 observational studies) were included. Most articles addressed sepsis/septic shock, while few studies evaluated early initiation of therapy in mild to moderate disease. The lack of randomized trials and the risk of confounding factors and biases in observational studies warrant caution in the interpretation of results. We conclude that the literature supports prompt administration of effective antibiotics for septic shock and bacterial meningitis, but there is no clear evidence showing that a delayed start of therapy is associated with worse outcome for less severe infectious syndromes.
Implications: For patients presenting with suspected bacterial infections, withholding antibiotic therapy until diagnostic results are available and a diagnosis has been established (e.g. by 4–8 h) seems acceptable in most cases unless septic shock or bacterial meningitis are suspected. This approach promotes the use of ecologically favourable antibiotics in the ED, reducing the risks of side effects and selection of resistance. **P. Nauclér, Clin Microbiol Infect 2021;27:175**

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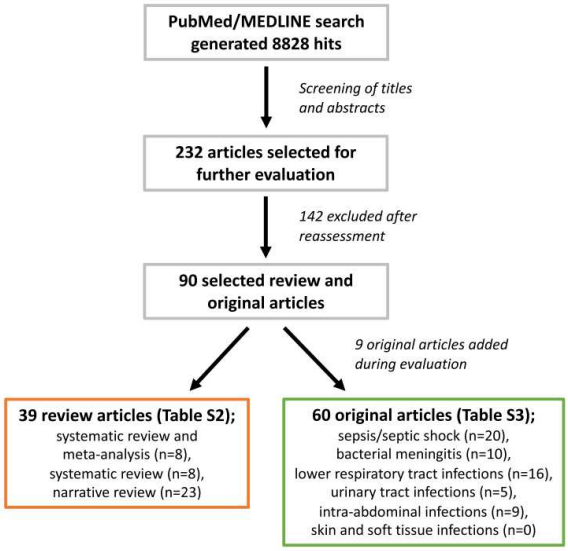

Fig. 1. Flow chart illustrating the search and screening process for relevant reviews and original articles providing information on early antibiotic therapy as a determinant of clinical outcome in community-onset bacterial infections.

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Table 1
Summary of main findings and limitations of the reviewed original studies.

Infectious syndrome	No. of studies	Summary of results and comments
Sepsis	0 RCTs 20 observational studies	• Data from observational and register studies indicate an increase in mortality with delays in antibiotic administration, especially in the most critically ill patients with septic shock. • The studies used different definitions of "time zero", including ED arrival, triage, shock recognition and commencement of a care bundle within 6 hours after ED arrival. • A specific cut-off time for mortality benefit (e.g., initiation of therapy <1 or <3 hours after presentation) has not been defined. • The quality of evidence is low, and few studies have explored the interaction of timeliness and appropriateness of antibiotic administration in relation to mortality.
Bacterial meningitis	0 RCTs 10 observational studies	• One prospective and nine retrospective observational studies all reported an association between delayed initiation of antibiotic therapy and poor clinical outcome. • Limitations include confounding biases, small sample size and that patients who receive antibiotics early differ from other patients (e.g., in clinical presentation and pathogens). • Neurological symptoms by the time appropriate antibiotic therapy is initiated may be more relevant as a prognostic marker than time to initiation of antibiotics.
Lower respiratory tract infections	0 RCTs 16 observational studies	• 7/9 retrospective studies, including one subgroup analysis in septic patients, suggest that a delayed administration of antibiotics >4-8 hours is associated with worse outcomes. • 4/8 prospective studies showed no benefit from early antibiotics, while the other four did not preclude an effect. • Studies demonstrating an effect were retrospective and registry-based studies relied on diagnosis codes for case identification. • Studies show discrepant results on differential effects according to disease severity. • Many of the studies suffer from potential biases that impede the causal inference of delayed onset of therapy.
Urinary tract infections	0 RCTs 5 observational studies	• No studies were found that specifically evaluated early vs. delayed antibiotic therapy for UTIs in the ED. • One prospective and 3/4 retrospective observational studies showed no association between inappropriate empirical antibiotic therapy and mortality. • The studies may have been liable to confounding or bias. • The available data suggest severity of illness and co-morbidities are more important risk factors for mortality than time to administration of antibiotics in the ED.
Intra-abdominal infections	4 RCTs 5 observational studies	• Four RCTs on early vs. delayed initiation of carbapenem therapy for acute necrotizing pancreatitis showed variable results. • Retrospective observational studies on inappropriate empiric therapy suggest no association with clinical outcome in acute cholangitis or cholecystitis but a potential association in septic cirrhotic patients who develop spontaneous bacterial peritonitis and for BSIs of intra-abdominal origin.
Skin and soft tissue infections	0 RCTs 0 observational studies	• We found no studies that assessed the impact of time to first antibiotic dose in patients with SSTIs in the ED.

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Time to antibiotics in the ED

Condition	Findings
Sepsis	Increase in mortality with delay of antibotics, particularly in septic shock No cut-off time point identified Quality of evidence low
Bacterial meningitis	Association between delay and poor outcome Confounders present in all studies
LRTI	Delay of 4-8 hours associated with worse outcomes Biases common
UTI	No studies on timing of antibiotic therapy

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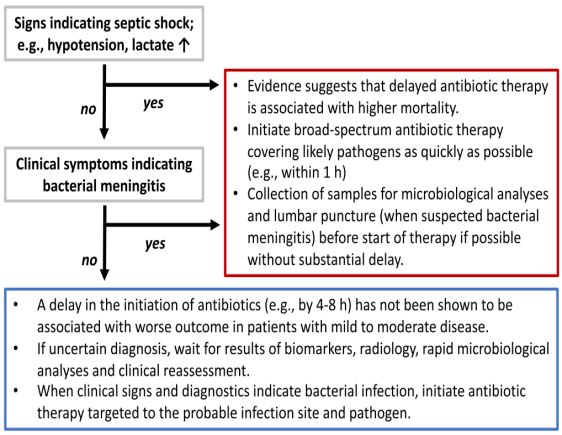

g. 2. Suggested approach to early or delayed antibiotic therapy for patients presenting to the emergency department with suspected bacterial infections.

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Table 1 Studies evaluating the impact of the timing of antibiotic administration on the survival of septic patients

Study	Method	*n*	Inclusion criteria	Location	Main conclusion
Ferrer et al[36]	Prospective	2,796	Severe sepsis	ICU	In-hospital mortality was 41.6% Antibiotic therapy within 1 h superior to antibiotic within 6 h
Puskarich et al[38]	Prospective	291	Septic shock	ED	In-hospital mortality was 18.9% No increase in mortality with each hour delay in antibiotic administration
Jalili et al[41]	Prospective	145	Sepsis	ED	In-hospital mortality was 21.4% Antibiotic administration time and mortality related only if APACHE score ≥21
Bloos et al[37]	Prospective	1,011	Severe sepsis, septic shock	ICU	28-d mortality was 34.9% if antibiotics were started within 1 h vs 36.2% if starter after 1 h Mostly surgical patients, source control was associated with decreased mortality
de Groot et al[39]	Prospective	1,168	Sepsis	ED	28-d mortality was 10% No association between time to antibiotics and survival except for the patients with the lowest severity (PIRO 1–7)[a]
Ryoo et al[42]	Prospective	426	Septic shock	ED	28-d mortality was 20% Mortality did not change with hourly delays in antibiotic administration up to 5 h after shock recognition
Alam et al[40]	Prospective	2,672	Sepsis	ED	28-d mortality was 8% Giving ceftriaxone in the ambulance did not lead to improved survival
Henriksen et al[56]	Retrospective	1,169	SIRS	ED	Antibiotic administration delay was shorter for patients with SIRS compared with patients without SIRS but no difference in mortality
Ferrer et al[46]	Retrospective	28,150	Severe sepsis, septic shock	ICU	In-hospital mortality was 29.7% Increase in mortality with the number of hours of delay for first antibiotic administration
Gaieski et al[47]	Retrospective	261	Severe sepsis, septic shock	ED	In-hospital mortality was 31% Qualification for early goal-directed therapy to administration of antibiotics is associated with mortality
Joo et al[48]	Retrospective	591	Severe sepsis, septic shock	ED	In-hospital mortality was 18.6% Early administration of antibiotics (<3 h) was associated with reduced mortality (22.9–16.2%)
Kumar et al[43]	Retrospective	2,731	Septic shock	ICU	Overall mortality was 56.2% Time to initiation of effective antimicrobials therapy was the single strongest predictor of outcome in multivariate analysis (every hour delay is associated with a 12% decreased probability of survival)
Liu et al[49]	Retrospective	35,000	sepsis	ED	Hospital mortality was 9.4% Each hour's delay in antibiotic administration was associated with a 0.3% increase in mortality for sepsis and 1.8% for septic shock
Seymour et al[44]	Retrospective	49,331	Sepsis, septic shock	ED	In-hospital mortality was 22.8% Patients who received antibiotics within 3–12 h had 14% higher odds of in-hospital death than those who received antibiotics within 3 h
Seymour et al[49]	Retrospective	2,683	Sepsis	ED	In-hospital mortality was 11% Emergency department delay in antibiotic administration was associated with increased in hospital mortality
Whiles et al[50]	Retrospective	3,929	Severe sepsis, septic shock	ED	Mortality was 12.8% Time to first antimicrobial was associated with progression, each hour was associated with an 8% increase in progression to septic shock Time to initial antimicrobial was also associated with in-hospital mortality
Wisdom et al[51]	Retrospective	220	Sepsis	ED	Intrahospital mortality was 28.6% No association between delays in antibiotics and mortality but a trend toward increased mortality for severe sepsis when delays exceeded 6 h from triage
Yokota et al[52]	Retrospective	1,279	Severe sepsis, septic shock	ICU	In-hospital mortality was 29% In the univariate but not in the multivariate analysis, administration of broad-spectrum antibiotics within 1 h was associated with a decreased mortality
Zhang et al[53]	Retrospective	1,058	Severe sepsis, septic shock	ICU	In-hospital mortality was 37.7% Time to appropriate antibiotic therapy (1 h increment) was an independent determinant of hospital length of stay

Early Antimicrobial Therapy for Sepsis: Does Each Hour Really Count?

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- Primarily the studies are retrospective
- Many therapeutic interventions: fluid resuscitation, vasopressors and source control.
- Difficult to identify a potential impact of one specific measure on mortality.
- Confounders: definition of sepsis, location of patients, severity (APACHE II, SAPS II, SOFA), organ failures etc.
- Balance between increased of unnecessary antibiotic and increase of AMR

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Lancet Infect Dis. 2012 October ; 12(10): 774–780. doi:10.1016/S1473-3099(12)70151-2.

Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study

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Summary

Background—Antimicrobial treatment in critically ill patients can either be started as soon as infection is suspected or after objective data confirm an infection. We postulated that delaying antimicrobial treatment of patients with suspected infections in the surgical intensive care unit (SICU) until objective evidence of infection had been obtained would not worsen patient mortality.

Methods—We did a 2-year, quasi-experimental, before and after observational cohort study of patients aged 18 years or older who were admitted to the SICU of the University of Virginia (Charlottesville, VA, USA). From Sept 1, 2008, to Aug 31, 2009, aggressive treatment was used: patients suspected of having an infection on the basis of clinical grounds had blood cultures sent and antimicrobial treatment started. From Sept 1, 2009, to Aug 31, 2010, a conservative strategy was used, with antimicrobial treatment started only after objective findings confirmed an infection. Our primary outcome was in-hospital mortality. Analyses were by intention to treat.

Findings—Admissions to the SICU for the first and second years were 762 and 721, respectively, with 101 patients with SICU-acquired infections during the aggressive year and 100 patients during the conservative year. Compared with the aggressive approach, the conservative approach was associated with lower all-cause mortality (13/100 [13%] *vs* 27/101 [27%]; p=0.015), more initially appropriate therapy (158/214 [74%] *vs* 144/231 [62%]; p=0.0095), and a shorter mean duration of therapy (12.5 days [SD 10.7] *vs* 17.7 [28.1]; p=0.0080). After adjusting for age, sex, trauma involvement, acute physiology and chronic health evaluation (APACHE) II score, and site of infection, the odds ratio for the risk of mortality in the aggressive therapy group compared with the conservative therapy group was 2.5 (95% CI 1.5–4.0).

Interpretation—Waiting for objective data to diagnose infection before treatment with antimicrobial drugs for suspected SICU-acquired infections does not worsen mortality and might be associated with better outcomes and use of antimicrobial drugs.

Timing of antibiotic therapy

- 2 year experimental before and after study
- NIH funded, 484 surgical ICU
- Aggressive vs. conservative (i.e. documenting infection prior to antibiotics)
- Assessed outcomes in the year before and after implementation of withholding abx until objective microbiological confirmation

Lancet Infec Dis 2012

Timing of antibiotic therapy

Main findings:

- Number of infections similar
- Case mix and patient management were similar
- Delay in initiation (fever to antibiotics): 6 (3-14)h vs 24 (9-44)h
- Associated with a halving in mortality rate (27% vs.13 %)
- Higher rate of appropriate antibiotics in infected patients (74% vs 62%)
- In patients with hypotension, median 16-hr delay was associated with 26% mortality vs 66% mortality in aggressive group
- Aggressive strategy OR 2.5 for mortality

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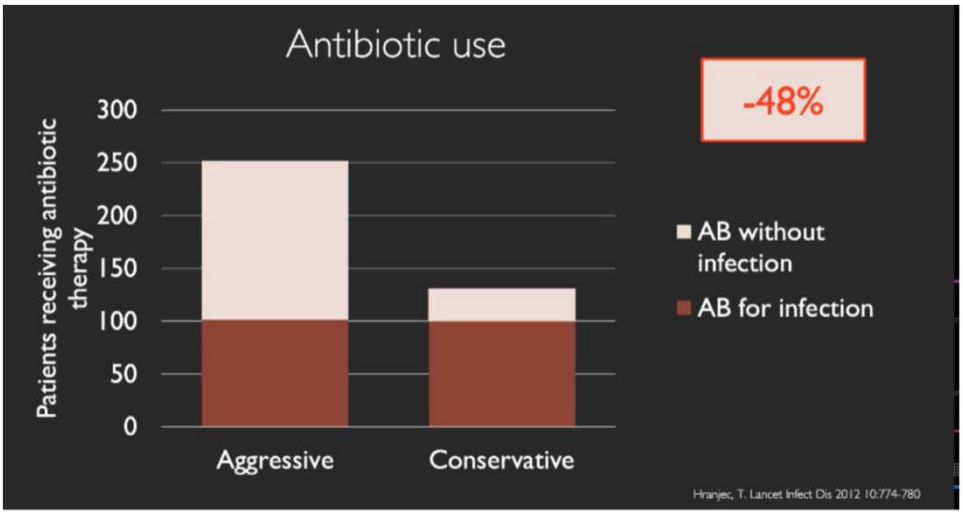
Timing of antibiotic therapy



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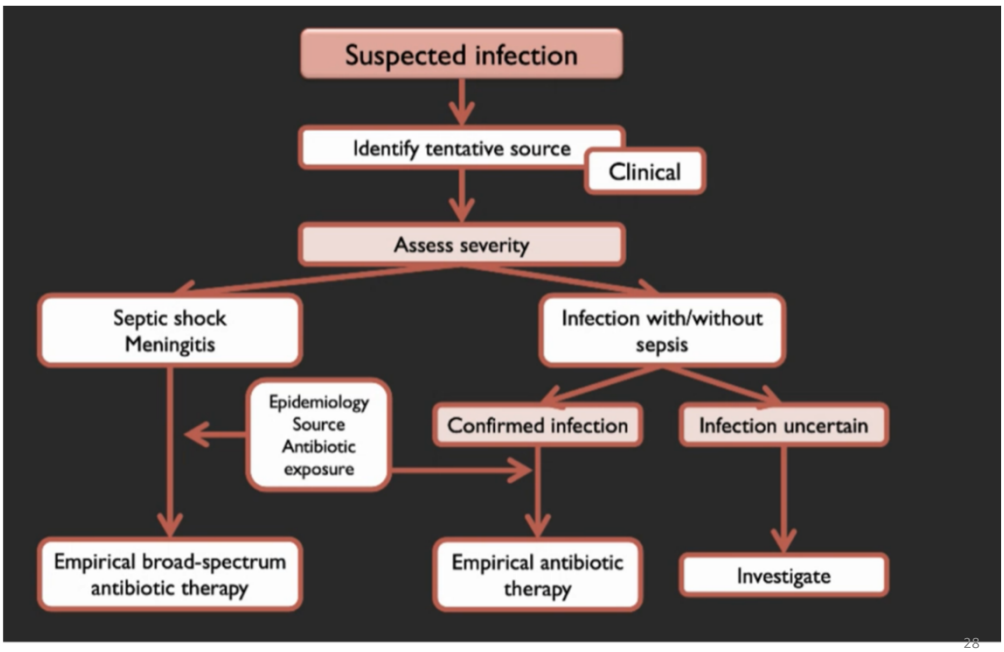
Urgency of antibiotic therapy

- Antibiotic urgency has been questioned in non-septic shock patients
- Pressure to initiate antibiotics
  - Infection diagnosis is often difficult
  - Inappropriate indication probably more frequent than we would think
- Many confounders
- Surrogate marker for overall quality of care



Who needs early antibiotics-summary

- Blanket policy of starting antibiotics at every patient on suspicion of sepsis carry potential harmful consequences (pan-drug-resistant microorganisms)
- Early antibiotics required in septic shock and bacterial meningitis
- Immediate antibiotics not always necessary- depending on patient clinical status and infection certainty
- Time-critical approach to confirm diagnosis of infection
- Think of alternative diagnoses and watch for mimics of sepsis
- Re-evaluate diagnosis
- Targeted investigations

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