



Antibiotics for sepsis- is each hour of delay really important?

Małgorzata Mikaszewska-Sokolewicz
Medical University Warsaw



“Each hour’s delay in initiating antibiotics costs lives”



Intensive Care Med (2004) 30:536–555
DOI 10.1007/s00134-004-2210-z

SPECIAL ARTICLE

R. Phillip Dellinger
Jean M. Carlet
Henry Masur
Herwig Gertlach
Thierry Calandra
Jonathan Cohen
Juan Gea-Banacloche
Didier Keh
John C. Marshall
Margaret M. Parker
Graham Ramsay
Janice L. Zimmerman
Jean-Louis Vincent
M. M. Levy

Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

C. Antibiotic therapy

1. Intravenous antibiotic therapy should be started within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained.

Grade E.



CONFERENCE REPORTS AND EXPERT PANEL

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



Andrew Rhodes^{1*}, Laura E. Evans², Waleed Alhazzani³, Mitchell M. Levy⁴, Massimo Antonelli⁵, Ricard Ferrer⁶, Anand Kumar⁷, Jonathan E. Sevransky⁸, Charles L. Sprung⁹, Mark E. Nunnally², Bram Rochweg³, Gordon D. Rubenfeld¹⁰, Derek C. Angus¹¹, Djillali Annane¹², Richard J. Beale¹³, Geoffrey J. Bellinghan¹⁴, Gordon R. Bernard¹⁵, Jean-Daniel Chiche¹⁶, Craig Coopersmith⁸, Daniel P. De Backer¹⁷, Craig J. French¹⁸, Seitaro Fujishima¹⁹, Herwig Gerlach²⁰, Jorge Luis Hidalgo²¹, Steven M. Hollenberg²², Alan E. Jones²³, Dilip R. Karnad²⁴, Ruth M. Kleinpell²⁵, Younsuk Koh²⁶, Thiago Costa Lisboa²⁷, Flavia R. Machado²⁸, John J. Marini²⁹, John C. Marshall³⁰, John E. Mazuski³¹, Lauralyn A. McIntyre³², Anthony S. McLean³³, Sangeeta Mehta³⁴, Rui P. Moreno³⁵, John Myburgh³⁶, Paolo Navalesi³⁷, Osamu Nishida³⁸, Tiffany M. Osborn³¹, Anders Perner³⁹, Colleen M. Plunkett²⁵, Marco Ranieri⁴⁰, Christa A. Schorr²², Maureen A. Seckel⁴¹, Christopher W. Seymour⁴², Lisa Shieh⁴³, Khalid A. Shukri⁴⁴, Steven Q. Simpson⁴⁵, Mervyn Singer⁴⁶, B. Taylor Thompson⁴⁷, Sean R. Townsend⁴⁸, Thomas Van der Poll⁴⁹, Jean-Louis Vincent⁵⁰, W. Joost Wiersinga⁴⁹, Janice L. Zimmerman⁵¹ and R. Phillip Dellinger²²

D. ANTIMICROBIAL THERAPY

1. We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock (strong recommendation, moderate quality of evidence; grade applies to both conditions).



TO BE COMPLETED WITHIN 3 HOURS:

- 1) Measure lactate level.
- 2) Obtain blood cultures prior to administration of antibiotics.
- 3) Administer broad spectrum antibiotics.
- 4) Administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L.

TO BE COMPLETED WITHIN 6 HOURS:

- 5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg.
- 6) In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥ 4 mmol/L, re-assess volume status and tissue perfusion and document findings according to Table 1.
7. Re-measure lactate if initial lactate elevated.

"Time of presentation" is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.



TABLE 1
DOCUMENT REASSESSMENT OF VOLUME STATUS AND TISSUE PERFUSION WITH:

EITHER:

- Repeat focused exam (after initial fluid resuscitation) including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings.

OR TWO OF THE FOLLOWING:

- Measure CVP.
- Measure ScvO₂.
- Perform bedside cardiovascular ultrasound.
- Perform dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge.

Antibiotic may have harmful effect:



Consequences



Quality-improvement programs are being driven by financial penalty.

- CMS 2017 reimbursement driven by quality of services/ care

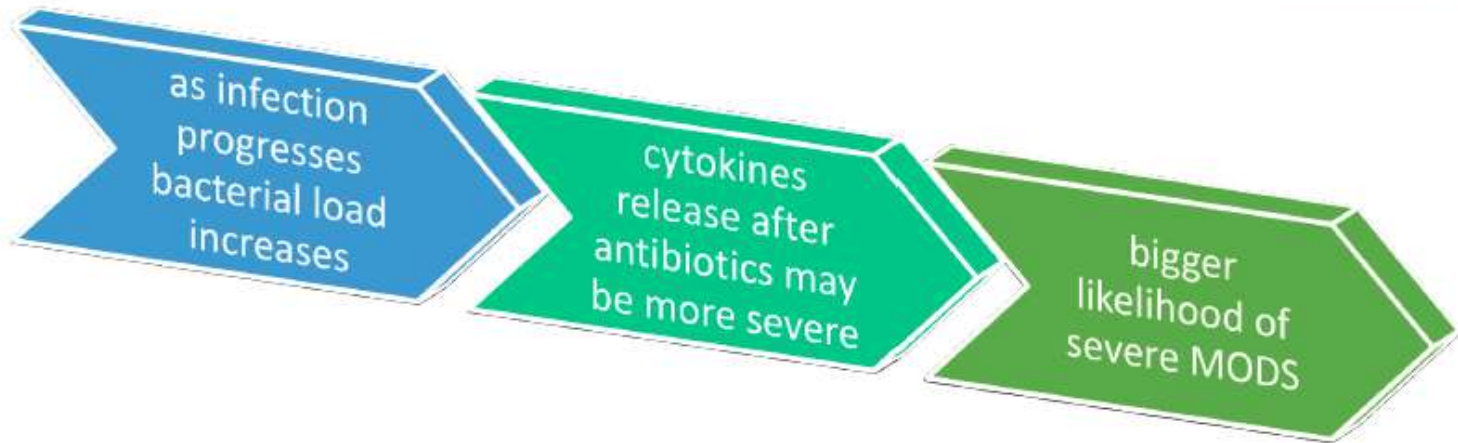


Evidence is not compelling

- Randomized human studies would be unethical
- Outcome of more severe infections is more time- sensitive than in less severe infections
- At some point timing of antibiotics or any intervention will not impact outcome



- In severe sepsis and septic shock mortality is not caused by infection but by physiological response to infection
- With every increase of SOFA by ≥ 2 mortality rises by 10%



Antibiotics should be given before sepsis with hypotension occurs as irreversible tissue damage may occur

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

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc

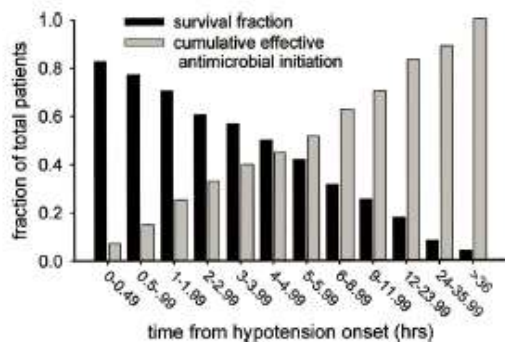
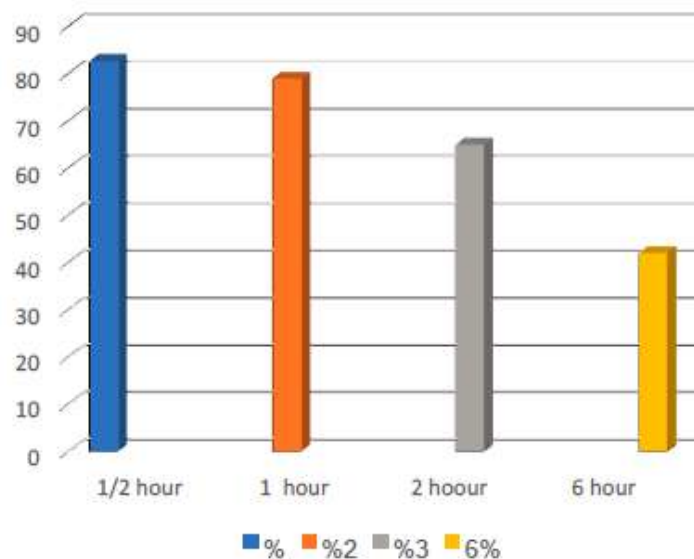
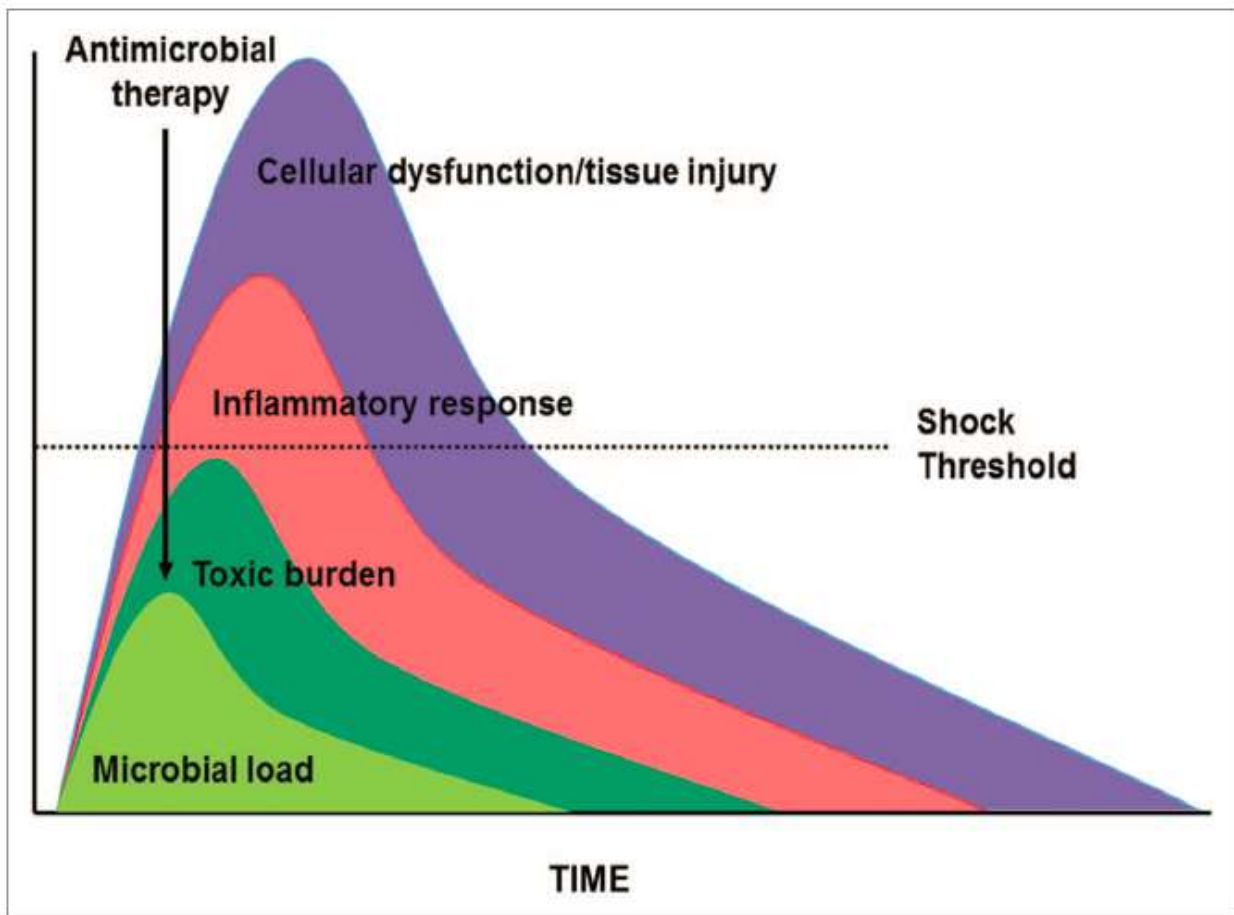
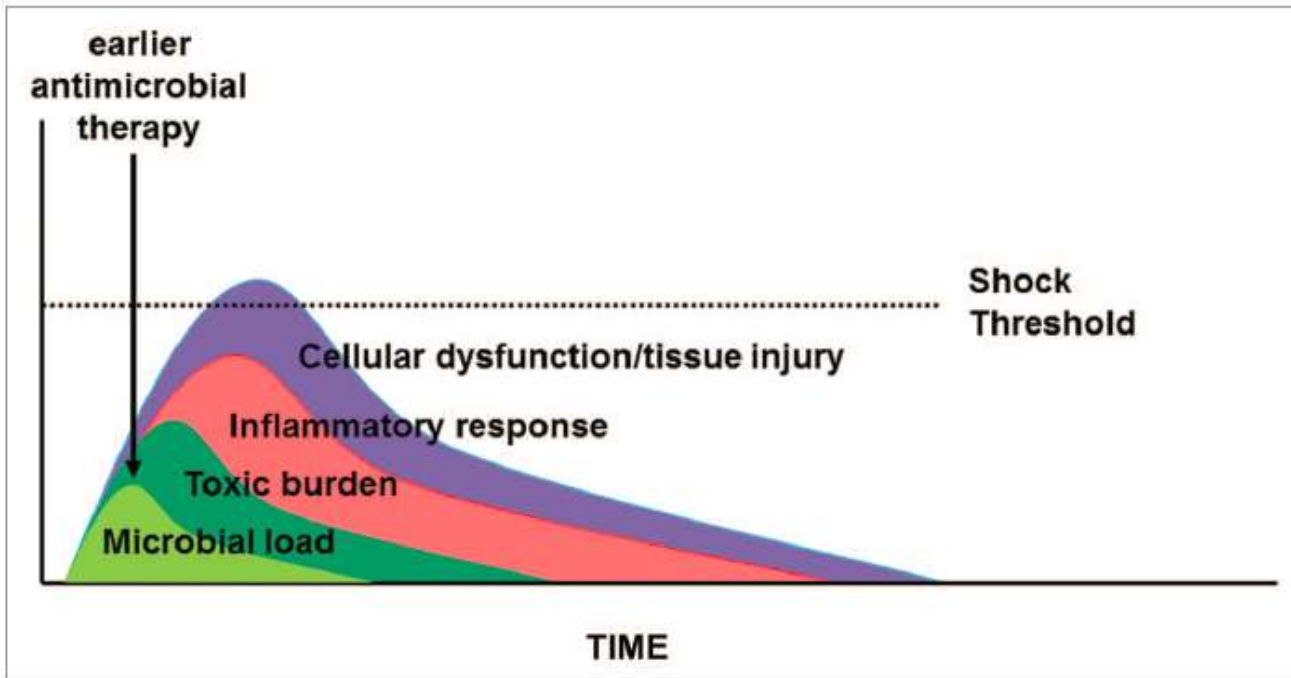


Chart Title







Etiology of Illness in Patients with Severe Sepsis Admitted to the Hospital from the Emergency Department

Alan C. Heffner^{1,3}, James M. Horton², Michael R. Marchick³, and Alan E. Jones³

¹Division of Critical Care Medicine, Carolinas Medical Center, Charlotte, North Carolina

²Division of Infectious Diseases, Department of Internal Medicine, Carolinas Medical Center, Charlotte, North Carolina

³Department of Emergency Medicine, Carolinas Medical Center, Charlotte, North Carolina



Single center study of 211 patients

Only 45% of patients admitted as sepsis has positive culture

In negative culture group

- 44% has clinical infection
- 8% atypical
- 32% mimics
- 16% indeterminate





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

Peter M. C. Klein Klouwenberg^{1,2,3*}, Olaf L. Cremer¹, Lonneke A. van Vught⁴, David S. Y. Ong^{1,2,3}, Jos F. Frencken^{1,3}, Marcus J. Schultz⁵, Marc J. Bonten^{2,3} and Tom van der Poll⁴



- Study performed in 2 ICU on population of 2579 patients
- “We determined the accuracy of the infection diagnosis made by clinicians in the context of presumed sepsis upon admission to the ICU and found that up to 43 % of patients treated for sepsis were unlikely to have had an infection on post-hoc assessment.”



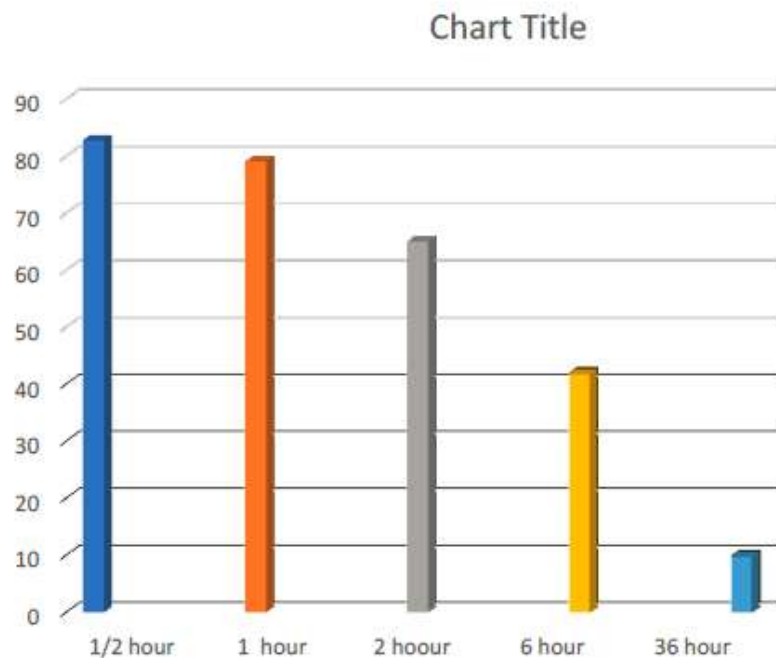
- Antibiotic sensitivities are rarely known before 36.
- Inadequate source control increase 28 D mortality to 42,% regardless of appropriateness of antibiotic therapy
- In vitro sensitivities may not be effective in 1/3 proven G(-) infections in humans





“An analysis performed on 17,990 patients within the Surviving Sepsis Campaign database saw no relationship between actual mortality and antibiotic commencement for up to a 5-hour delay, regardless of place geography, infection source, organ failures, hypotension (resolved and unresolved), mechanical ventilation, “





- Each hour delay resulted in 7,6 increase in mortality
- 558 patients received appropriate antibiotic therapy before commencement of hypotension- survival in group was 52.2% (lower than in those receiving treatment within the first 5 hours post -hypotension.)

Outcome is determined primarily by patient and disease factors

Gram-negative bacteraemia; a multi-centre prospective evaluation of empiric antibiotic therapy and outcome in English acute hospitals

J. M. Fitzpatrick¹, J. S. Biswas², J. D. Edgeworth², J. Islam³, N. Jenkins⁴, R. Judge⁵, A. J. Lavery⁶, M. Melzer⁷, S. Morris-Jones⁸, E. F. Nsutebu⁹, J. Peters¹, D. G. Pillay⁴, F. Pink², J. R. Price⁸, M. Scarborough¹⁰, G. E. Thwaites¹¹, R. Tilley², A. S. Walker^{10,11} and M. J. Llewelyn^{1,12}, on behalf of the United Kingdom Clinical Infection Research Group

1) Department of Infectious Diseases and Microbiology, Royal Sussex County Hospital, Brighton, 2) Centre for Clinical Infection and Diagnostics Research, Department of Infectious Diseases, Kings College London and Guy's and St Thomas' Hospitals NHS Foundation Trust, London, 3) Department of Microbiology, Surrey and Sussex Healthcare NHS Trust, Redhill, 4) Department of Microbiology, Infection and Tropical Medicine, Heart of England NHS Trust, Birmingham, 5) Department of Microbiology, Plymouth Hospitals NHS Trust, Plymouth, 6) Department of Clinical Microbiology and Virology, UCLH NHS Foundation Trust, 7) Department of Infection, Barts Health NHS Trust, London, 8) Tropical and Infectious Disease Unit Royal Liverpool University Hospital, Liverpool, 9) Department of Microbiology, Western Sussex Hospitals NHS Foundation Trust, Chichester, 10) NIHR Oxford Biomedical Research Centre, John Radcliffe Hospital, 11) Nuffield Department of Medicine, University of Oxford, Oxford and 12) Division of Medicine, Brighton and Sussex Medical School, Falmer, UK

A recent prospective study of 679 adults with gram-negative bacteremia in 10 English hospitals identified initial empiric therapy as inappropriate in 34%, yet 30-day mortality was identical (15%).

A Systematic Review of the Methods Used to Assess the Association between Appropriate Antibiotic Therapy and Mortality in Bacteremic Patients

Jessina C. McGregor,¹ Shayna E. Rich,² Anthony D. Harris,^{2,4} Eli N. Perencevich,^{2,4} Regina Osih,³ Thomas P. Lodise, Jr.,⁵ Ram R. Miller,² and Jon P. Furuno²

¹Oregon State University College of Pharmacy, Portland; Departments of ²Epidemiology and Preventive Medicine and ³Medicine, University of Maryland School of Medicine, and ⁴Veterans Affairs Maryland Health Care System, Baltimore; and ⁵Albany College of Pharmacy, Albany, New York



- Nearly half of 51 reviewed studies failed to show an association between inappropriate empiric antibiotic choice and increased mortality in patients with proven bacteremia .

Table 2. Differences in the definition of appropriate antibiotic therapy.

Appropriate antibiotic therapy definition characteristic	No. (%) of studies ^a
Accounted for the in vitro antibiotic susceptibility test results	40 (87)
Specified at what point during the patient's admission that antibiotic therapy was assessed	37 (80)
Assessed empiric and/or definitive therapy ^b	34 (74)
Recorded the time at which antibiotic susceptibility test results became available	11 (24)
Included route of administration	17 (37)
Included dosing of antibiotic	16 (35)
Measured time to appropriate therapy	2 (4)

^a Among the 46 studies that provided a definition of appropriate antibiotic therapy.

^b Empiric therapy refers to antibiotic regimen prescribed before the receipt of culture and antibiotic susceptibility test results; definitive therapy refers to the antibiotic regimen prescribed after the receipt of these results.





Each of these prospective studies has failed to show a relationship between delay in antibiotic administration within 5 to 6 hours of patient presentation and mortality.

Bloos F, Crit Care 2014;18:R42.

Fitzpatrick JM, Clin Microbiol Infect 2016;22:244–251.

Puskarich MA, Crit Care Med 2011;39: 2066–2071.

Kaasch AJ, Infection 2013;41: 979–985.

Ryoo SM, Am J Med Sci 2015;349:328–333.

de Groot B, Crit Care 2015;19:194.

Hranjec T, Lancet Infect Dis 2012;12: 774–780



Impact of time to antibiotics on survival in patients with severe sepsis or septic shock goal-directed therapy was initiated in the emergency department*

David F. Gaieski, MD; Mark E. Mikkelsen, MD, MSCE; Roger A. Band, MD;
Jesse M. Pines, MD, MBA, MSCE; Richard Massone, MD; Frances F. Furia, MD; Frances S. Shofel
Goyal, MD



- The mean age of the 261 patients was 59 +/- 16 yrs;
- In-hospital mortality was 31%.
- Median time from triage to antibiotics was 119 mins (interquartile range, 76-192 mins) and from qualification to antibiotics was 42 mins (interquartile range, 0-93 mins).
- When analyzed for time from triage to appropriate antibiotics, there was a significant association at the <1 hr (mortality 19.5 vs. 33.2%; odds ratio, 0.30 [95% confidence interval, 0.11-0.83]; p = .02) time cutoff;
- **CONCLUSIONS:**
- Elapsed times from triage and qualification for early goal-directed therapy to administration of appropriate antimicrobials are primary determinants of mortality in patients with severe sepsis and septic shock treated with early goal-directed therapy

Association Between Timing of Antibiotic Administration and Mortality from Septic Shock in Patients Treated with a Quantitative Resuscitation Protocol

Michael A. Puskarich, MD, Stephen Trzeciak, MD, Nathan I. Shapiro, MD, Ryan C. Arnold, MD, James M. Horton, MD, Jonathan R. Studnek, PhD, Jeffrey A. Kline, MD, and Alan E. Jones, MD* On behalf of the Emergency Medicine Shock Research Network (EMSHOCKNET)

Department of Emergency Medicine (MAP, JRS, JAK, AEJ), Department of Medicine, (JMH) Carolinas Medical Center, Charlotte, NC, Departments of Medicine, Division of Critical Care Medicine (ST), and Emergency Medicine (ST, RCA), Cooper University Hospital, Camden, New Jersey (ST), Department of Emergency Medicine and Center for Vascular Biology Research, Beth Israel Deaconess Medical Center, Boston, Massachusetts (NIS)



Table 5

In-hospital mortality: Shock recognition to initial antibiotics

Time to antibiotics	N	Mortality (%)	Difference (%)	OR*	95% CI	Adjusted OR*	95% CI
Prior to shock recognition	119	11.8					
After shock recognition	172	23.8	12	2.35	1.12-4.53	2.59	1.17-5.74
≤ 1 hour	101	25.8	-4.7	1.29	0.63-2.67	0.93	0.41-2.12
>1 hour	71	21.1					
≤ 2 hours	145	24.1	-1.9	1.11	0.42-2.98	0.69	0.21-2.22
>2 hours	27	22.2					
≤ 3 hours	164	23.8	1.2	0.94	0.18-4.82	0.84	0.13-5.52
>3 hours	8	25.0					

N = number of patients, OR = odds ratio, CI = confidence interval

* Odds of death with increasing delays in antibiotic administration

A delay in antibiotics until after shock recognition, as compared to before, was associated with increased mortality; however if antibiotics are administered after shock recognition there is no increase in mortality with hourly delays.



Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement Program*



Ricard Ferrer; Ignacio Martin-Loeches; Gary Phillips; Tiffany M. Osborn; Sean Townsend; R. Phillip Dellinger; Antonio Artigas; Christa Schorr; Mitchell M. Levy

- A total of 17,990 patients received antibiotics after sepsis identification
- In-hospital mortality was 29.7% for the cohort as a whole.
- There was a statically significant increase in the probability of death associated with the number of hours of delay for first antibiotic administration.
- Hospital mortality adjusted for severity (sepsis severity score), ICU admission source (emergency department, ward, vs ICU), and geographic region increased steadily after 1 hour of time to antibiotic administration.
- Results were similar in patients with severe sepsis and septic shock, regardless of the number of organ failure.

The association between time to antibiotics and relevant clinical outcomes in emergency department patients with various stages of sepsis: a prospective multi-center study

Bas de Groot^{1*}, Annemieke Ansems², Daan H Gerling¹, Douwe Rijpsma², Paul van Amstel³, Durk Linzel³, Piet J. Kostense³, Marianne Jonker³ and Evert de Jonge¹



- 1,168 included patients,
- 112 died (10%),
- 85% and 95% received antibiotics within three and six hours,
- No association between time to antibiotics and surviving days outside the hospital or mortality was found.
- Conclusions: In ED patients with mild to severe sepsis who received antibiotics within six hours after ED presentation, a reduction in time to antibiotics was not found to be associated with an improvement in relevant clinical outcomes.

Reason for delays of antibiotics administration



Patient related factors

- Age and comorbidities may predispose patients to have atypical presentation
- Difficult venous canulation
- History of drug response/reactions



Reason for delays of antibiotics administration

System level factors

- Overcrowded ED
- Inadequate ED staffing
- Delays in diagnostic testing





Quality assurance

- There are intended and unintended consequences of antibiotic timing measurement.
- Measurement of antibiotic timing may be associated with overuse and misuse of antibiotics.
- For quality assurance timing of antibiotic administration must be measured otherwise performance in other areas may decrease too

Take home message:



- Controversies exists but patients with severe should be given appropriate antibiotics as soon as possible
- In many countries therapeutic guidelines recommend administration of antibiotics within one hour of emergency department presentation
- And for in-patients within one hour of recognition of severe sepsis and septic shock.





Thank you very much for invitation your time and attention

