DOES TIMING OF ANTIBIOTICS IMPACT OUTCOME IN SEPSIS ?

Saravana Kumar MD

HEAD,DEPT OF EM,DR MEHTA'S HOSPITALS
CHENNAI,INDIA

drsaravanakumar.ep@gmail.com

JOINT SECRETARY
SOCIETY FOR EMERGENCY MEDICINE,INDIA

3rd INTERCONTINENTAL EMERGENCY MEDICINE CONGRESS | 3rd INTERNATIONAL CRITICAL CARE AND EMERGENCY MEDICINE CONGRESS | EPAT Emergency Physicians Association of Turkey


love is a shrine of colour.
beauty is a stone of colour.
time is a flood of colour.
homage is a ferry of colour.
life is an infinity of colour.
incredible is the tag of colour.
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Greetings!


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ISRO
INDIA

Surviving Sepsis Campaign

RECOMMENDATIONS: INITIAL RESUSCITATION AND INFECTION ISSUES

3rd Edition 2012 (published 2013) / Revised 2015

Administration of effective intravenous antimicrobials **Within The First Hour** of recognition of **septic shock** (grade 1B) and **severe sepsis** without septic shock (grade 1C) as the goal of therapy.

TO BE COMPLETED WITHIN 3 HOURS OF TIME OF PRESENTATION

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Kumar et al (2004) critical care Med

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

- A retrospective cohort study :July 1989 and June 2004. USA
- 14 ICU,2154 patients
- Outcome – survival till discharge
- 14.5%, 32.5% ,**51.4%** of patients received antibiotic therapy within 1, 3 and 6 hours (80 % appropriate)
- **79.9 % survival rate if AB in < 1 hour of onset of hypotension.**
- **7.6 % decrease in survival for each hour delay (6 hours)**
- Early hypotension = decrease in survival inspite of early AB.

Clec'h C, Timsit et al(2004)
Intensive Care Medicine.

Efficacy of adequate early antibiotic therapy in ventilator-associated pneumonia: influence of disease severity.

- Prospective study :6 ICU in France
- 142 patients ,VAP after 48 hrs
- Outcome – ICU mortality / hospital mortality
- **Day 0 vs Day 2**
- **ICU mortality 7 % vs 37 %**
- **Hospital Mortality 15% vs 44%**

Michael A. Puskarich et al (2011)
Criti Care Medicine.

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

- 3 ED in USA (2007-2009)
- 291 patients,prospective, parallel group
- 172/291 – received AB after shock recognition
- Outcome – in hospital mortality
- Design : timing of AB from triage and shock recognition
- Broad spectrum AB based in institution protocol
- Median time of AB 115 mins

Michael A. Puskarich et al (2011)
Criti Care Medicine.

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

NO association between timing of antibiotic administration from ED triage and hospital mortality (over all 55/291)

In-hospital mortality: Triage to initial antibiotics

Time to antibiotics	N	Mortality (%)	Difference (%)	OR*	95% CI	Adjusted OR*	95% CI
≤ 1 hour	65	16.9	2.6	1.18	0.57–2.46	1.81	0.74–4.44
>1 hour	226	19.5					
≤ 2 hours	155	21.3	−5.1	0.71	0.39–1.30	1.07	0.54–2.16
>2 hours	136	16.2					
≤ 3 hours	223	20.6	−7.4	0.59	0.27–1.27	0.66	0.27–1.63
>3 hours	68	13.2					
≤ 4 hours	255	20.4	−12.1	0.35	0.10–1.20	0.39	0.08–1.90
>4 hours	36	8.3					
≤ 5 hours	274	19.7	−13.8	0.25	0.03–1.96	0.69	0.07–6.86
>5 hours	17	5.9					
≤ 6 hours	281	19.6	−19.6	---	---	---	---
>6 hours	10	0					

N – number of patients; OR – odds ratio; CI – confidence interval

* Odds of death with increasing delays in antibiotic administration

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Michael A. Puskarich et al (2011)
Criti Care Medicine.

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

- A delay in antibiotics until shock recognition, was associated with increased mortality; however there is no increase in mortality with hourly delays

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	12	2.35	1.12–4.53	2.59	1.17–5.74
After shock recognition	172	23.8					
≤ 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

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Mohammad Jalili et al (2012)
Acta Medica Iranica

Effect of Door-to-Antibiotic Time on Mortality of Patients with Sepsis in Emergency Department: A Prospective Cohort Study

- ED in Iran (2007-2009)
- Prospective cohort
- Inhospital mortality
- 145 patients
- 3 groups based on APACHE II
- < 10,11-20,> 21
- Median time for AB 104 minutes

Mohammad Jalili et al (2012)
Acta Medica Iranica

Effect of Door-to-Antibiotic Time on Mortality of Patients with Sepsis in Emergency Department: A Prospective Cohort Study

- Significant mortality if delayed AB in APACHE group 3 patients

Table 4. Analysis of outcome in relation to severity of sepsis based on APACHE II score.

APACHE score	Outcome	Door-to-antibiotic time			Total
		< 60 minutes	60-120 minutes	> 120 minutes	
≤10	Resolution	13	30	12	55
	Death	0	0	0	0
	Total	13	30	12	55
11-20	Resolution	11	32	12	55
	Death	0	6	1	7
	Total	11	38	13	62
≥21	Resolution	1	2	0	3
	Death	1	10	13	24
	Total	2	12	13	27

Ferrer et al (2014)
Critical care med

Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program.

- (2005 – 2010) Retrospective analysis of a large dataset collected
- n = 17,990
- Time to first antibiotic administration within 6 hours of sepsis identification and the effect on mortality

Ferrer et al (2014)
Critical care med

Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program.

- **Delay in first antibiotic administration was associated with increased in hospital mortality**
- Linear increase in the mortality for each hour delay in antibiotic administration
- The adjusted hospital mortality odds ratios (OR) steadily increase from 1.00 to 1.52 as time to antibiotic administration increases from 0 to 6 hours
- The probability of mortality increases from 24.6% to 33.1%

Young Min Joo et al
Critical and Experimental Emergency Medicine 2014

Impact of timely antibiotic administration on outcomes in patients with severe sepsis and septic shock in the emergency department

- Samsung medical center,Korea
- Prospective analysis of sepsis registry (2008-2012)
- 591 patients of severe sepsis / septic shock
- AB within 3 hrs vs > 3hrs.
- Primary outcomes : in-hospital mortality
- Secondary :length of stay (ICU), and recovery from organ failure (SOFA change in 48 hrs)

Young Min Joo et al
Critical and Experimental Emergency Medicine 2014

Impact of timely antibiotic administration on outcomes in patients with severe sepsis and septic shock in the emergency department

- The number of patients who received early antibiotic administration (< 3 hours):377 patients (63.8%)
- The in-hospital mortality rate was 16.2% in the early administration group (n=377) and 22.9% for the delayed administration group (n=214), with a significant difference (P=0.04)

Young Min Joo et al
Critical and Experimental Emergency Medicine 2014

Impact of timely antibiotic administration on outcomes in patients with severe sepsis and septic shock in the emergency department

Table 2. Comparison of outcomes including in-hospital mortality, delta SOFA, and length of hospital stay

Variable	All patients (n = 591)	Early group (n = 377)	Delayed group (n = 214)	P-value
In-hospital mortality	110 (18.6)	61 (16.2)	49 (22.9)	0.04
SOFA score				
Baseline	7 (4-9)	7 (4-10)	6.5 (3-9)	0.01
48 hours	4 (2-7)	4 (2-7)	4 (1-8)	0.61
Delta SOFA	2 (0-4)	2 (0-5)	1 (-1 to 3)	<0.01
In-hospital LOS (day)				
All patients	12 (7-22)	11 (7-21)	14.5 (8-24)	<0.01
Survivors only	12 (8-22)	11 (8-22)	15 (9-23)	<0.01
ICU admission	303 (51.3)	190 (50.4)	113 (52.8)	0.57
LOS in ICU (day)	3 (2-7)	3 (2-6)	3 (2-8)	0.12

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Young Min Joo et al
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Impact of timely antibiotic administration on outcomes in patients with severe sepsis and septic shock in the emergency department

Multivariable logistic regression analysis for in-hospital mortality

Early administration of antibiotics was independently associated with reduction of the in-hospital mortality rate,LOS (28% reduction),reversal of organ failure

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Ryoo et al (April 2015)
American Journal of the medical sciences.

Prognostic Value of Timing of Antibiotic Administration in Patients With Septic Shock Treated With Early Quantitative Resuscitation

- ED in Korea (2010-2012)
- Retrospective cohort , 426 - septic shock patients only.
- Outcome – 28 day mortality
- Median time – 91 mins
- **Appropriate antibiotic – 91.8%**
- **82 % received < 3 hours**
- No Mortality change with hourly delays in antibiotic administration up to 5 hours after shock recognition

Ryoo et al (April 2015)
American Journal of the medical sciences.

Prognostic Value of Timing of Antibiotic Administration in Patients With Septic Shock Treated With Early Quantitative Resuscitation

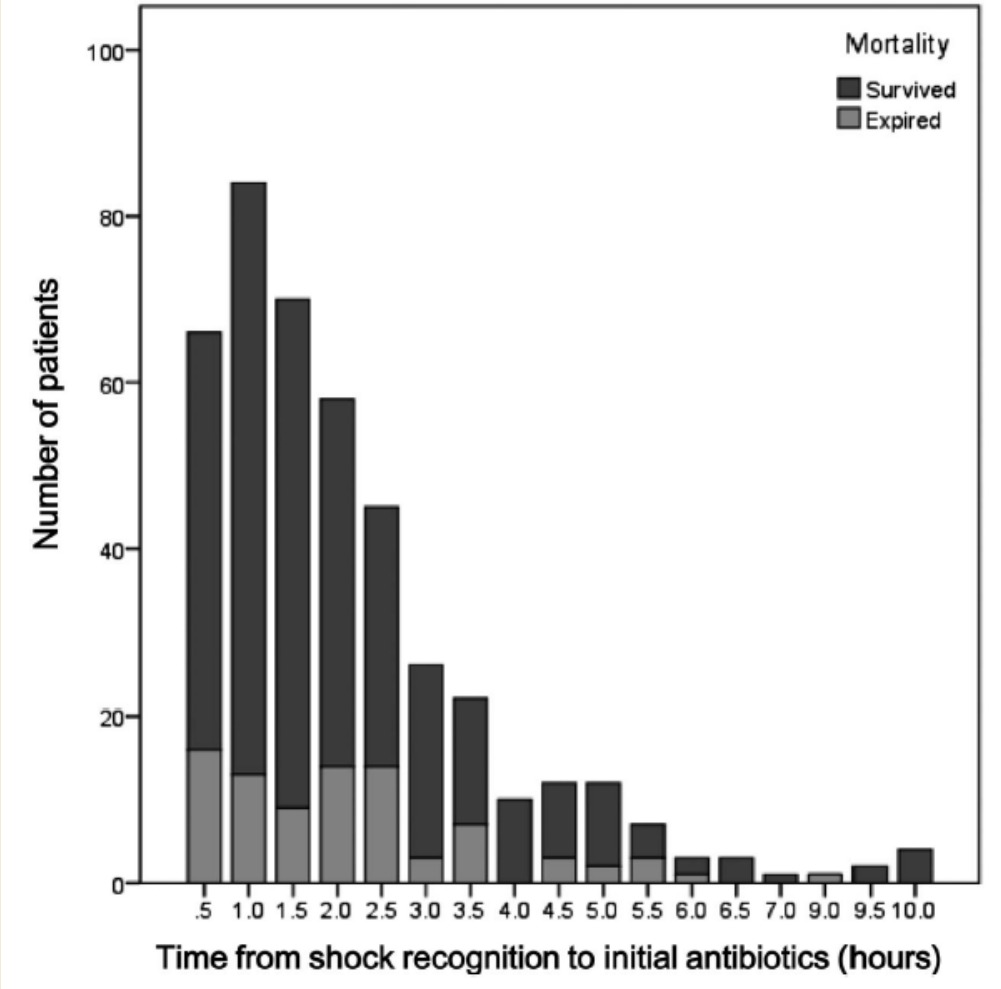
- 86 expired / 340 survived
- 20.2% 28day mortality

Initial vital signs		
Systolic BP, mm Hg	81.0 ± 16.8	79.8 ± 15.7
Diastolic BP, mm Hg	50.1 ± 14.8	48.2 ± 9.6
Pulse rate per minute	102.2 ± 22.8	111.5 ± 28.5
Respiratory rate per minute	21.8 ± 4.7	25.9 ± 7.7
SpO_2, %	95.4 ± 8.5	92.3 ± 8.6
Achievement of early resuscitation goals	163 (46.3)	26 (29.5)
MAP ≥65, mm Hg	328 (96.5)	80 (93.0)
CVP ≥8, mm Hg	278 (81.8)	67 (77.9)
$ScvO_2$ ≥70%	184 (54.1)	35 (40.7)
Laboratory findings		
WBC, $\times 10^3/\mu L$	10.8 (5.1–15.2)	6.2 (2.2–14.4)
Platelet, $\times 10^3/\mu L$	155.5 (96.0–236.8)	109.0 (51.0–168.5)
Creatinine, mg/dL	1.3 (1.0–2.1)	2.0 (1.3–3.0)
Total bilirubin, mg/dL	1.2 (0.8–2.2)	1.5 (0.9–5.7)
CRP, mg/dL	13.4 (5.9–22.4)	18.1 (6.9–30.0)
D-dimer, μg/mL	3.0 (8.3–1.0)	5.8 (2.4–10.6)
Procalcitonin, ng/mL	8.0 (1.5–36.4)	20.0 (4.0–60.2)
Lactic acid, mmol/L	2.7 (1.5–4.6)	5.4 (2.9–8.4)
SOFA score	7.7 ± 2.8	10.3 ± 2.9

- Failure to achieve early resus goal = > mortality.

Ryoo et al (April 2015)
American Journal of the medical sciences.

Prognostic Value of Timing of Antibiotic Administration in Patients With Septic Shock Treated With Early Quantitative Resuscitation



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Sterling SA et al(2015)
Critical care med

The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis

- Meta-analysis of 11 / 1123 publications (16,178 patients)
- Primary outcome – Mortality
- Utilized a scoring system to determine study quality
- All studies included were considered moderate to high quality
- Antibiotic timing
  - ≤3 hours vs >3 hours from triage
  - ≤1 hour vs > 1 hour from shock/severe sepsis recognition

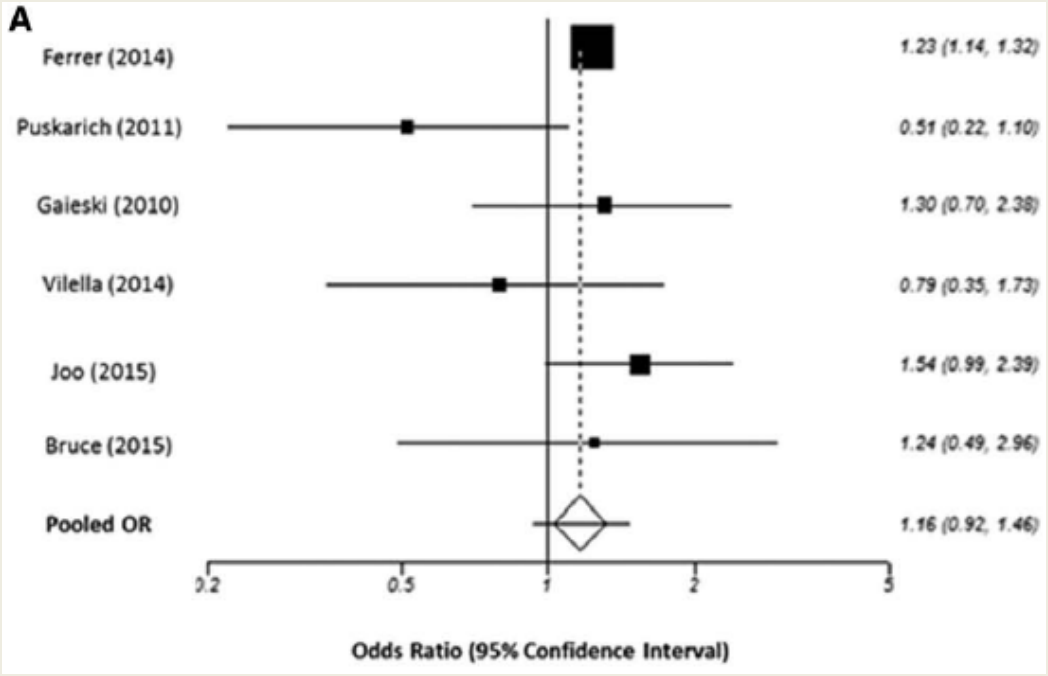
Sterling SA et al(2015)
Critical care med

The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis

- Antibiotic timing from triage (6 of 11 studies):
  - ≤3 hours –> 10,208 patients –> 2,574 died
  - >3 hours –> 5,970 patients –> 1,793 died

Sterling SA et al(2015)
Critical care med

The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis



Pooled OR 1.16

(95% CI, p = 0.21)

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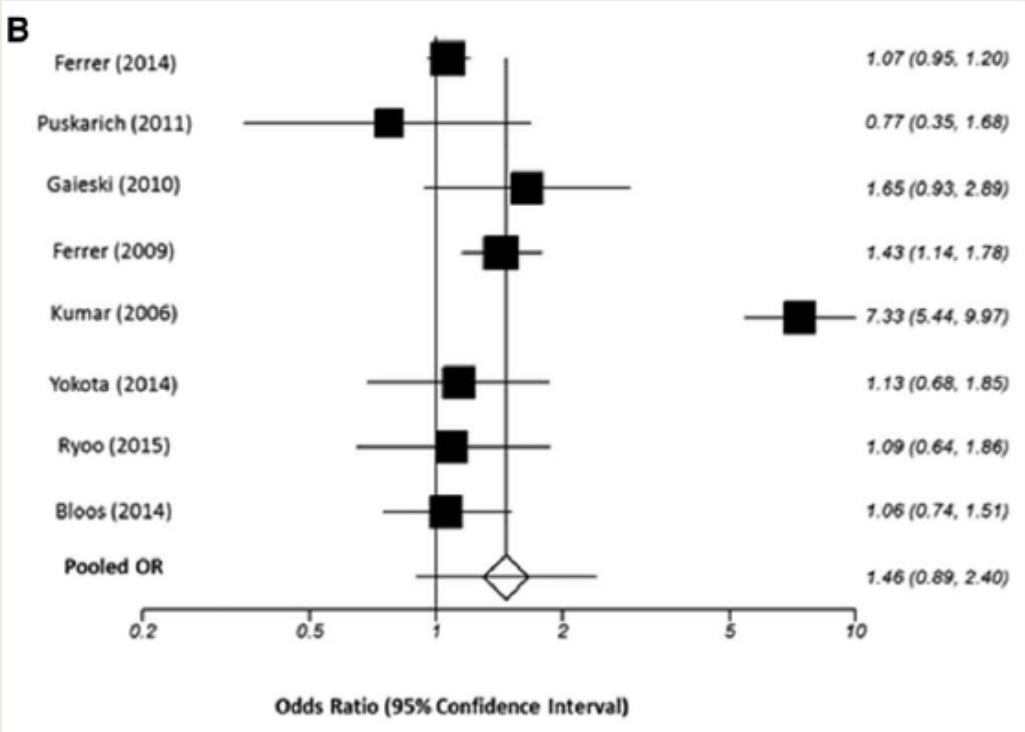
Sterling SA et al(2015)
Critical care med

The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis

- Antibiotic timing from shock/severe sepsis recognition (8 of 11 studies):
  - ≤1 hour –> 3335 patients –> 1,174 died
  - > 1hour –> 7,682 patients –> 3,581 died

Sterling SA et al(2015)
Critical care med

The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis



Pooled OR 1.46

(95% CI, p = 0.13)

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Sterling SA et al(2015)
Critical care med

The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis

- Sensitivity Analysis of the Effect of time to Antibiotics from severe sepsis/shock recognition

  <1 hour –> 2,318 patients –> 848 deaths
  1 – 2 hours –> 1,298 patients –> 471 deaths
  2 – 3 hours –> 853 patients –> 323 deaths
  3 – 4 hours –> 615 patients –> 245 deaths
  4 – 5 hours –> 453 patients –> 193 deaths
  >5 hours –> 2,386 patients –>1,537 deaths

No statistically significant increase in the pooled ORs for each hourly incremental delay in antibiotic administration

Discussion

- No prospective, randomized, controlled trial
- Most studies excluded immunocompromised / pediatric age group
- **"Approriate** Antibiotic" ?
- It is obvious that failure to administer effective broad-spectrum antibiotics will be detrimental to patient outcomes, but the exact time when this occurs is still doubtfull because sepsis has a complex pathophysiology that has a spectrum of severity as opposed to actual categories of disease.

Take to ER points

Early identification and Agressive resuscitation to be given more emphasis than timing of AB.

AB AT THE EARLIEST

BUT DONT CONSIDER IT A QUALITY METRIC


Incredible India
Thank you
all &
EPAT