SITA
Società Italiana di Terapia Antinfettiva
Antibatterica Antivirale Antifungina

12° CONGRESSO NAZIONALE

CATANIA | 17-18 novembre 2022

Tempo-dipendenza e inquadramento clinico

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Starting empirical antimicrobial treatment

1. Certainity of diagnosis
2. Risk of delaying treatment
3. Enviromental damage caused by the use of antimicrobial drugs

Surviving Sepsis Campaign Guidelines 2016

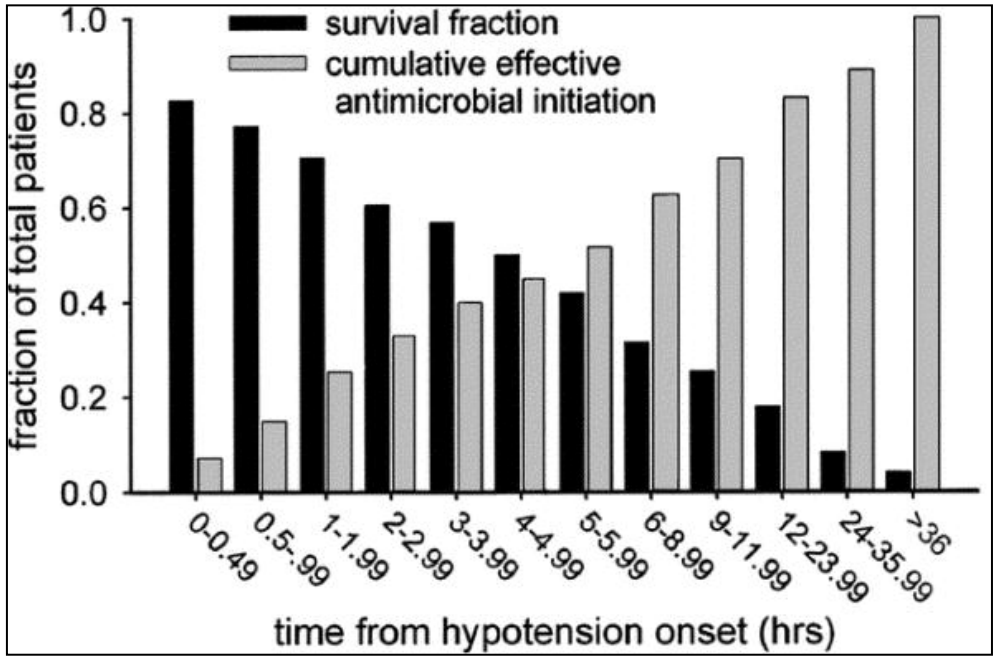
- We recommend that **administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock** (strong recommendation, moderate quality of evidence; grade applies to both conditions).

Rhodes A. et al. Intensive Care Med (2017) 43:304–377

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

Kumar A et al. Crit Care Med 2006;34:1589-96

- 2,154 septic shock patients who received effective antimicrobial therapy
- Median time to antimicrobial administration **6 hours**
- Overall mortality **56%**

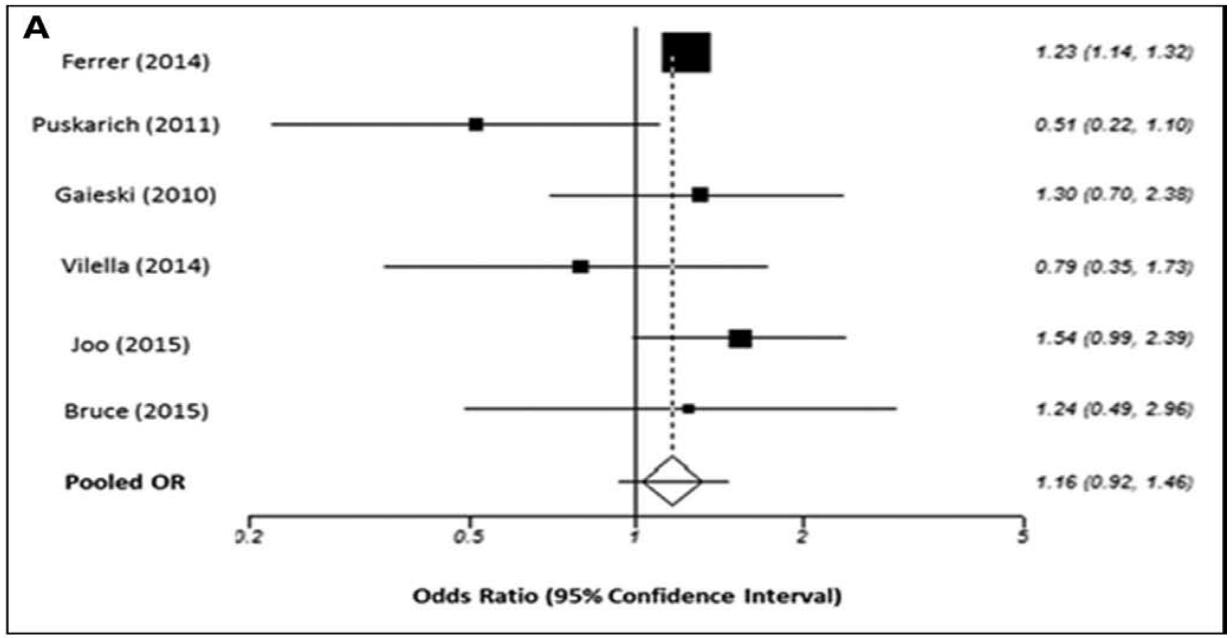


Each hour of delay decreased survival by 7.6%

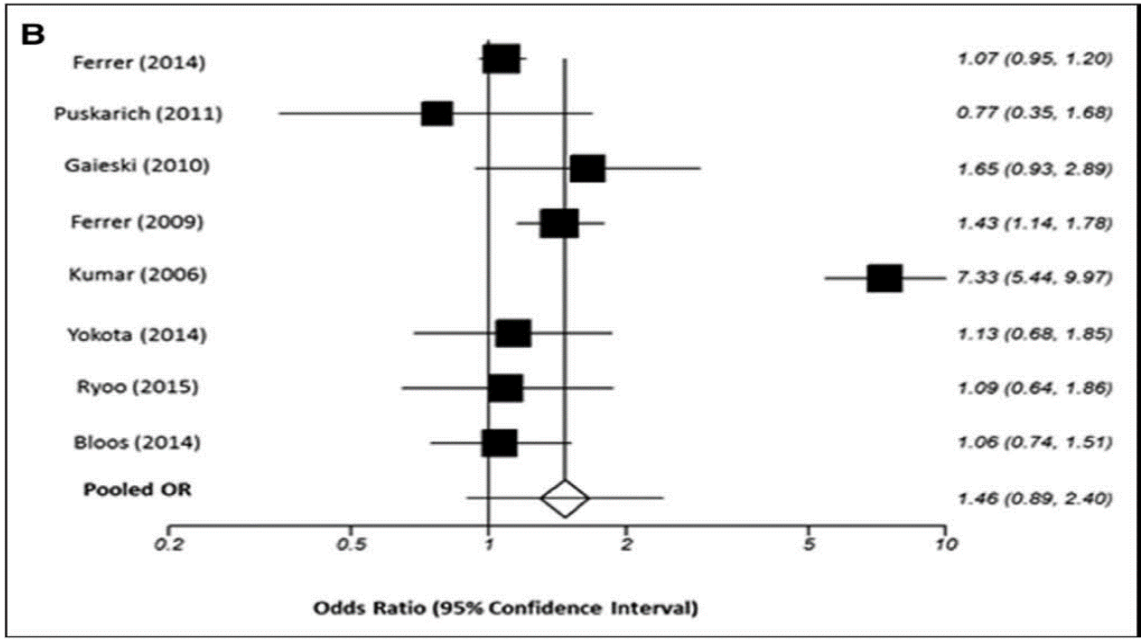
The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis

Sterling S et al. Crit Care Med 2015; 43:1907–1915

- 11/18 eligible studies were included:
  - ✓ 16,178 pts evaluable for antibiotic administration from ED triage
  - ✓ 11,017 pts from severe sepsis/septic shock recognition



Pooled OR for mortality and time to antibiotics in >3 hr from triage time



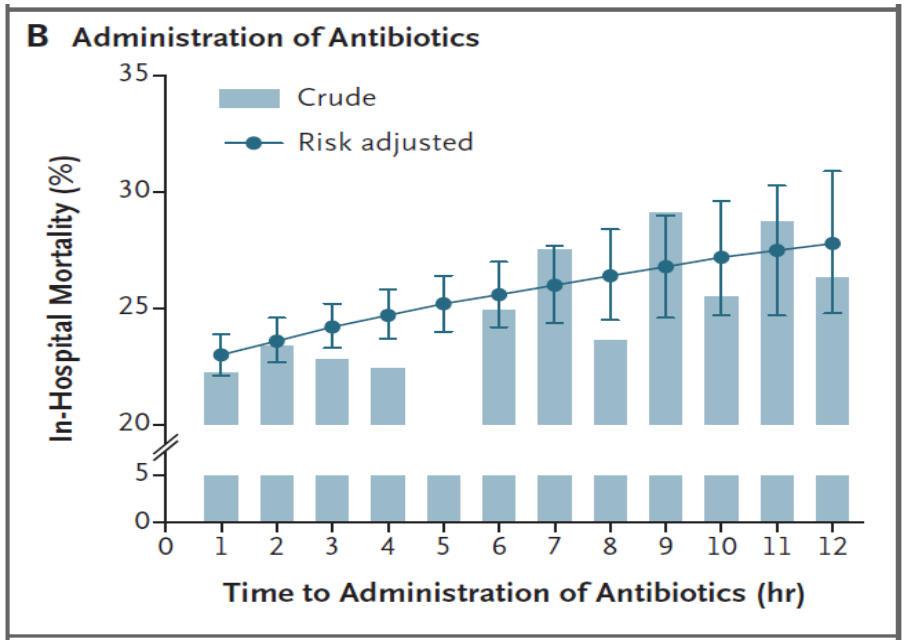
Pooled OR for mortality and time to antibiotics in >1 hr from SS/SS recognition

Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

Seymour C.W. et al N Engl J Med 2017;376:2235-44

Retrospective study on 48331 patients at 149 hospitals reported to the NYSDOH from 2014 to 2016, managed according to local protocols for sepsis including a 3-hour bundle of care (blood cultures, broad-spectrum antibiotic agents, and lactate measurement)

- Median time to administration of broad spectrum antibiotics 0.95 (IQR 0.35-1.95) h
- Overall in-hospital mortality 22.8%



OR 1.04 per hour
(95% CI, 1.03 to 1.06) P<0.001

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The timing of early antibiotics and hospital mortality in sepsis

Liu VX et al. Am J Respir Crit Care Med 2017;196:856–863

Retrospective study of 35000 randomly selected adults with sepsis hospitalized through the ED at 21 hospitals in Northern California in 2010-2013 who received antibiotics within 6 hours of ED registration time

- Median time to antibiotic administration 2.1 (IQR 1.4–3.1) hours
- Overall in-hospital mortality 9.4% (3.9% sepsis, 8.8% severe sepsis, 26% septic shock)

aOR 1.09 per hour (95% CI, 1.05 to 1.13) P<0.001
Increase in absolute mortality:

- **0.3% for sepsis**
- **0.4% for severe sepsis**
- **1.8% for shock**

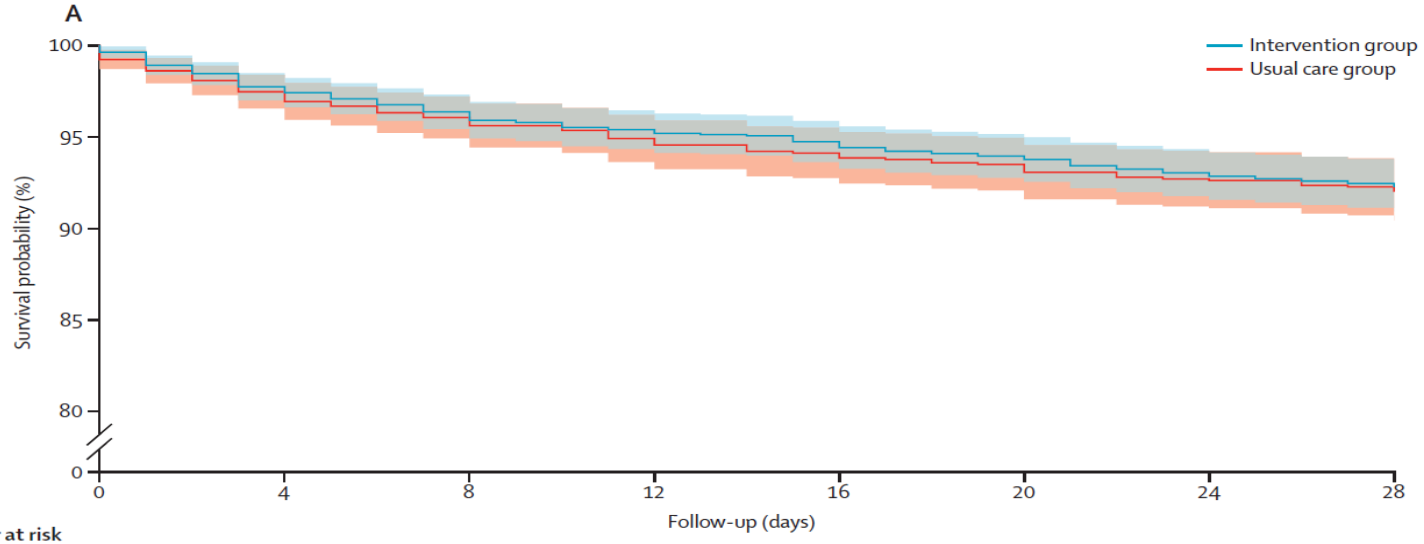
Model	Odds Ratio for hospital mortality, per elapsed hour until antibiotic administration	95% CI	p-value
Unadjusted	0.89	0.86 – 0.91	<0.001
+ Sepsis severity strata	0.96	0.93 – 0.99	0.013
+ Severity of illness	1.08	1.04 – 1.12	<0.001
+ Demographics	1.09	1.05 – 1.13	<0.001
Fully adjusted model, in each subgroup			
Sepsis only	1.09	1.00 – 1.19	0.046
Severe sepsis only	1.07	1.01 – 1.24	0.014
Septic shock only	1.14	1.06 – 1.23	0.001

Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial

Alam N. et al. Lancet Respir Med 2017

Controlled open-label trial in the Netherlands on 2672 adults (1535 in the intervention group) with a diagnosed or suspected infection (inclusion criteria temperature >38°C or <36°C, and at least one of HR >90/' or RR >20/'), to compare the effects of administration of IV ceftriaxone 2000 mg in the ambulance in addition to usual care (fluid resuscitation and supplementary oxygen)

- Median time to antibiotics: intervention group 26 min (IQR 19–34) before arriving at the ED; usual care group 70 min (IQR 36–128) after arriving at the ED.



28-day overall mortality 8% in both arms

(relative risk 0·95, 95% CI 0·74–1·24)

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ED door-to-antibiotic time and long-term mortality in sepsis.

Peltan ID, Brown SM, Bledsoe JR, et al Chest 2019; 155:938–946

- A retrospective cohort study on 10811 adult patients admitted to non-trauma ED with clinical sepsis in 4 hospitals from 2013 to 2017 in Utah, USA.

- The primary aim of the study was the **association of door-to-antibiotic time** (the time in hours from ED arrival to first antibiotic initiation) **with long-term mortality.**

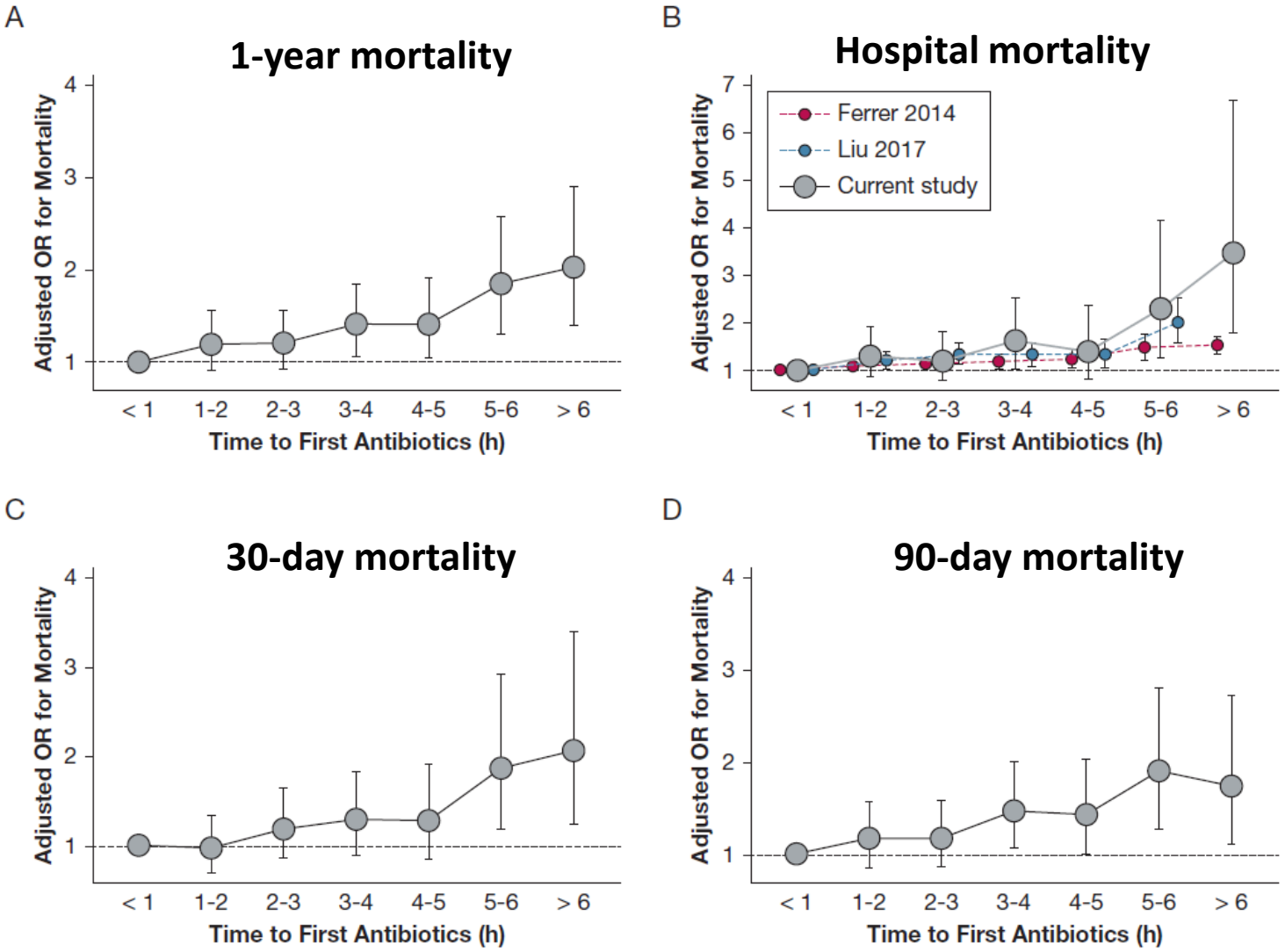
TABLE 2] Adjusted Association of Door-to-Antibiotic Time and Mortality in ED Patients With Sepsis

	1-Year Mortality			In-Hospital Mortality			30-Day Mortality			90-Day Mortality		
Variable	Adjusted OR[a] (95% CI)		*P* Value	Adjusted OR[a] (95% CI)		*P* Value	Adjusted OR[a] (95% CI)		*P* Value	Adjusted OR[a] (95% CI)		*P* Value
Door-to-antibiotic time, h	1.10	(1.05-1.14)	< .001	1.16	(1.07-1.26)	< .001	1.12	(1.06-1.18)	< .001	1.09	(1.04-1.15)	< .001
Door-to-antibiotic time > 1 h	1.26	(0.98-1.62)	.070	1.32	(0.91-1.92)	.14	1.12	(0.83-1.52)	.46	1.24	(0.94-1.65)	.13
Door-to-antibiotic time > 3 h	1.27	(1.13-1.43)	< .001	1.42	(1.13-1.80)	.003	1.28	(1.08-1.52)	.005	1.32	(1.14-1.52)	< .001
Door-to-antibiotic time interval												
≤ 1 h	Reference			Reference			Reference			Reference		
> 1 to ≤ 2 h	1.19	(0.91-1.56)	.20	1.29	(0.87-1.93)	.21	0.97	(0.70-1.35)	.85	1.17	(0.86-1.58)	.31
> 2 to ≤ 3 h	1.20	(0.92-1.56)	.18	1.20	(0.79-1.82)	.39	1.19	(0.86-1.65)	.30	1.17	(0.87-1.59)	.30
> 3 to ≤ 4 h	1.40	(1.06-1.85)	.018	1.61	(1.03-2.53)	.036	1.29	(0.90-1.83)	.16	1.47	(1.07-2.01)	.019
> 4 to ≤ 5 h	1.41	(1.04-1.91)	.025	1.39	(0.82-2.37)	.22	1.28	(0.86-1.91)	.23	1.43	(1.00-2.03)	.049
> 5 to ≤ 6 h	1.84	(1.31-2.57)	< .001	2.28	(1.26-4.16)	.007	1.87	(1.20-2.92)	.006	1.90	(1.28-2.81)	.001
> 6 h	2.02	(1.40-2.90)	< .001	3.45	(1.78-6.67)	< .001	2.06	(1.25-3.40)	.004	1.74	(1.11-2.73)	.015

[a]Adjusted for pooled triage acuity score; receipt of prehospital medical care; MEDS score; SOFA score; initial vital signs (systolic blood pressure, abnormal Glasgow Coma Scale, heart rate, temperature, respiratory rate, and oxygen saturation); ED disposition (ICU vs ward); comorbidity score; marital status; insurance type; age; sex; Hispanic ethnicity or non-white race; hospital; non-English preferred language; initial WBC count; and initial lactate level tested and > 2 mmol/L. See Table 1 legend for expansion of abbreviations.

ED door-to-antibiotic time and long-term mortality in sepsis.

Peltan ID, Brown SM, Bledsoe JR, et al Chest 2019; 155:938–946



Outcome of Immediate Versus Early Antibiotics in Severe Sepsis and Septic Shock: A Systematic Review and Meta-analysis

Rothrock SG et al. Ann Emerg Med. 2020;76:427-441

Purpose: to compare mortality rates in patients with severe sepsis and septic shock who received immediate antibiotics versus early antibiotics (0 to 1 versus >1 to 3 hours).

Inclusion criteria were adults (18 years) with severe sepsis or septic shock described in English-language publications or in unpublished literature after December 31, 2000.

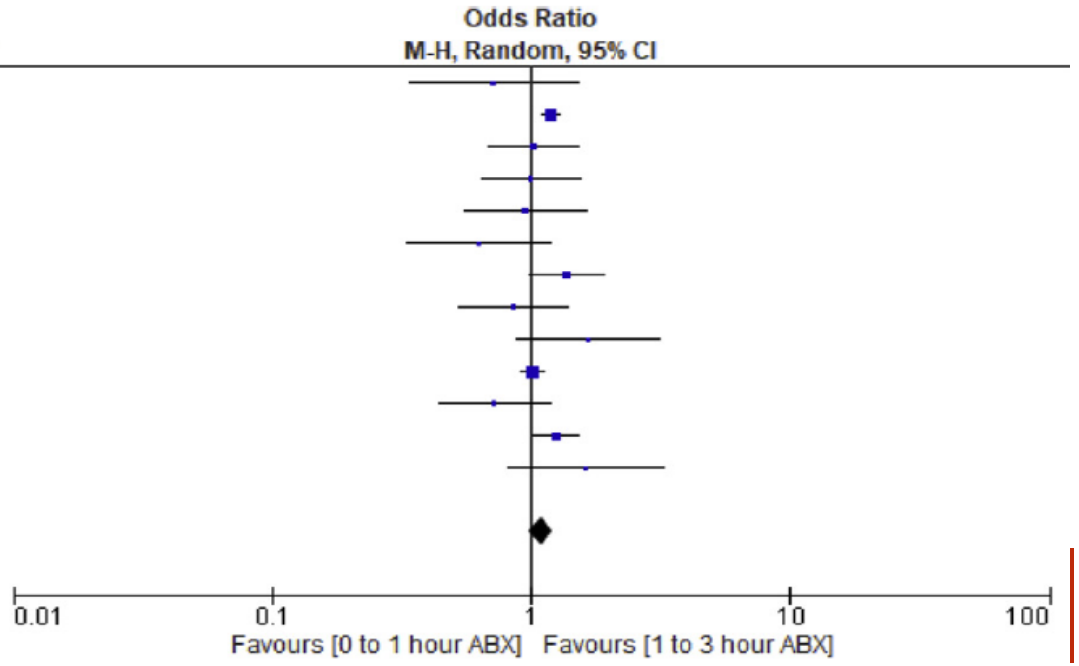
Forest diagram of odds ratios comparing mortality with immediate versus early antibiotics:

all studies

	0 to 1 hour Anbitiotics		1 to 3 hour Antibiotics			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Puskarich 2011	11	65	35	158	1.9%	0.72 [0.34, 1.51]	2011
Ferrer 2014	1512	4728	2155	7615	24.2%	1.19 [1.10, 1.29]	2014
Bloos 2014	65	186	86	249	5.8%	1.02 [0.68, 1.52]	2014
De Groot 2015	46	330	47	336	5.0%	1.00 [0.64, 1.54]	2015
Ryoo 2015	29	150	40	199	3.6%	0.95 [0.56, 1.62]	2015
Drumheller 2016	16	90	46	180	2.6%	0.63 [0.33, 1.19]	2016
Whiles 2017	55	450	142	1541	7.7%	1.37 [0.99, 1.91]	2017
Filbin 2018	32	149	59	243	4.2%	0.85 [0.52, 1.39]	2018
Alam 2018	31	281	16	230	2.7%	1.66 [0.88, 3.12]	2018
Leisman 2019	1046	5399	699	3641	21.9%	1.01 [0.91, 1.13]	2019
Hwang 2019	20	178	159	1067	4.1%	0.72 [0.44, 1.19]	2019
Peltan 2019	139	599	1082	5559	14.2%	1.25 [1.02, 1.53]	2019
Castano 2019	15	57	33	183	2.2%	1.62 [0.81, 3.27]	2019
Total (95% CI)		**12662**		**21201**	**100.0%**	**1.09 [0.98, 1.21]**	
Total events	3017		4599				

Heterogeneity: Tau² = 0.01; Chi² = 20.61, df = 12 (P = 0.06); I² = 42%

Test for overall effect: Z = 1.56 (P = 0.12)



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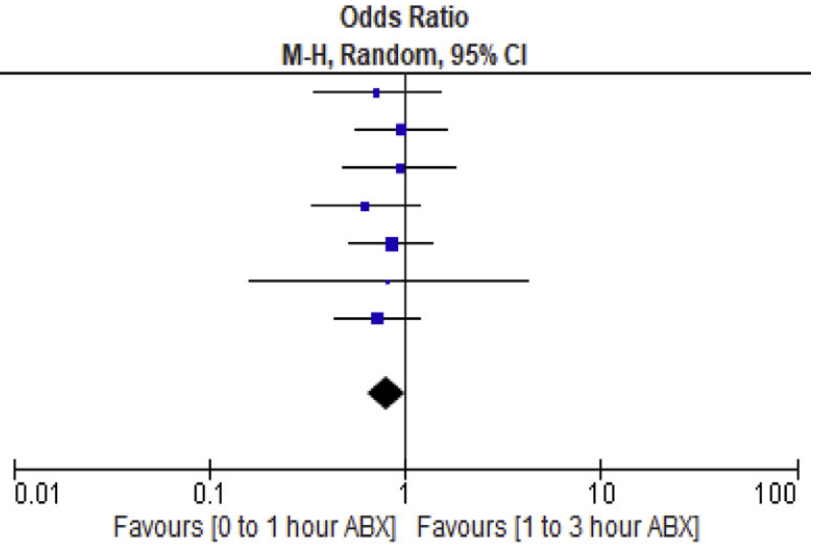
Rothrock SG et al. Ann Emerg Med. 2020;76:427-441

Forest diagram of odds ratios comparing mortality with immediate versus early antibiotics: septic shock

	0 to 1 hour Antibiotics		1 to 3 hour Antibiotics			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Puskarich 2011	11	65	35	158	9.5%	0.72 [0.34, 1.51]	2011
Ryoo 2015	29	150	40	199	18.8%	0.95 [0.56, 1.62]	2015
De Groot 2015	26	113	21	87	12.3%	0.94 [0.49, 1.81]	2015
Drumheller 2016	16	90	46	180	13.2%	0.63 [0.33, 1.19]	2016
Filbin 2018	32	149	59	243	22.4%	0.85 [0.52, 1.39]	2018
Alam 2018	7	24	3	9	2.0%	0.82 [0.16, 4.25]	2018
Hwang 2019	20	178	159	1067	21.8%	0.72 [0.44, 1.19]	2019
Total (95% CI)		**769**		**1943**	**100.0%**	**0.80 [0.64, 1.01]**	
Total events	141		363				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.50$, $df = 6$ ($P = 0.96$); $I^2 = 0\%$

Test for overall effect: $Z = 1.87$ ($P = 0.06$)



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Controversies about rapid treatment

1. Absence of data from randomized trials
2. Potential for adverse effects **(Antimicrobial overuse)**
3. Challenging implementation in environments where staff are often overworked (ED, ICU)
4. Changes in patients' characteristics over time
5. Tendency to include patients with less severe illness over time

***Klompas M et al, JAMA 2018;* 320:1433–1434**

Early administration of antibiotics for suspected sepsis

NEJM February 7, 2019

Two case vignettes

- Mand with hypoxemia
- Woman with AKI

- Do not administer antibiotics

  Michael Klompas

- Administer antibiotics immediately

  Laura Evans

Potential risks of witholding therapy
as compared with
the risk of therapy itself

Association of Adverse Events With Antibiotic Use in Hospitalized Patients

Tamma P et al, JAMA Intern Med. 2017;177(9):1308-1315.

- **1488 patients** with at least 24 hours of any parenteral or oral antibiotic therapy
- Most common indications for antibiotic therapy were UTI (179 [12%]), SSTI (119 [8%]), and CAP (104 [7%])
  - 298 (**20%**) patients experienced **at least 1 antibiotic-associated ADE**
  - The most common **clinically relevant ADEs were gastrointestinal, renal, and hematologic** abnormalities, accounting for 78 (42%), 45 (24%), and 28 (15%), respectively
  - **56 (20%) non–indicated antibiotic regimens** were associated with an ADE
  - 138 **(9.2%)** patients presented a 90-day ADE: **54 CDI and 84 MDRO infections (VRE)**

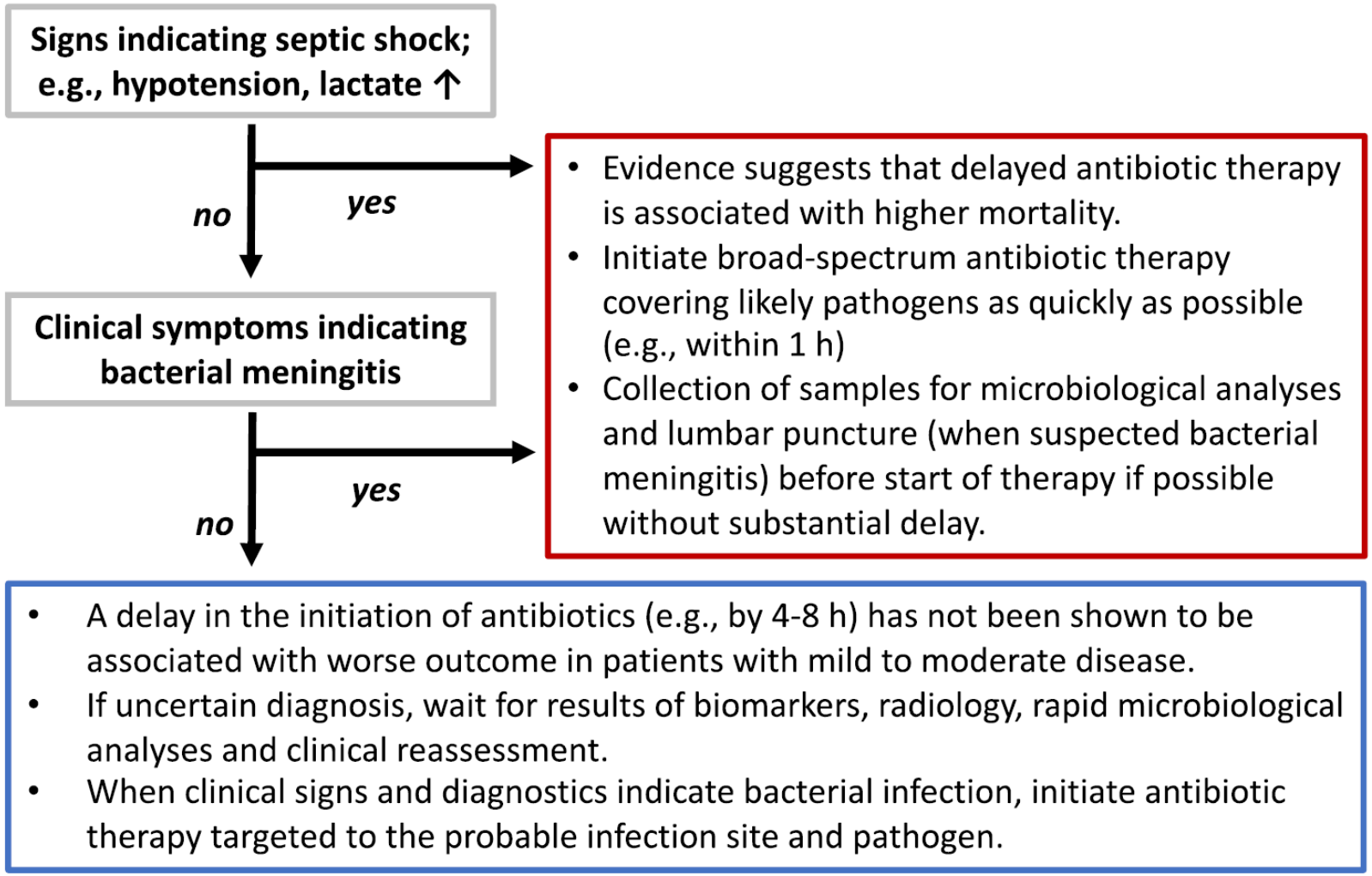
Impact of time to antibiotic therapy on clinical outcome in patients with bacterial infections in the emergency department: implications for antimicrobial stewardship

Naucler et al. Clin Microbiol Infect 2020

Sepsis	• 0 RCTs • 20 observational studies
Bacterial meningitis	• 0 RCTs • 10 observational studies
LRTI	• 0 RCTs • 16 observational studies
UTI	• 0 RCTs • 5 observational studies
IAI	• **4 RCTs** • 5 observational studies
SSI	• 0 RCTs • 0 observational studies

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

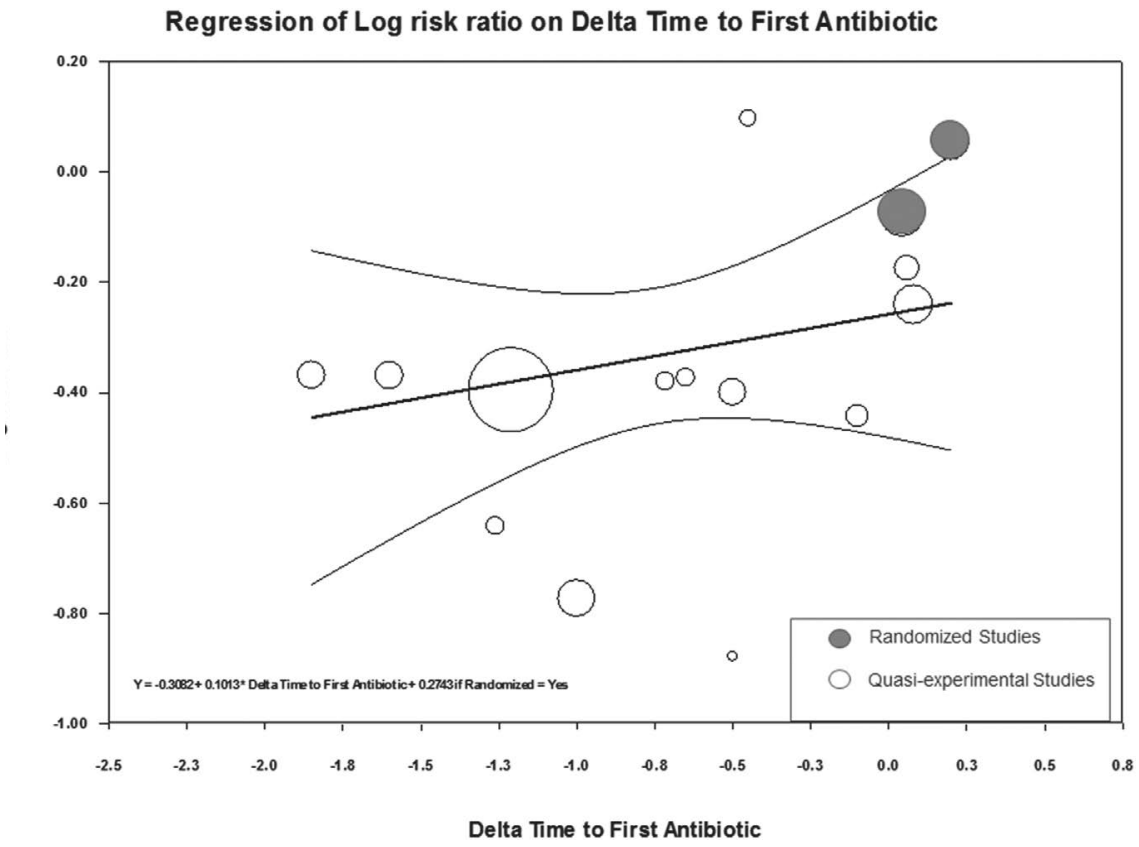
Naucler et al. Clin Microbiol Infect 2020



Early goal-directed therapy for sepsis: A novel solution for discordant survival outcomes in clinical trials.

Kalil AC et al , Crit Care Med 2017; 45:607–614

- 31 obs studies (n = 15,656), 6 RCT (n=4,342)
  - Obs: mortality reduction (RR = 0.73, 0.67–0.80)
  - RCT non significant mortality reduction(RR = 0.92 0.78–1.07)



- Factors that explained the statistically significant mortality differences between RCT and obs studies **were time-to-first antibiotic, ≤ 6 hours (R2 = 94%), 4 hours (R2 = 99%), 3 hours (R2 = 99%), and appropriate antibiotic use (R2 = 96%)**

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

Gaieski et al. Crit Care Med 2010; 38:1045–53

Retrospective analysis on 261 patients undergoing EGDT at an ED, in 2005-2006.

- Median time to antibiotics 119 mins from triage (IQR 76–192), 42 mins from qualification (IQR 0–93)
- In-hospital mortality 31%

Table 4. In-hospital mortality: Triage to ED antibiotics

				Adjusted			
Cutoffs	Number	Mortality, %	Difference, %	OR	95% CI	*p*	Probability of Death
≤1 hr	46	26.1	6.0	0.51	0.21–1.22	.13	.20 vs. .28
>1 hr	215	32.1					
≤2 hrs	136	30.9	0.3	0.72	0.38–1.37	.30	.25 vs. .28
>2 hrs	125	31.2					
≤3 hrs	187	29.4	5.7	0.64	0.32–1.29	.21	.25 vs. .31
>3 hrs	74	35.1					
≤4 hrs	217	30.0	6.4	0.80	0.35–1.84	.59	.27 vs. .29
>4 hrs	44	36.4					
≤5 hrs	237	32.1	−11.2	0.86	0.56–6.15	.31	.28 vs. .16
>5 hrs	24	20.8					

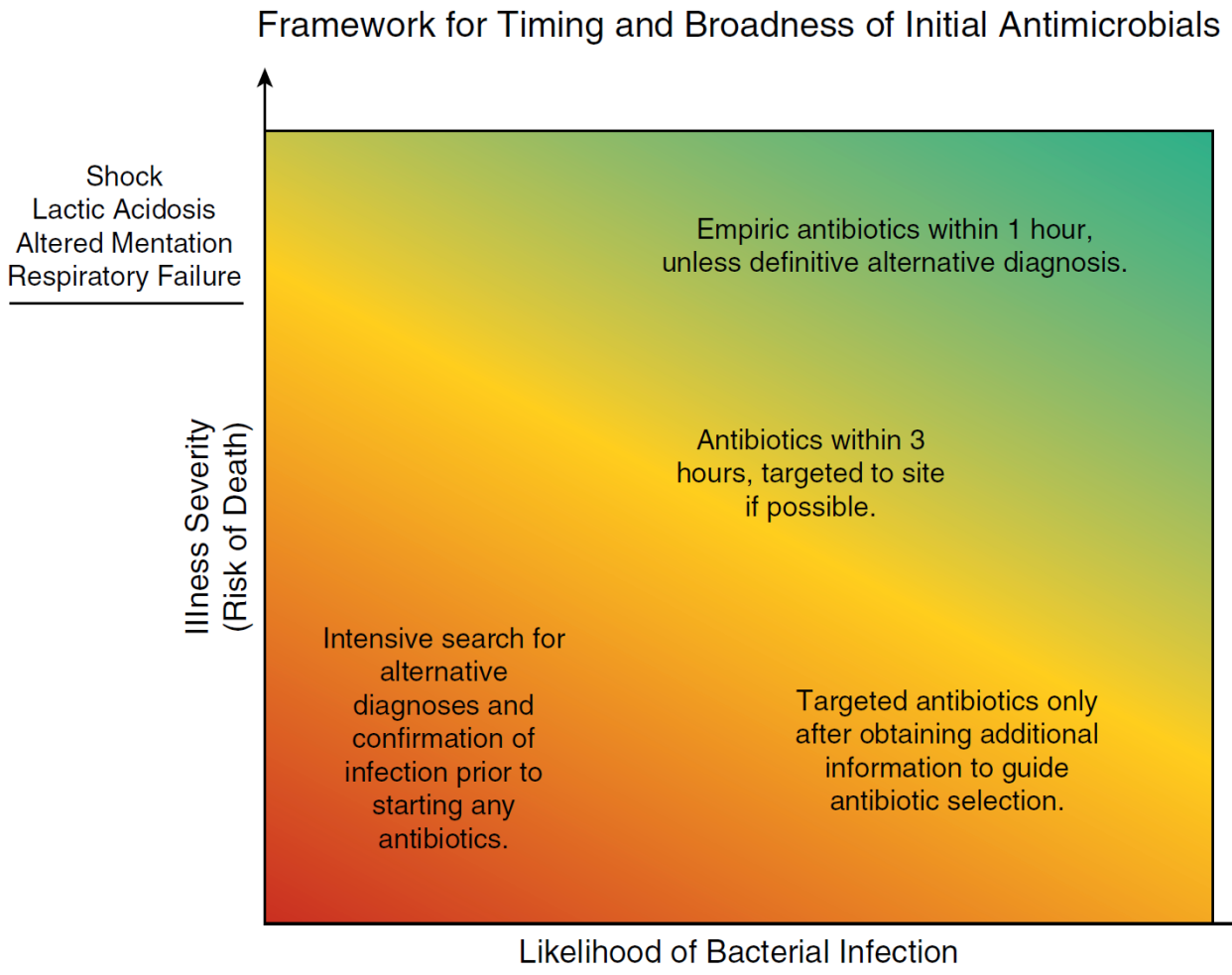
Table 6. In-hospital mortality: Time from triage to appropriate antibiotics

				Adjusted			
Cutoffs	Number	Mortality, %	Difference, %	OR	95% CI	*p*	Probability of Death
≤1 hr	41	19.5	13.7	0.30	0.11–0.83	.02	.13 vs. .29
>1 hr	220	33.2					
≤2 hrs	124	28.2	5.4	0.54	0.29–1.03	.06	.22 vs. .31
>2 hrs	137	33.6					
≤3 hrs	172	27.9	9.2	0.53	0.27–1.01	.05	.23 vs. .34
>3 hrs	89	37.1					
≤4 hrs	200	28.5	10.8	0.62	0.31–1.24	.18	.25 vs. .34
>4 hrs	61	39.3					
≤5 hrs	218	30.7	1.8	0.82	0.37–1.79	.62	.27 vs. .29
>5 hrs	43	32.6					

Improving Sepsis Treatment by Embracing Diagnostic Uncertainty

Prescott Annals ATS Volume 16 Number 4| April 2019

Illness Severity (Risk of Death): A summary assessment of the patient's risk of death based on pre-existing risk factors (e.g. age, chronic medical condition, immune-suppression) and acute physiological derangements.



Likelihood of Bacterial infection: A summary assessment based on clinical signs and symptoms of infection; initial laboratories; imaging.

FAST MICROBIOLOGY

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Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

Evans, L., Rhodes, A., Alhazzani, W. et al. Intensive Care Med 47, 1181–1247 (2021).

- For adults with possible **septic shock** or a high likelihood for sepsis, we recommend administering antimicrobials immediately, ideally within **1 hr** of recognition (**strong recommendation, low quality of evidence**)

- For adults with possible sepsis **without shock, we suggest a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobials within 3 hr** from the time when sepsis was first recognized (**weak recommendation, very low quality of evidence**)

Starting appropriate empirical antimicrobial treatment

Clinical severity

Septic shock, SOFA≥2

Current time

- Site of infection acquisition
  - CA, HCA, HA
- Infection source
  - High (primary, lung) vs. low risk (urinary) sources
- Individual patient risk factors for MDR and/or opportunistic pathogens
  - Immunosuppression
  - Prior exposure to antibiotics
  - Prior colonization or infection with MDR pathogens
- Local epidemiology

Starting appropriate (quasi)empirical antimicrobial treatment

Clinical severity

Septic shock, SOFA≥2

Near future

Artificial intelligence

- Decision support tools

Fast microbiology

- Rapid molecular tests (syndromic tests)
- Rapid phenotypic tests

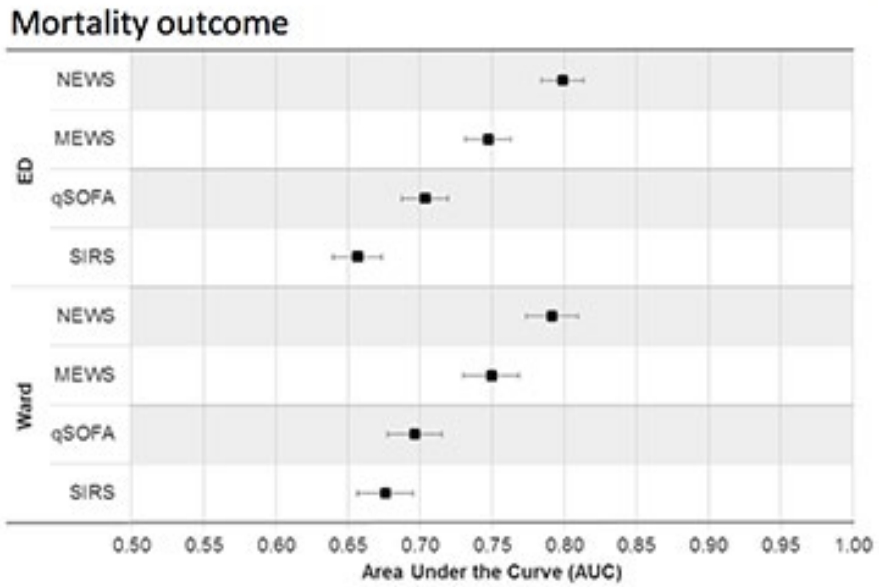
Grazie

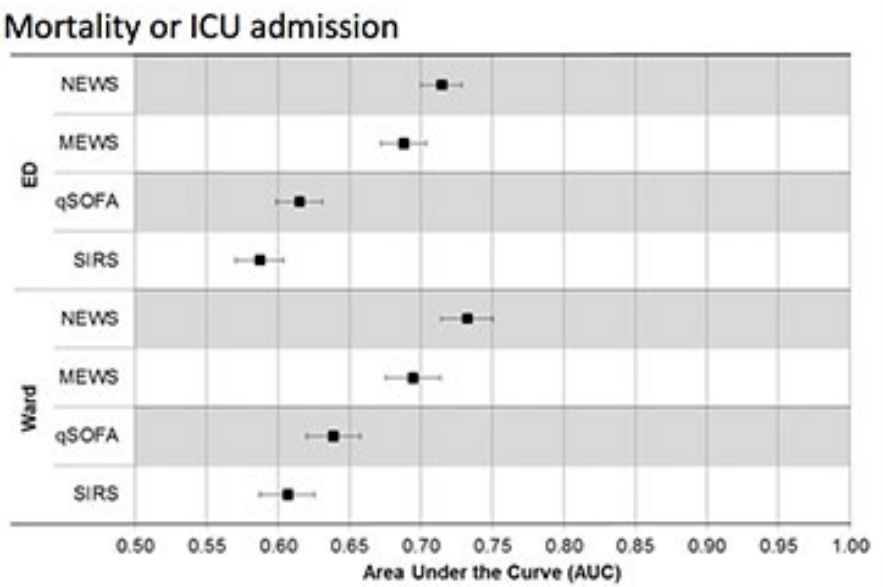
Components of SIRS, qSOFA, MEWS, and NEWS

	SIRS	qSOFA	MEWS	NEWS
Temperature	✓		✓	✓
Heart rate	✓		✓	✓
Blood pressure		✓	✓	✓
Respiratory rate	✓	✓	✓	✓
Oxygen saturation				✓
Use of supplemental oxygen				✓
Mental status		✓	✓	✓
Leukocyte count	✓			
Urine Output			✓	

30,677 patients in the emergency department and ward at the University of Chicago

Overall test performance





Select cutoffs to predict mortality or ICU transfer

	Sensitivity	Specificity
SIRS ≥ 2	91%	13%
qSOFA ≥ 2	54%	67%
NEWS ≥ 7	77%	53%
NEWS ≥ 8	67%	66%
NEWS ≥ 9	54%	78%

qSOFA is an insensitive and late indicator of deterioration

Churpek et al. American Journal of Respiratory and Critical Care Medicine 2016; 195:7