

Sepsa in trajanje antibiotičnega zdravljenja

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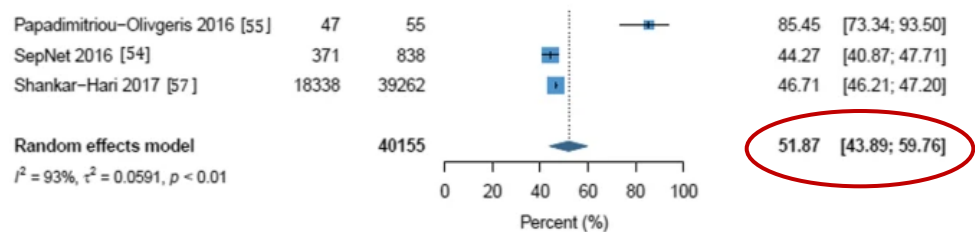
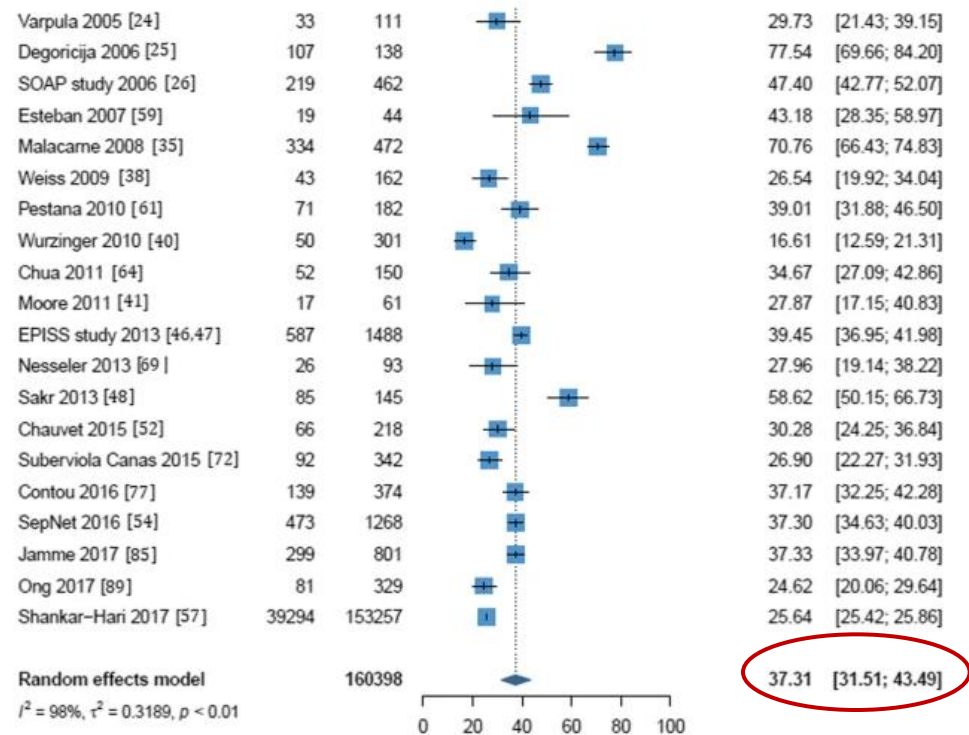
$$T' = T \sqrt{1 - \frac{v^2}{c^2}}$$

**THE FASTER YOU MOVE THROUGH SPACE
THE SLOWER YOU MOVE THROUGH TIME**

Sepsa in antibiotično zdravljenje

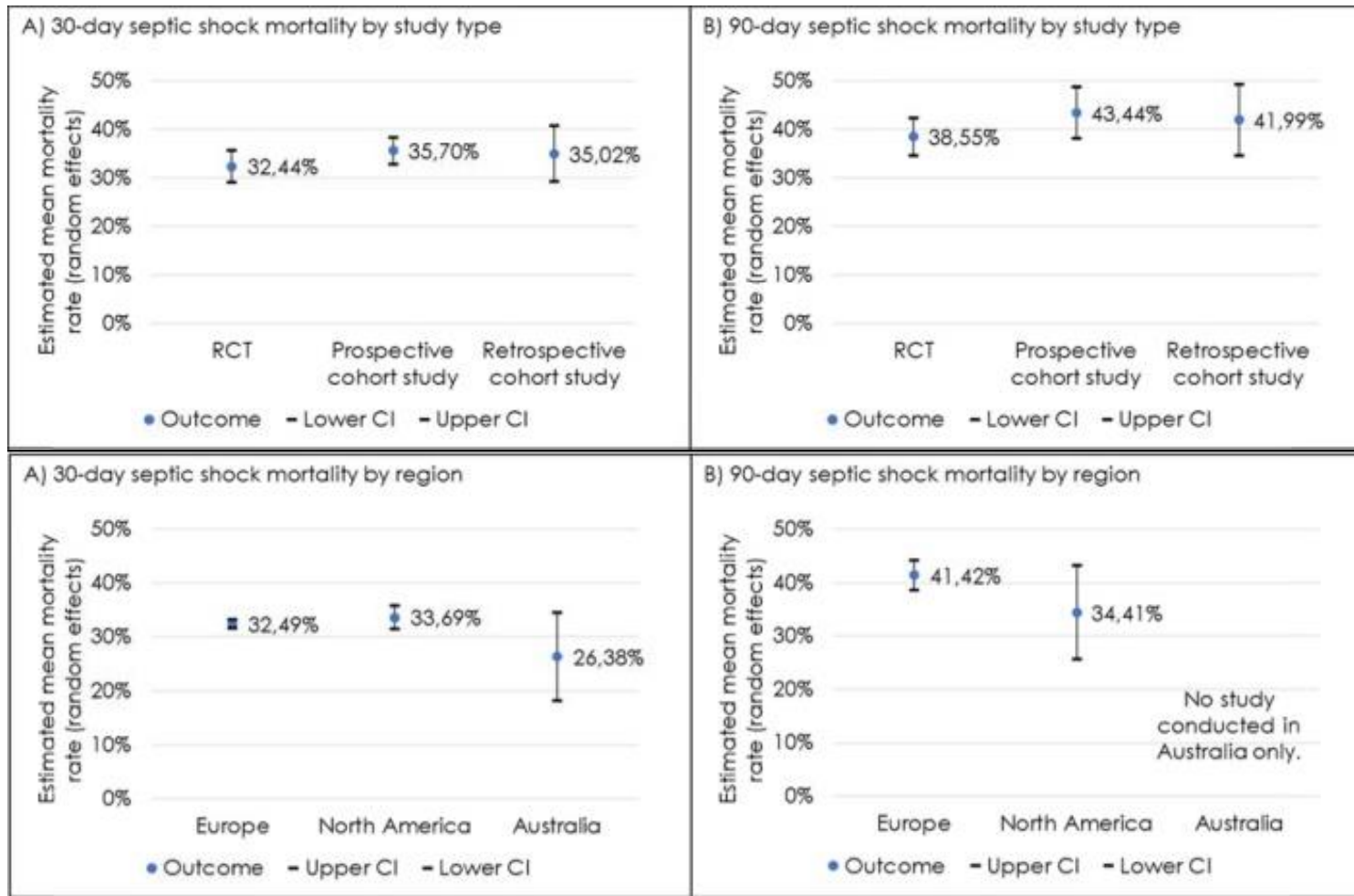
- Začetek zdravljenja
 - Pri življenjsko ogrožajočih okužbah (npr. sepsi, meningitisu) vsaka ura zamude pri začetku učinkovite antibiotične terapije poveča smrtnost.
- Trajanje zdravljenja
 - Prekratko zdravljenje → tveganje za ponovitev.
 - Predolgo zdravljenje → tveganje za odpornost, stranski učinki, superinfekcije.
 - Pristop temelji na: Klinični sliki, etiologiji, odstranitvi žarišča okužbe, biomarkerjih...

Septični šok in smrtnost



Septični šok in smrtnost

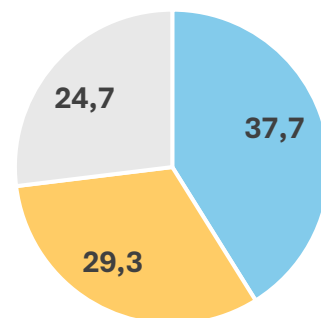
Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019— results from a systematic review and meta-analysis



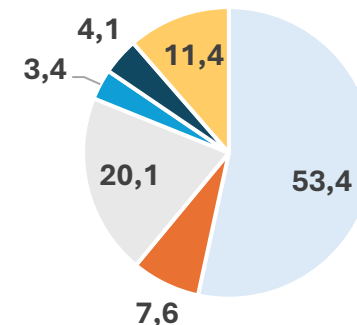
Vir okužbe in odstranitev žarišča

GUIDELINES

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021



CVK Sekundarna okužba Neznani izvor



pljuča GIT
sečila kirurška rana
koža in mehka tkiva drugo

- določi mesto in vir okužbe pri bolnikih s sepso ali septičnim šokom
- potreben poseg za nadzor okužbe se izvede takoj, ko je to medicinsko in logistično izvedljivo (6 do 12 h)
- takojšnja odstranitev znotrajžilnega katetra v kolikor je ta ocenjen kot vir okužbe in po vzpostavitvi drugega žilnega pristopa (septični šok in kandidemija)

Review

Importance of timely and adequate source control in sepsis and septic shock

Overview of selected recent studies investigating the impact of the timing of source control procedures in patients with sepsis and septic shock.

First author	Population	Definition of early source control	Impact on mortality
De Pascale G ^[15]	Patients in the ICU with intra-abdominal infection ($n=1077$)	2–6 h	Early source control: OR=0.50, 95% CI: 0.34 to 0.73
Reitz KM ^[19]	Community-acquired sepsis requiring source control ($n=4962$)	<6 h	Early source control: aOR=0.71, 95% CI: 0.63 to 0.80
Rüddel H ^[18]	ICU patients with sepsis requiring surgical source control ($n=1595$)	NA	All patients: aOR=1.008, 95% CI: 0.997 to 1.02 per hour delay Septic shock patients only: aOR=1.013, 95% CI: 1.001 to 1.026 per hour delay
Boyd-Carson H ^[29]	Patients requiring emergency laparotomy for perforated peptic ulcer ($n=3809$)	NA	aOR=1.04, 95% CI: 1.02 to 1.07 per hour delay Shocked patients aOR=1.06, 95% CI: 1.01 to 1.11 per hour delay;
Karvellas CJ ^[30]	Patients with cholecystitis associated septic shock ($n=196$)	<16 h	Delayed source control: OR=4.45, 95% CI: 1.88 to 10.70
Kim H ^[16]	Patients with septic shock visiting the ED ($n=524$)	<6 h	Delayed source control: aOR=1.418, 95% CI: 0.724 to 2.779
Martínez ML ^[31]	Patients with sepsis or septic shock admitted to the ICU ($n=1090$)	<12 h	Delayed source control: OR=1.082, 95% CI: 0.756 to 1.548

aOR: Adjusted odds ratio; CI: Confidence interval; ED: Emergency department; ICU: Intensive care unit; NA: Not available; OR: Odds ratio.

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

Critical Care Medicine



Time to Antibiotics

Recommendations

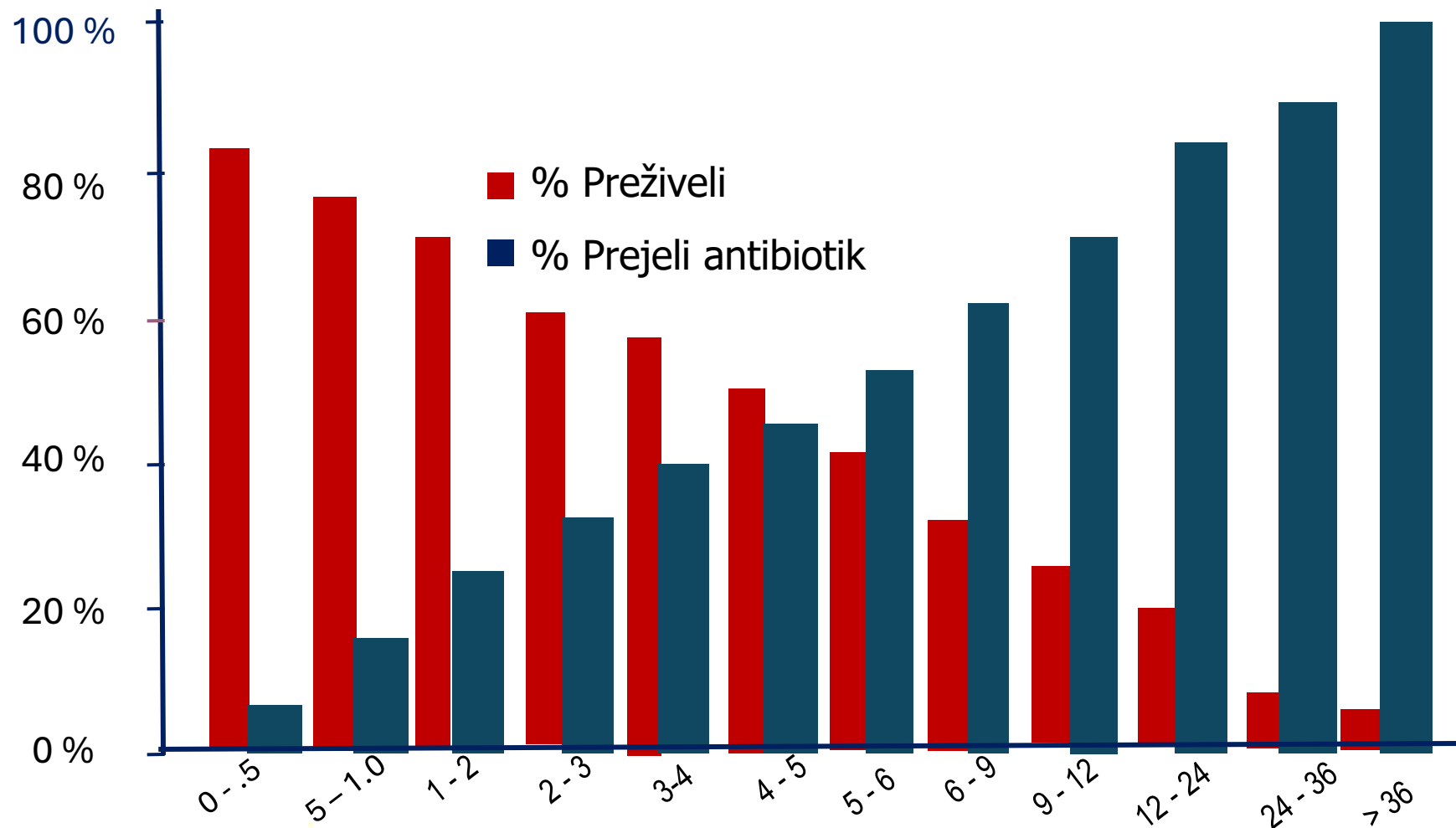
12. For adults with possible septic shock or a high likelihood for sepsis, we **recommend** administering antimicrobials immediately, ideally within one hour of recognition.

Strong recommendation, low quality of evidence (septic shock)

Strong recommendation, very low quality of evidence (sepsis without shock)

Samo 50% bolnikov s septičnim
šokom je dobilo antibiotik v prvih
6. urah

Čas do antibiotične terapije



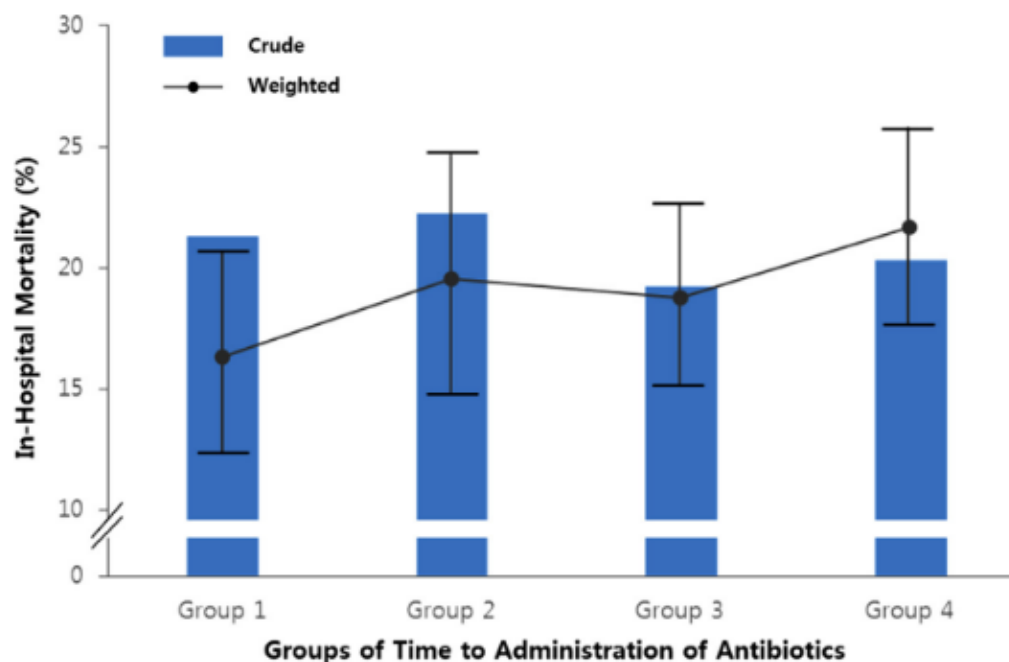
Čas do antibiotične terapije

Avtor	n	Tip raziskave	Čas do antibiotika v min (mediana)	Razmerje obetov za smrt
Gaieski DF, et al. Crit Care Med 2010	261	Retrospektivna	119	0,30 <1h : >1h
Daniels R, et al. Emerg Med J 2011	567	Prospektivn, opazovalna	121	0,62 <1h : >1h
Levy MM, et al. Intensive Care Med 2010	15.022	Retrospektivna, multicentrična		0,86 <1h : >3h
Ferrer R, et al. Crit Care Med 2014	28.150	Retrospektivna, multicentrična		1,52 >6h : <1h
Im Y, et al. Crit Care 2022	3.035 septični šok	Multicentrična, opazovalna	141	0,66 <1h : >1h
Seymour CW, et al. N Engl J Med 2017	49.331	Retrospektivna, multicentrična	57	1,14 3-12 : <3h
Liu VX, et al. Am J Respir Crit Care Med 2017	35.000	Retrospektivna, multicentrična	120	1,07/sepsa in 1,14/sep.šok 1-6h : <1h
Peltan ID, et al. Chest 2019	10.811	Retrospektivna, multicentrična	166	1,29 /1,20/1,61 > 1h />2h/ >3h

Time to Antibiotics and the Outcome of Patients with Septic Shock: A Propensity Score Analysis



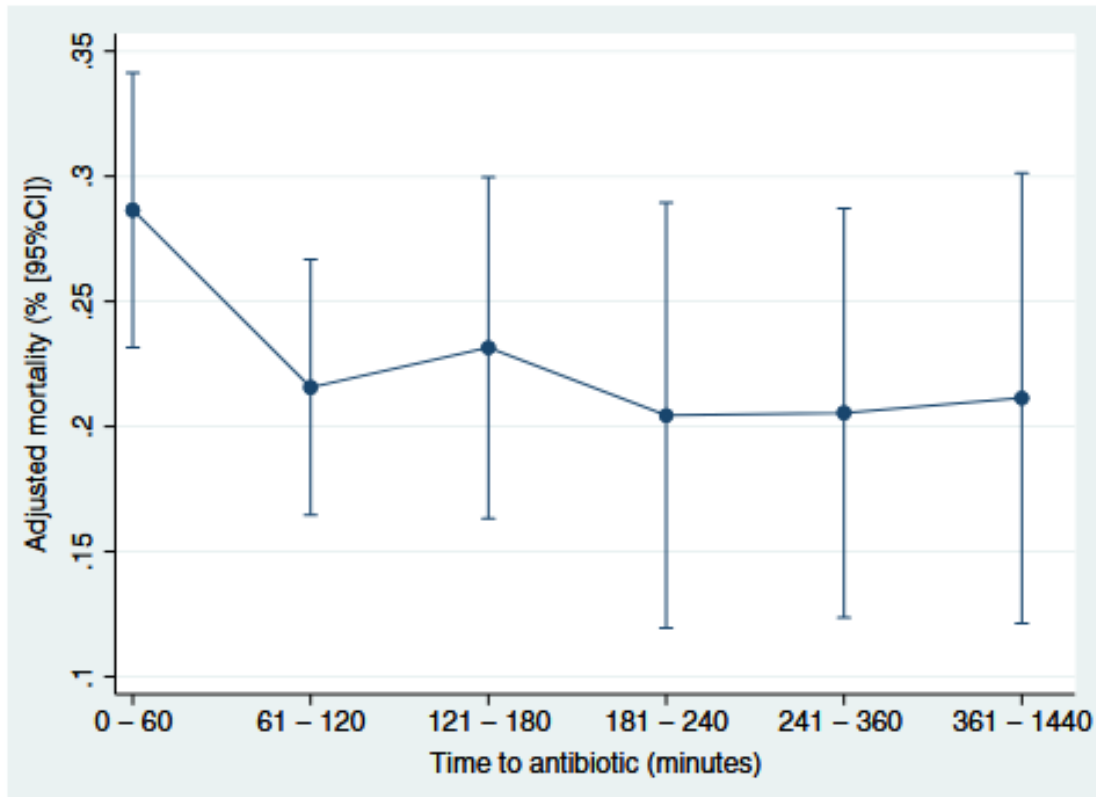
- N=2250 bolnikov s septičnim šokom
- Prospektivna, opazovalna, multicentrična raziskava
- Čas do antibiotika 150 min. (<60, <120, <180, >180)
- Razmerje obetov za smrt = 1,28/1,18/1,63 (> 1h />2h/ >3h)



Ko BS, et al. Am J Med 2020;133:485-91.



Implementation of earlier antibiotic administration in patients with severe sepsis and septic shock in Japan: a descriptive analysis of a prospective observational study



- N = 1184 bolnikov s sepsa ali septičnim šokom
- Prospektivna, opazovalna, multicentrična raziskava
- Čas do antibiotika 102 min. (<60, <120, <180, <240, <360, <1440)
- Razmerje obetov za smrt = 0,99

Abe T, et al. *Crit Care* 2019;23:360.

Door-to-antibiotic time and mortality in patients with sepsis: Systematic review and meta-analysis[☆]



- N = 42 raziskav
- N = 190.896 bolnikov s sepso / septičnim šokom
- Razmerje obetov za smrt 0,83 = antibiotik < 1h (p=0,1)
- Razmerje obetov za smrt 0,80 = antibiotik < 3h (p=0,01)
- Razmerje obetov za smrt 0,57 = antibiotik < 6h (p=<0,01)

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



HHS Public Access

Author manuscript

Crit Care Med. Author manuscript; available in PMC 2016 September 01.

- N = 11 raziskav
- N = 16.178 bolnikov s sepso / septičnim šokom
- Razmerje obetov za smrt 1,46 = antibiotik > 1h (p=0,13)
- Razmerje obetov za smrt 1,16 = antibiotik > 3h (p=0,21)

Čas in preživetje bakterij

Čas, ki ga antibiotik potrebuje, da uniči določeno število bakterij je odvisen od:

- **Vrste antibiotika:**

- **Baktericidni** (ubijajo) – npr. betalaktami, aminoglikozidi
- **Bakteriostatski** (ustavijo rast) – npr. makrolidi, tetraciklini

- **Odmerka antibiotika in koncentracije**

- **Vrste bakterije**

- **Faze rasti bakterije**

- Bakterije v fazi aktivne delitve so bolj občutljive

- **Časa izpostavljenosti**

Čas antibiotičnega zdravljenja seapse

- Povzročitelj
- Vir okužbe
- Uspešnost nadzora nad virom
- Klinični odgovor na zdravljenje
- Mikrobiološki odgovor
- Biokemični odgovor
- Imunski status bolnika
- Okužba z VOB
- Prisotnost zapletov

Čas antibiotičnega zdravljenja seapse

GUIDELINES

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021



Recommendation

30. For adults with an initial diagnosis of sepsis or septic shock and adequate source control, we **suggest** using shorter over longer duration of antimicrobial therapy

Weak recommendation, very low quality of evidence

Population/syndrome	RCT/systematic review (data extracted from)		Shorter duration	Longer duration	Outcomes
Pneumonia	[301]	Capellier (2012)	8 days	15 days	No difference
	[301, 302]	Chastre (2003)	8 days	15 days	No difference
	[302]	El Moussaoui (2006)	3 days	8 days	No difference
	[301–303]	Fekih Hassen (2009)	7 days	10 days	No difference
	[302, 303]	File (2007)	5 days	7 days	No difference
	[302, 303]	Kollef (2012)	7 days	10 days	No difference
	[302, 303]	Leophonte (2002)	5 days	10 days	No difference
	[301]	Medina (2007)	8 days	12 days	No difference
	[302, 303]	Siegel (1999)	7 days	10 days	No difference
Bacteremia	[302]	Tellier (2004)	5 days	7 days	No difference
	[302]	Chaudhry (2000)	5 days	10 days	No difference
	[302]	Runyon (1991)	5 days	10 days	No difference
Intra-abdominal infection	[304]	Yahav (2018)	7 days	14 days	No difference
	[305]	Montravers (2018)	8 days	15 days	No difference
	[293]	Sawyer (2015)	Max. 5 days	Max. 10 days	No difference
Urinary tract infection	[290]	Peterson (2008)	5 days	10 days	No difference

Čas antibiotičnega zdravljenja seapse



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Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com



Duration of antibiotic therapy for *Staphylococcus aureus* bacteraemia:
the long and the short of it

Avtor	Raziskava	Vzorec	Rezultati- atb. zdravljenje
Chong 2013	prospektivna	111 bolnikov	<14 dni : ≥14 dni = ponovitev 7,9% : 0%
Malanoski 1995	retrospektivna	102 bolnika	<10 dni : 10 do 15 dni = ponovitev 4,7% : 0%
Zeylemaker 2001	retrospektivna	57 bolnikov	≤14 dni : >14 dni = zapleti 48% : 53%; smrtnost 31% : 20%
Raad 1992	retrospektivna	55 bolnikov	< 10 dni : ≥10 dni = ponovitev 16% : 0%
Jensen 2002	prospektivna	278 bolnikov	< 14 dni = 34% smrtnost / > 14 dni OR za smrt 0,84
Pigrau 2003	retrospektivna	64 bolnikov	10 do 14 dni = v 3 mesecih brez ponovitve
Fatkenheuer 2004	retrospektivna	229 bolnikov	< 14 dni : ≥ 14 dni = brez razlik v preživetju
Kreisel 2006	retrospektivna	397 bolnikov	≤ 14 dni = RR ponovitev 0,68 (MRSA je OR 2,11)

Čas antibiotičnega zdravljenja sepse

- Staphylococcus aureus = 14 dni
 - brez IE (UZ srca)
 - ni drugih septičnih žarišč (klinična ocena, UZ, CT, MRI, PET CT...)
 - negativne kontrolne HK < 72 h
 - klinični odgovor < 72 h

Čas antibiotičnega zdravljenja sepse



CLINICAL THERAPEUTICS



A Systematic Review and Meta-analysis of Antibiotic Treatment Duration for Bacteremia Due to *Enterobacteriaceae*

- ≤ 10 dni : > 10 dni
- N=4/2865 bolnikov
- 30 dnevna smrtnost RR 0,99
- 90 dnevna smrtnost RR 1,16
- Ozdravitev RR 1,02
- Ponovitev v 90 dneh RR 1,08

Čas antibiotičnega zdravljenja sepse

Duration of antibiotic treatment for Gram-negative bacteremia – Systematic review and individual participant data (IPD) meta-analysis



- 7 ali 14 dni
- 3 RCT / 1186 bolnikov
- 90 dnevna smrtnost OR 1,08
- 30 dnevna smrtnost OR 1,08
- Ponovitev OR 1
- Ponovni sprejem OR 0,96
- Brez statistično pomembnih razlik glede na spol, starost, vir okužbe, imunski status ali HD status ob sprejemu

Čas antibiotičnega zdravljenja sepse

RESEARCH



Antimicrobial treatment for 7 versus 14 days in patients with bacteremia: a meta-analysis of randomized controlled trials

90 dnevna smrtnost

- Hipotenzija ali vazopresorna terapija RR = 0,89
- Urosepsa RR = 0.87
- Druge primarne okužbe RR = 1,04

Biomarkerji in trajanje zdravljenja sepse

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

Critical Care Medicine



Recommendation

31. For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear, we **suggest** using procalcitonin **AND** clinical evaluation to decide when to discontinue antimicrobials over clinical evaluation alone.
Weak recommendation, low quality of evidence.

Biomarkerji in trajanje zdravljenja seapse

Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial



De Jong E, et al. Lancet Infect Dis 2016;16:819-27.

PCT < 0.5 µg/L ali ≥ 80% znižanje

	Procalcitonin-guided group (n=761)	Standard-of-care group (n=785)	Between-group absolute difference in means (95% CI)	p value
Antibiotic consumption (days)				
Daily defined doses in first 28 days	7.5 (4.0 to 12.8)	9.3 (5.0 to 16.5)	2.69 (1.26 to 4.12)	<0.0001
Duration of treatment	5.0 (3.0 to 9.0)	7.0 (4.0 to 11.0)	1.22 (0.65 to 1.78)	<0.0001
Antibiotic-free days in first 28 days	7.0 (0.0 to 14.5)	5.0 (0 to 13.0)	1.31 (0.52 to 2.09)	0.0016
Mortality (%)				
28-day mortality	149 (19.6%)	196 (25.0%)	5.4% (1.2 to 9.5)	0.0122
1-year mortality	265 (34.8%)	321 (40.9%)	6.1% (1.2 to 10.9)	0.0158
Adverse events				
Reinfection	38 (5.0)	23 (2.9)	-2.1% (-4.1 to -0.1)	0.0492
Repeated course of antibiotics	175 (23.0)	173 (22.0)	-1.0% (-5.1 to 3.2)	0.67
Time (days) between stop and reinstitution of antibiotics	4.0 (2.0 to 8.0)	4.0 (2.0 to 8.0)	-0.22 (-1.31 to 0.88)	0.96
Costs				
Total cumulative costs of antibiotics	€150 082	€181 263	NA	NA
Median cumulative costs antibiotics per patient	€107 (51 to 229)	€129 (66 to 273)	€33.6 (2.5 to 64.8)	0.0006
Length of stay (days)				
On the intensive care unit	8.5 (5.0 to 17.0)	9.0 (4.0 to 17.0)	-0.21 (-0.92 to 1.60)	0.56
In hospital	22.0 (13.0 to 39.3)	22.0 (12.0 to 40.0)	0.39 (-2.69 to 3.46)	0.77

Data are median (IQR), n (%), or mean (95% CI). Between-group absolute differences were calculated using the mean values, percentage differences, and 95% CIs. NA=not applicable.

Biomarkerji in trajanje zdravljenja seapse

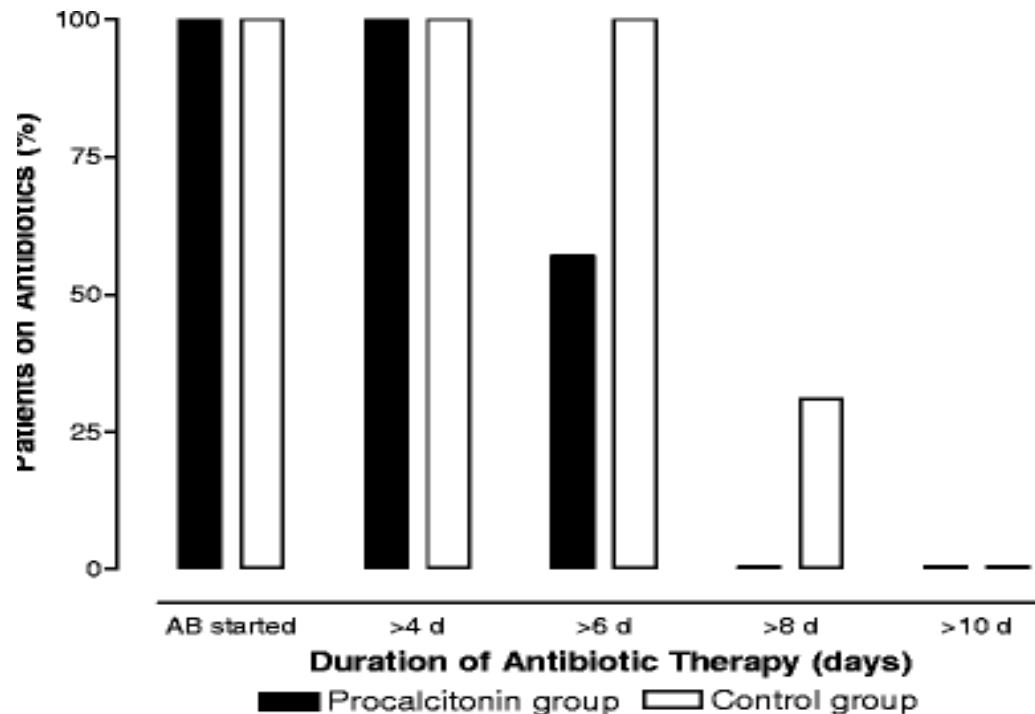
Langenbecks Arch Surg (2009) 394:221–226
DOI 10.1007/s00423-008-0432-1

CONTROLLED PROSPECTIVE CLINICAL TRIALS

Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: results of a prospective randomized study

S. Schroeder • M. Hochreiter • T. Koehler •
A.-M. Schweiger • B. Bein • F. S. Keck • T. von Spiegel

**NAČRTOVANJE
ZDRAVLJENJA**



PCT vodena terapija = 6,6 dni
Kontrolna skupina = 8,3 dni
Izhod enak
Stroški znižani za 17,8%

Biomarkerji in trajanje zdravljenja seapse

Clinical Infectious Diseases

MAJOR ARTICLE



Procalcitonin-guided Antibiotic Treatment in Patients
With Positive Blood Cultures: A Patient-level
Meta-analysis of Randomized Trials

Meier MA, et al. *Clin Infect Dis* 2019;69:388-96.

- 13 raziskav („RCT“) in 523 bolnikov
- PCT <0.25 µg/L (oddelek) < 0.5 µg/L (EIT)

Endpoint	Control Group	PCT Group	Adjusted OR or Difference (95% CI) ^a , PValue
Overall	270	253	
Antibiotic therapy	15.6 ± 12.8	12.7 ± 10.9	-2.86 (-4.88 to -.84), P = .006
30-d mortality, No. (%)	54 (20.0)	42 (16.6)	0.82 (.57–1.16), P = .263
Length of hospital stay	22.5 ± 21.9	21.2 ± 24.0	-1.48 (-5.27 to 2.30), P = .443
Length of ICU stay	13.3 ± 14.6	13.6 ± 16.4	0.55 (-2.48 to 3.57), P = .723

Benefits and Harms of Procalcitonin- or C-Reactive Protein-Guided Antimicrobial Discontinuation in Critically Ill Adults With Sepsis: A Systematic Review and Network Meta-Analysis*



- 18 raziskav („RCT“) in 5023 bolnikov s sepso/septičnim šokom na EIT
- PCT 1 µg/L ali 25-50%; **0.5 µg/L ali ≥ 80%**; 0,25 µg/L ali 90%; 0,1 µg/L ali 80-90%
- CRP 5 dni antibiotik / ≥50% znižanje
- IE in *S.aureus* sepsa izključeni

C Sepsis recurrence

	No. of patients	No. of RCTs	Certainty of the evidence	Estimated absolute risk difference, per 1000 patients (95% CI)	Network risk ratio (95% CI)
Compared with SOC					
PCT	3162	10	Low	+2 (-4 to +10)	1.06 (0.89 to 1.25)
CRP	130	1	Very low	+3 (-31 to +171)	1.08 (0.22 to 5.27)

Zaključki

- Antibiotik bolnikom s sepsa rešuje življenje.
- Predolga antibiotična terapija je škodljiva.
- Klinična ocena je pri kritično bolnih nezanesljiva.
- Biomarkerji so nam lahko v pomoč pri odločitvi.
- Zdravljenje v skladu s smernicami ne vključuje vseh pomembnih kriterijev.
- Individualni pristop z uporabo algoritmov in „AI“ je lahko rešitev v prihodnosti.