Protimikrobno zdravljenje bolnikov s sepso-Kdaj začeti in kdaj končati?

Natalija Planinc Strunjaš

13.september 2019, svetovni dan sepse

UKC Ljubljana

SEPSA in SEPTIČNI ŠOK

SEPSA

- infekcijska bolezen, ki jo sproži okužba in bolnika neposredno ogroža, kaže se z motnjo v delovanju organov in neustreznim odzivom gostitelja na okužbo

  SOFA (Sequential [Sepsis-related] Organ Failure Assessment) >2

  →bolnišnična smrtnost >10%

SEPTIČNI ŠOK

- sepsa s hipotenzijo neodzivno na tekočinsko zdravljenje, serumska vrednost laktata je >2 mmol/L ob odsotnosti hipovolemije, bolniki potrebujejo podporo z vazoaktivnimi zdravili za vzdrževanje srednjega krvnega tlaka>65 mmHg

  →bolnišnična smrtnost >40%

Protimikrobno zdravljenje bolnikov s sepso

Kdaj začeti?

The Surviving Sepsis Campaign Bundle: 2018 Update

Mitchell M. Levy, MD, MCCM[1]; Laura E. Evans, MD, MSc, FCCM[2]; Andrew Rhodes, MBBS, FRCA, FRCP, FFICM, MD (res)[3]

Priporočen začetek protimikrobnega zdravljenja znotraj 1 ure od spoznane sepse

TABLE 1. Bundle Elements With Strength of Recommendations and Under-Pinning Quality of Evidence (12, 13)

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 mean arterial pressure ≥ 65 mm Hg	Strong recommendation, moderate quality of evidence

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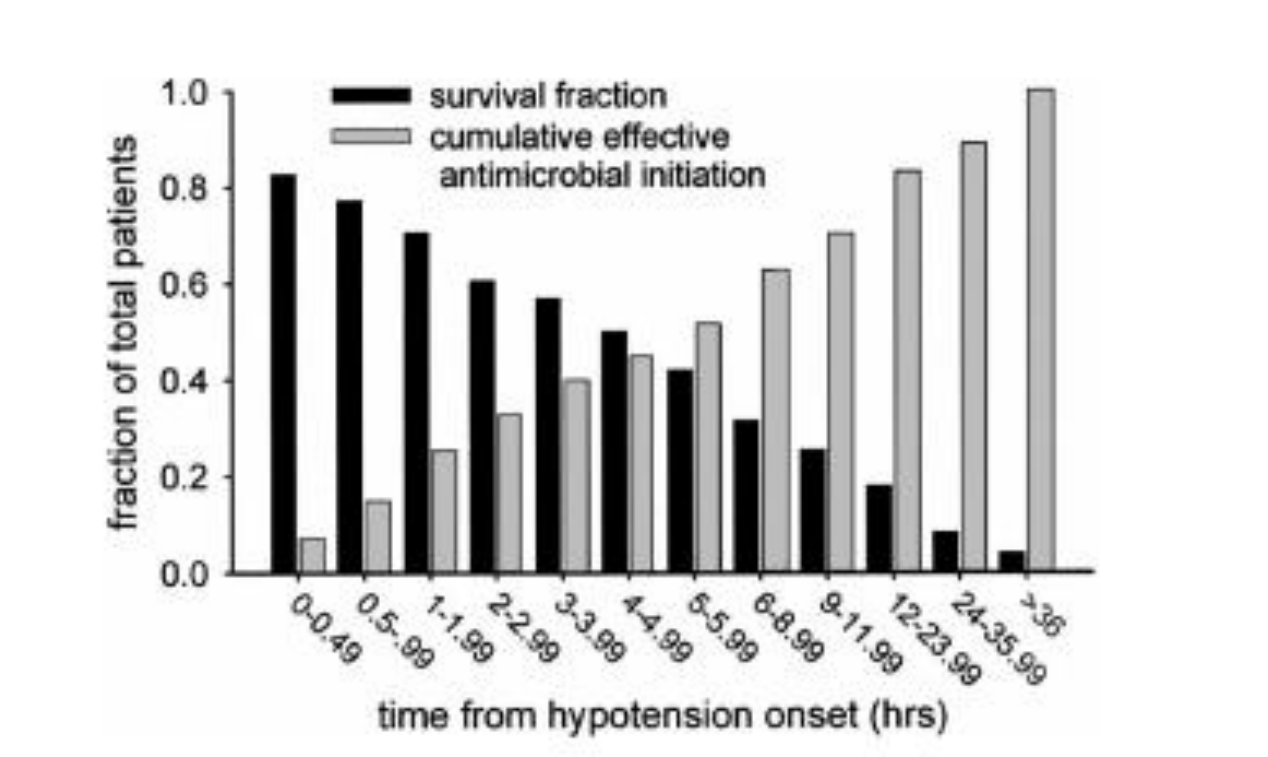
Kumar in sodelavci

- Restrospektivna analiza (1989 – 2004)



Z vsako uro zamude pri uvedbi protimikrobnega zdravljenja po razvoju hipotenzije se **preživetje zmanjša za 7.6%**

Kumar et al, Crit Care Med 2006

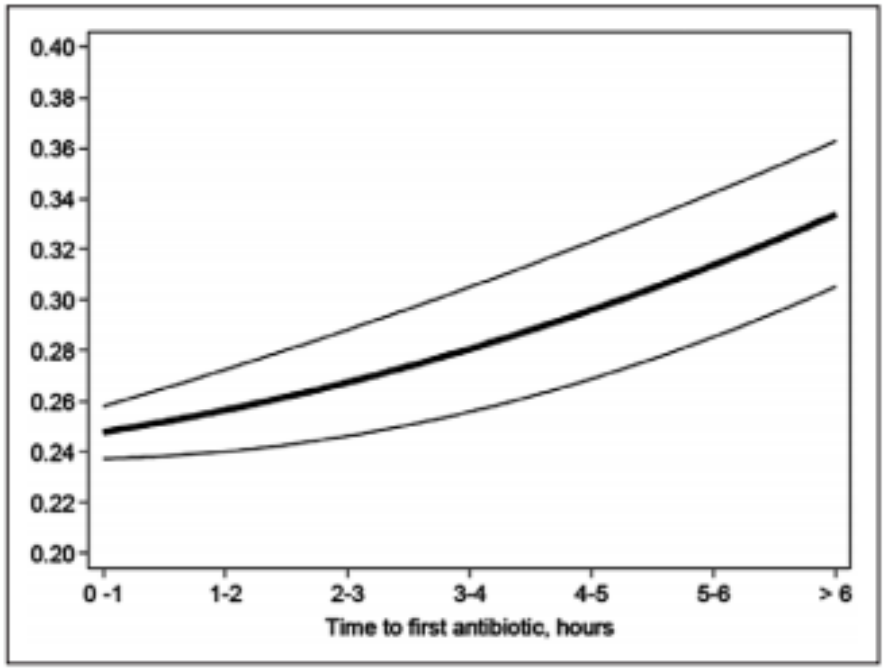


Figure 2. Predicted hospital mortality and the associated 95% CIs for time to first antibiotic administration. The results are adjusted by the sepsis severity score (SSS), ICU admission source (emergency department [ED], ward, vs ICU), and geographic region (Europe, United States, and South America). Probability of hospital mortality is based on the subject having the following specific characteristics: the patient is from the United States, admission source is the ED, and the SSS is 52 (median of all observations).

Ferrer in sod.

- Retrospektivna analiza (2005-2010)
- 17.990 bolnikov (Evropa, ZDA in Južna Amerika)

Linearen padec preživetja z vsako uro zamude pri uvedbi protimikrobnega zdravljenja

→ **Po prilagoditvi glede na**

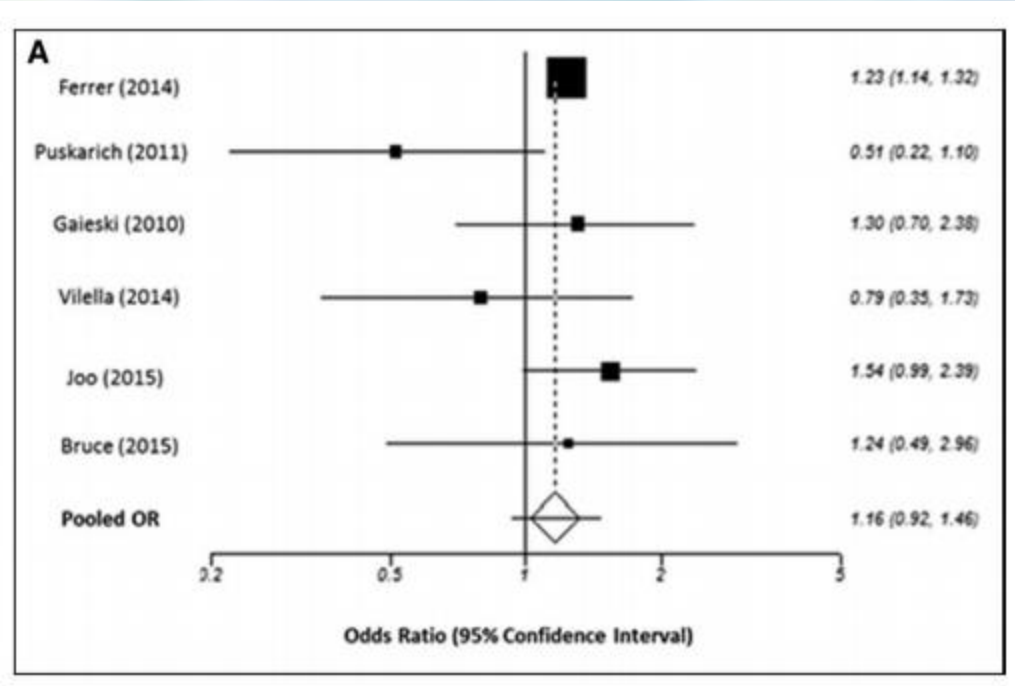
- resnost bolezni
- lokacije pred sprejemom v OIZ
- geografsko regijo

Patient Characteristic, *n* (%)	Antibiotic Timing (Hr)							
	0.0–1.0	1.0–2.0	2.0–3.0	3.0–4.0	4.0–5.0	5.0–6.0	> 6.0	*p*[a]
n	4,728	4,595	3,020	1,734	1,037	640	2,239	
Hospital mortality	1,512 (32.0)	1,292 (28.1)	863 (28.6)	517 (29.8)	337 (32.5)	234 (36.6)	885 (39.6)	< 0.001

Ferrer et al, Crit Care Med 2015

Sterling in sodelavci 2015

- Metaanaliza
- Zgodja uvedba protimikrobnega zdravljenja **ne vpliva na preživetje**



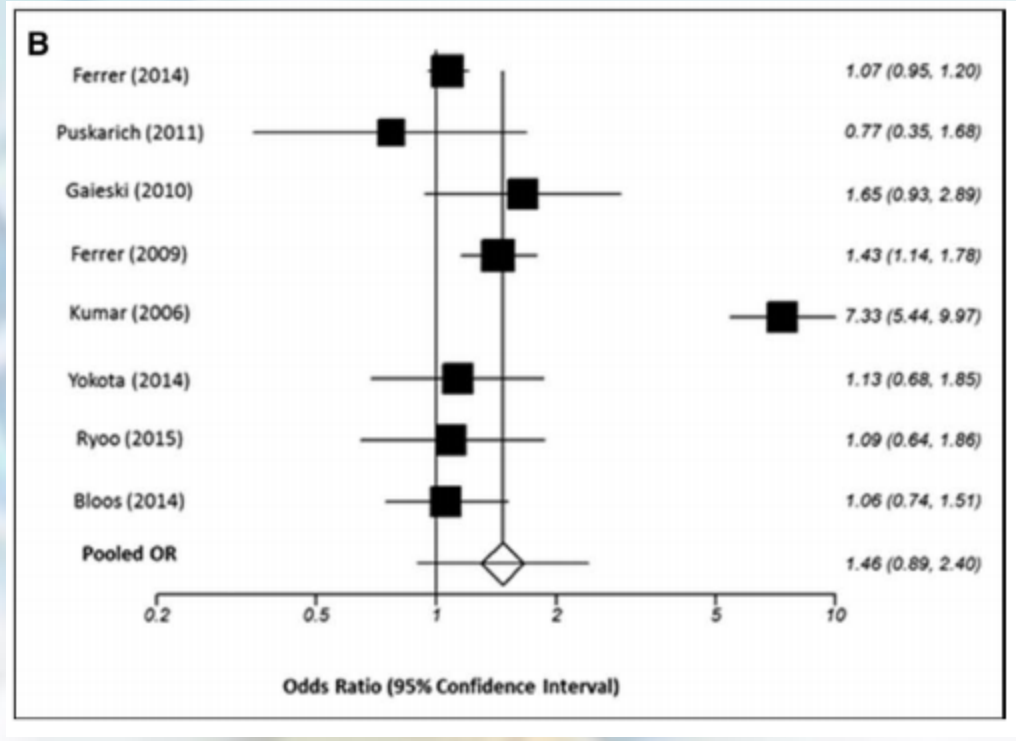


Figure 2. Summary of forest plots. **A**, Pooled odds ratios for mortality and time to antibiotics in less than or more than 3hr from triage time. **B**, Pooled odds ratios for mortality and time to antibiotics in less than or more than 1 hr from severe sepsis/shock recognition.

Alam et al.

- PHANTASi raziskava
- 1. prospektivna randomizirana kontrolirana raziskava, ki je primerjala uvedbo protimikrobnega zdravljenja v prehospitalnem okolju s standardno oskrbo

	Usual care group (n=1137)	Intervention group (n=1535)	Relative risk (95% CI)	Risk difference (%, 95% CI)	p value
28 day mortality	93 (8%)*	120 (8%)	0·95 (0·74 to 1·24)	−0·37 (−2·5 to 1·7)	0·78
90 day mortality	134 (12%)*	178 (12%)	0·98 (0·80 to 1·21)	−0·20 (−2·7 to 2·3)	0·87
Median TTA in the ED (min)	70 (36–128)	..	..	..	..
TTA in the ED (min)					
0–60	410 (42%)	..	..	..	..
61–120	254 (26%)	..	..	..	..
121–180	125 (13%)	..	..	..	..
181–240	78 (8%)	..	..	..	..
>240	56 (6%)	..	..	..	..
Missing	50 (5%)	..	..	..	..
No antibiotics in the ED	164 (14%)	..	..	..	..
Intensive care unit admission	98 (9%)	155 (10%)	1·17 (0·92 to 1·49)	1·5 (−0·73 to 3·7)	0·19
28 day re-admission	119 (10%)	102 (7%)	..	..	0·0004
Median length of stay (days)					
Intensive care unit	3 (2–8)	4 (2–10)	..	..	0·28
Hospital	6 (3–9)	6 (4–10)	..	..	0·12

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Table 2: Outcomes

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National Early Warning Score (in the ambulance)*		
0	1 (<1%)	0
1–4	145 (19%)	192 (19%)
5–6	241 (31%)	306 (30%)
≥7	382 (50%)	521 (51%)
qSOFA score (in the ambulance)†		
<2	872 (83%)	1132 (78%)
≥2	181 (17%)	318 (22%)
DNR policy in place at admission	437 (38%)	609 (40%)
Severity of sepsis		
Non-severe sepsis	424 (37%)	579 (38%)
Severe sepsis	657 (58%)	868 (57%)
Septic shock	37 (3%)	66 (4%)
Other diagnosis	19 (2%)	22 (1%)

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Dokazala izvedljivost prehospitalnega prepoznavanja in zdravljenja sepse!

99% skladnost s protokolom v intervencijski skupini

Višja stopnja kontaminacije hemokultur (več po Gramu pozitivnih bakterij)

Manj pozitivnih urinokultur

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161–240	76 (6%)	..	..	..	..
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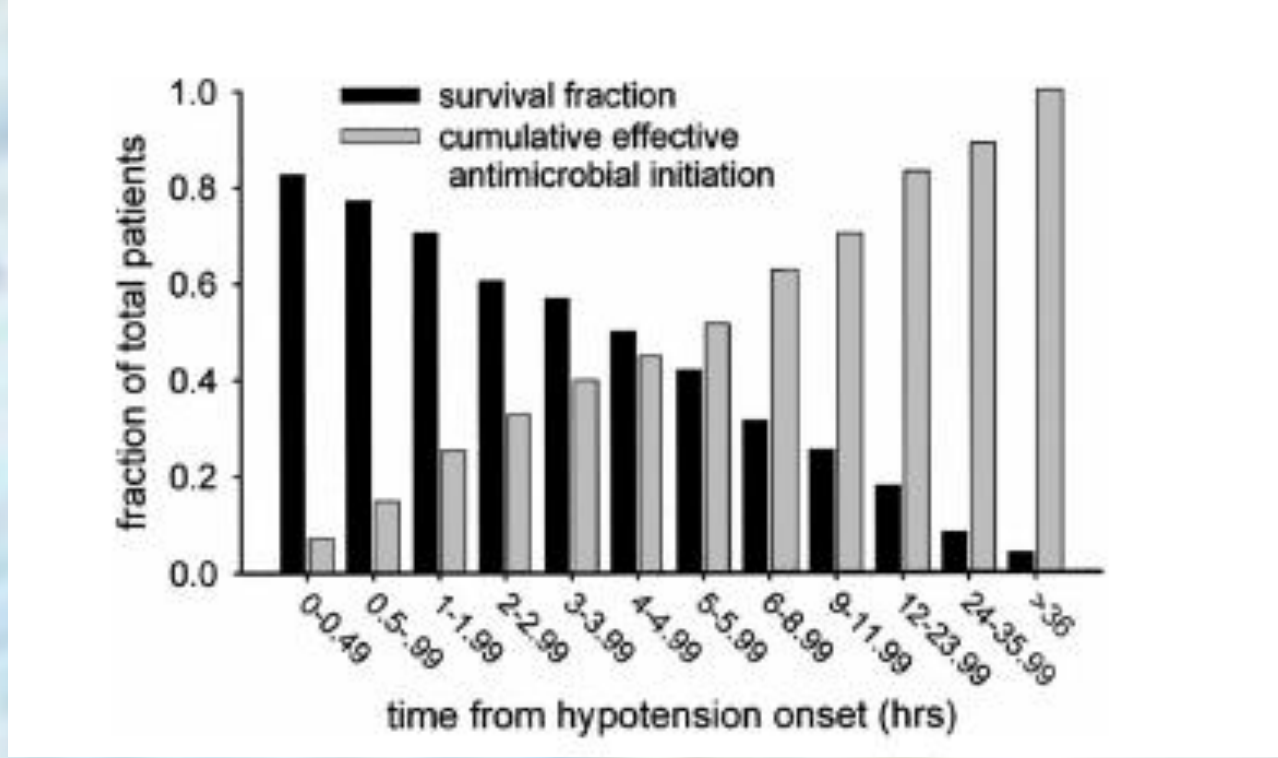
Kumar in sodelavci

- Restrospektivna analiza (1989 – 2004)

Čas do antibiotika 6h



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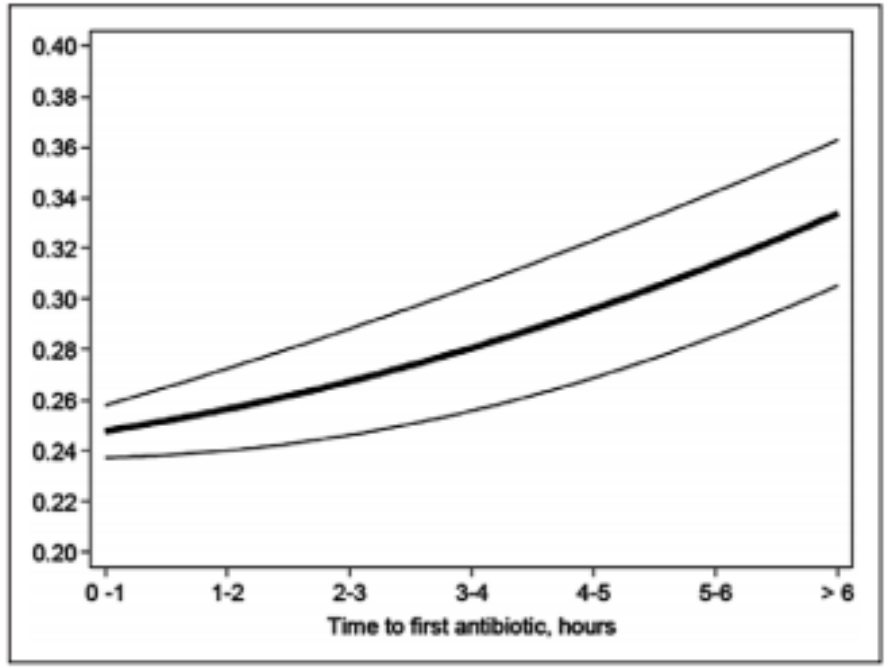
Kumar et al, Crit Care Med 2006

26% bolnikov prejelo antibiotik v 1h
12% v >6h



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Standardna skupina 70 min
Intervencijska skupina 26 min

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Delay Within the 3-Hour Surviving Sepsis Campaign Guideline on Mortality for Patients With Severe Sepsis and Septic Shock

Lisiane Pruinelli, PhD, RN[1]; Bonnie L. Westra, PhD, RN, FAAN, FACMI[1,2]; Pranjul Yadav, PhD[3]; Alexander Hoff[3]; Michael Steinbach, PhD[3]; Vipin Kumar, PhD[3]; Connie W. Delaney, PhD, RN, FAAN, FACMI[1,2]; Gyorgy Simon, PhD[2,4]

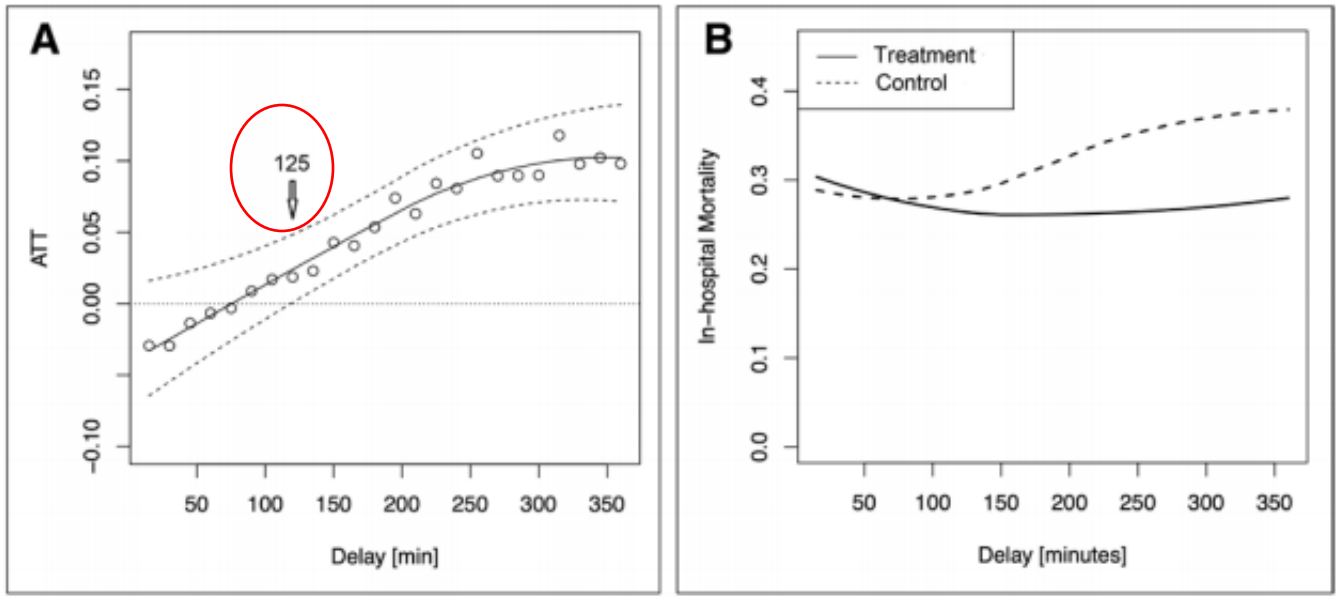


Figure 3. A, Casual effect and (**B**) survival probabilities of the antibiotics recommendation timing on in-hospital mortality between treatment and control groups. ATT = average treatment effect in the treated.

Cilj: določiti kdaj zamuda pri posamezni komponenti svežnja postane škodljiva in vpliva na smrtnost

n = 5072; 27.8% (n=1412) znotraj bolnišnična smrtnost

Rezultati:

- Laktat 20 min
- Hemokulture 50 min
- Tekočine 100 minut
- Protimikrobno zdravljenje 125 min

Protimikrobno zdravljenje bolnikov s sepso

Kdaj končati?

I/ex

Kakšne bodo posledice?

Relaps?

A bom spodbudil odpornost povzročitelja?

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

10. We suggest that an antimicrobial treatment duration of 7–10 days is adequate for most serious infections associated with sepsis and septic shock (weak recommendation, low quality of evidence).

- Manj stranskih učinkov
- Manj razvoja odpornosti
- Manj okužb z *Clostridium difficile*

CORRECTED PROOF

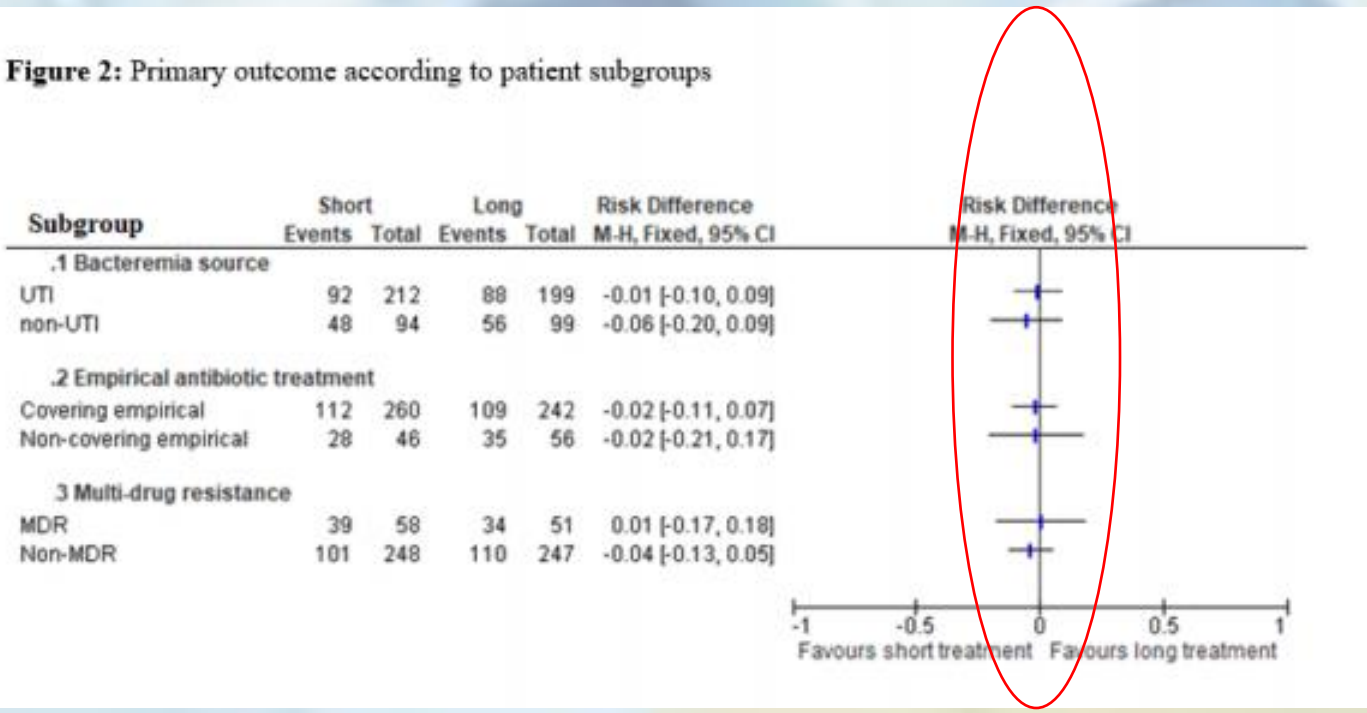
Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial

Dafna Yahav ✉, Erica Franceschini, Fidi Koppel, Adi Turjeman, Tanya Babich, Roni Bitterman, Ami Neuberger, Nesrin Ghanem-Zoubi, Antonella Santoro, Noa Eliakim-Raz ... Show more

Clinical Infectious Diseases, ciy1054, https://doi.org/10.1093/cid/ciy1054

Published: 11 December 2018 **Article history** ▾

Figure 2: Primary outcome according to patient subgroups



Outcome	Short arm (7 days) N=306 patients	Long arm (14 days) N=298 patients	Risk difference (95% confidence interval)	P-value
Primary outcome	140 (45.8)	144 (48.3)	-2.6 (-10.5 to 5.3)	0.527
90 day all-cause mortality	36 (11.8)	32 (10.7)	1.0 (-4.0 to 6.1)	0.702
Readmissions	119 (38.9)	127 (42.6)	-3.7 (-11.5 to 4.1)	0.363
Extended hospitalization beyond 14 days	15 (4.9)	19 (6.4)	-1.5 (-5.1 to 2.2)	0.483
Distant complications	2 (0.7)	1 (0.3)	-	1.0
Relapse of bacteremia	8 (2.6)	8 (2.7)	-0.07 (-2.6 to 2.5)	0.957
Suppurative complications	16 (5.2)	10 (3.4)	1.8 (-1.4 to 5.1)	0.257
14-day mortality	7 (2.3%)	4 (1.3%)	0.95 (-1.42 to 3.44)	0.288
28-day mortality	15 (4.9%)	13 (4.4%)	0.54 (-2.98 to 4.06)	0.753
New clinically or microbiologically documented infection	70 (22.9)	68 (22.8)	0.06 (-6.6 to 6.8)	0.987
Functional capacity needs assistance/dependent in ADL or bedridden at 30	150 (51.4) (292 patients)	163 (57.2) (285 patients)	-5.8 (-13.9 to 2.3)	0.031

CORRECTED PROOF

Shortening Antibiotic Treatment Durations for Bacteremia

Nick Daneman ✉, Robert A Fowler

Clinical Infectious Diseases, ciy1057, https://doi.org/10.1093/cid/ciy1057
Published: 11 December 2018 **Article history** ▾

Kritike

- Predvsem enterobakterije (? ali je mogoče njihove ugotovitve ekstrapolirati na po Gramu negativne ne-fermentativne bakterije ali po Gramu pozitivne organizme)
- Stabilni bolniki ob vključitvi

catheter associated infection.[13] Actual treatment durations were even longer (median 14 days) in a multicentre observational study.[10] Therefore, if 7 days is non-inferior to 14 days of treatment for bacteremia this would represent a major change in practice in North America; we have estimated that the drug-acquisition cost-savings alone would be CAD$678-798 Million/year in North America, and CAD$1.4-1.6 Billion/year in Europe.[14] The results of Dr. Yahav et al.'s study ought to be generalizable to

RESEARCH Open Access

7 versus 14 days of antibiotic treatment for critically ill patients with bloodstream infection: a pilot randomized clinical trial

Nick Daneman[1*], Asgar H. Rishu[2], Ruxandra Pinto[2], Pierre Aslanian[3], Sean M. Bagshaw[4], Alex Carignan[5], Emmanuel Charbonney[6], Bryan Coburn[7], Deborah J. Cook[8], Michael E. Detsky[9], Peter Dodek[10], Richard Hall[11], Anand Kumar[12], Francois Lamontagne[13], Francois Lauzier[14], John C. Marshall[15], Claudio M. Martin[16], Lauralyn McIntyre[17], John Muscedere[18], Steven Reynolds[19], Wendy Sligl[4], Henry T. Stelfox[20], M. Elizabeth Wilcox[21], Robert A. Fowler[22] and on behalf of the Canadian Critical Care Trials Group

- Bolniki v OIZ
- Izključeni:
  - nevtropenični/ PKMC/TX solidnih organov
  - žilni vsadki
  - okužbe s potrebnim prolongiranim zdravljenjem (IE, osteomielitis, sep.artritis, abscesi..
  - Samo 1 pozitivna HK (KNS, *B cereus*, Corynebacterije – kontaminacija?)
  - HK *S aureus*/glive

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

12. We suggest that shorter courses are appropriate in some patients, particularly those with rapid clinical resolution following effective source control of intra-abdominal or urinary sepsis and those with anatomically uncomplicated pyelonephritis (weak recommendation, low quality of evidence).

11. We suggest that longer courses are appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *S. aureus*, some fungal and viral infections, or immunologic deficiencies, including neutropenia (weak recommendation, low quality of evidence).

Ocena potrebnega trajanja zdravljenja pri kritično bolnih bolnikih mora vključevati:

- dejavnike gostitelja (zlasti imunski status)
- vrsto in lastnosti povzročitelja
- mesto in vrsto okužbe

Hvala za pozornost

13. SEPTEMBER
SVETOVNI DAN SEPSE

13. september
stojnice v centru Ljubljane, Maribora in Celja

13. september
ob 9.00 strokovno srečanje v UKC Ljubljana

15. september
ob 10.00 tek Stop sepsi v Mostecu v Ljubljani (prijave na simona.rojs@kclj.si)