Pozni zapleti sepse – vzroki in rešitve

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JAMA. 2010 Oct 27;304(16):1833-4. doi: 10.1001/jama.2010.1546.

The lingering consequences of sepsis: a hidden public health disaster?

Angus DC.

Comment on

Long-term cognitive impairment and functional disability among survivors of severe sepsis. [JAMA. 2010]

PMID: 20978262 DOI: 10.1001/jama.2010.1546

[Indexed for MEDLINE]

Publication types, MeSH terms +

LinkOut - more resources +

Pozni zapleti sepse

- ponovna hospitalizacija – najpogosteje zaradi okužbe
- pogostejše okužbe
- kardiovaskularni zapleti – miokardni infarkt, možganska kap, možganska krvavitev, nenadna srčna smrt, ventrikularne motnje srčnega ritma
- kognitivni upad
- funkcionalne okvare
- slabša kvaliteta življenja
- potreba po stalni oskrbi
- depresija
- smrt

BMI

spol

osnovne bolezni

zapleti

razvade

organska odpoved

funkcionalni status pred boleznijo

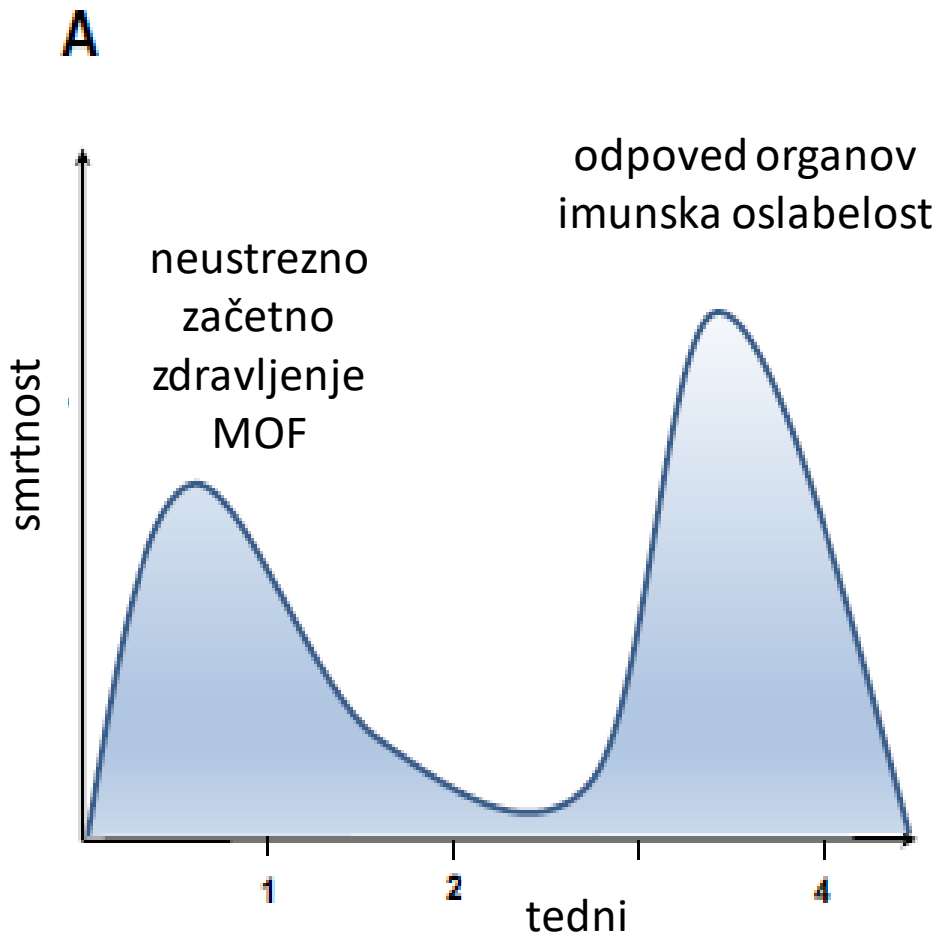
usteznost zdravljenja

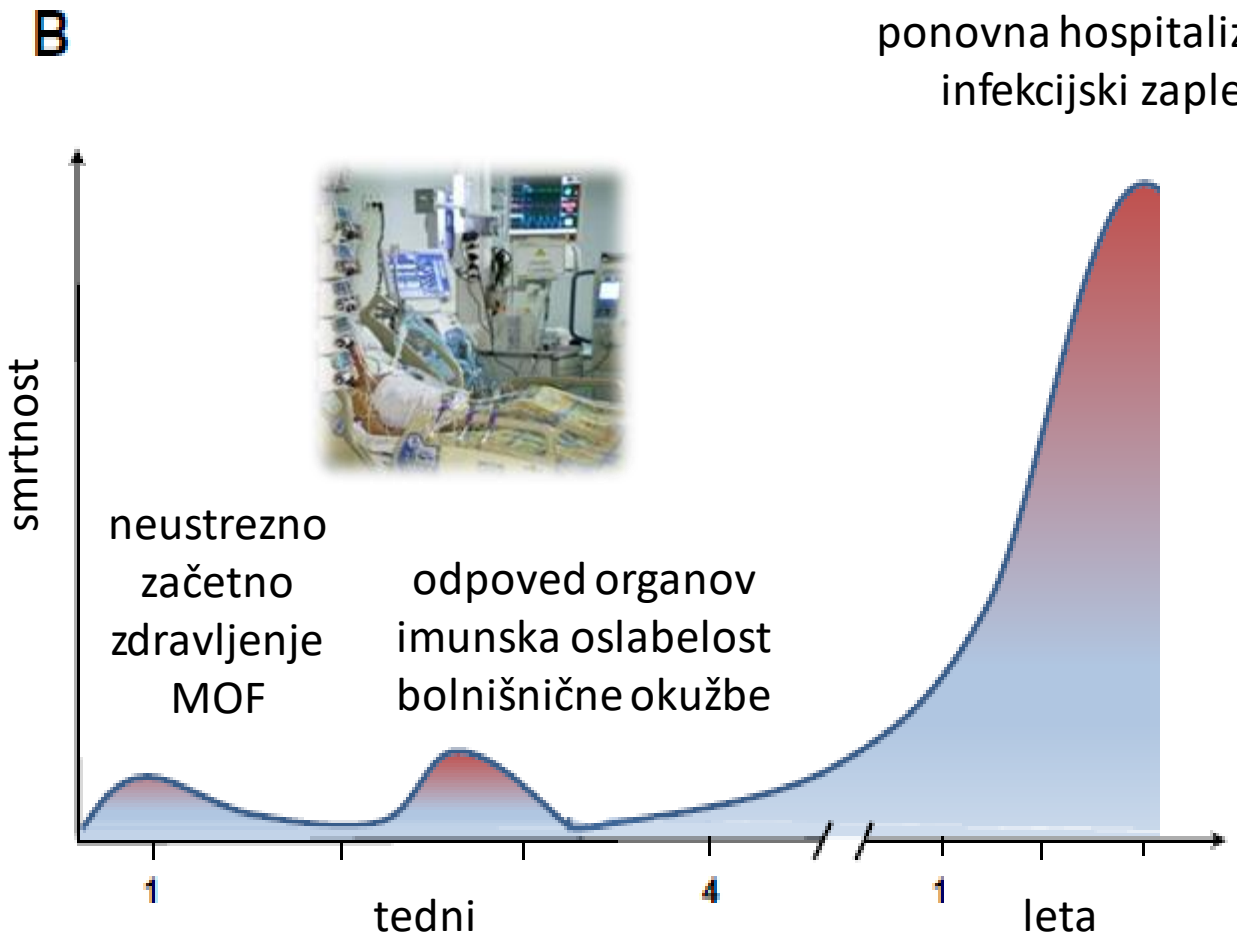
kirurški poseg

etiologija sepse

Smrt zaradi sepse

visoka starost
imunska oslabelost
kronične bolezni
kronično vnetje
kronično katabolno stanje
ponovna hospitalizacija
infekcijski zapleti





Delano et al, Immun Rev 2016; 274: 330-353

RESEARCH Open Access

Evidence for a causal link between sepsis and long-term mortality: a systematic review of epidemiologic studies

Manu Shankar-Hari[1,2*†], Michael Ambler[1†], Viyaasan Mahalingasivam[1], Andrew Jones[1,2], Kathryn Rowan[3] and Gordon D. Rubenfeld[4]

Abstract

Background: In addition to acute hospital mortality, sepsis is associated with higher risk of death following hospital discharge. We assessed the strength of epidemiological evidence supporting a causal link between sepsis and mortality after hospital discharge by systematically evaluating the available literature for strength of association, bias, and techniques to address confounding.

Methods: We searched Medline and Embase using the following 'mp' terms, MESH headings and combinations thereof - sepsis, septic shock, septicemia, outcome. Studies published since 1992 where one-year post-acute mortality in adult survivors of acute sepsis could be calculated were included. Two authors independently selected studies and extracted data using predefined criteria and data extraction forms to assess risk of bias, confounding, and causality. The difference in proportion between cumulative one-year mortality and acute mortality was defined as post-acute mortality. Meta-analysis was done by sepsis definition categories with post-acute mortality as the primary outcome.

Results: The literature search identified 11,156 records, of which 59 studies met our inclusion criteria and 43 studies reported post-acute mortality. In patients who survived an index sepsis admission, the post-acute mortality was 16.1 % (95 % CI 14.1, 18.1 %) with significant heterogeneity ($p < 0.001$), on random effects meta-analysis. In studies reporting non-sepsis control arm comparisons, sepsis was not consistently associated with a higher hazard ratio for post-acute mortality. The additional hazard associated with sepsis was greatest when compared to the general population. Older age, male sex, and presence of comorbidities were commonly reported independent predictors of post-acute mortality in sepsis survivors, challenging the causality relationship. Sensitivity analyses for post-acute mortality were consistent with primary analysis.

Conclusions: Epidemiologic criteria for a causal relationship between sepsis and post-acute mortality were not consistently observed. Additional epidemiologic studies with recent patient level data that address the pre-illness trajectory, confounding, and varying control groups are needed to estimate sepsis-attributable additional risk and modifiable risk factors to design interventional trials.

Keywords: Sepsis, Mortality, Causality, Bias, Confounding factors (epidemiology)

16,1% bolnikov umre v prvem letu po sepsi!!

- starost, osnovne bolezni – napovedni dejavniki
- moški spol
- funkcionalni status
- večina poroča o skupinah bolnikov pred l. 2005!!
- smrt zaradi sepse ali kritične bolezni?

Crit Care 2016; 20: 101

Late mortality after sepsis: propensity matched cohort study

Hallie C Prescott,[1, 2, 3, 4] John J Osterholzer,[1, 4] Kenneth M Langa,[1, 2, 3, 5] Derek C Angus,[6]
Theodore J Iwashyna[1, 2, 3, 4, 5, 7]

Ali je pozna smrtnost posledica sepse ali osnovnih bolezni in stanj?

- 960 bolnikov s sepso ≥ 65 let
  - – povp. starost 79 let, 12% DSO, ena funkcionalna motnja, 2 osnovni bolezni
- kontrolne skupine:
  - ne-hospitalizirani
  - hospitalizirani z okužbo brez sepse
  - hospitalizirani zaradi vnetne bolezni neinfekcijske etiologije
- pomanjkljivosti: stare definicije sepse, vključeni bolniki 1998-2010

BMJ 2016

eTable E: Adjusted rates of mortality versus comparisons by time period

Time Period	**Sepsis versus Not Currently Hospitalized** (Adjusted Percentages[a]) (Sepsis 95% CI) (Non-Hosp. 95% CI)	**Sepsis versus Non-sepsis infection** (Adjusted Percentages[a]) (Sepsis 95% CI) (Infection 95% CI)	**Sepsis versus Sterile Inflammation** (Adjusted Percentages[a]) (Sepsis 95% CI) (Sterile Inflam. 95% CI)
0 - 30 day	**26.2% versus 0.8%** (23.2%-29.3%) (0.2%-1.3%)	**26.0% versus 7.1%** (22.9%-29.0%) (5.4%-8.9%)	**24.4% versus 4.8%** (20.5%-27.9%) (2.9%-6.6%)
31 - 90 day	**12.1% versus 1.4%** (9.4%-14.7%) (0.6%-2.3%)	**14.3% versus 6.4%** (11.6%-17.2%) (4.6%-8.1%)	**15.1% versus 4.8%** (11.5%-18.6%) (2.9%-6.6%)
91-180 day	**9.6% versus 2.6%** (7.0%-12.1%) (1.5%-3.7%)	**9.8% versus 5.8%** (7.2%-12.4%) (4.0%-7.5%)	**9.5% versus 5.3%** (6.3%-12.8%) (3.4%-7.3%)
181 day – 1 year	**11.6% versus 4.2%** (8.7%-14.5%) (2.8%-5.6%)	**12.8% versus 9.0%** (9.7%-15.8 %) (6.4%-10.5%)	11.4% versus 7.3% (7.8%-15.0%) (4.9%-9.7%)
>1 year – 2 year	**16.0% versus 10.7%** (12.5%-19.5%) (8.6%-12.9%)	15.7% versus 16.1% (12.1%-19.0%) (13.2%-19.2%)	17.0% versus 13.1% (10.9%-16.3%) (12.5%-21.5%)
31 day – 2 year	**40.4% versus 18.3%** (36.5%-44.2%) (15.7%-20.8%)	**42.8% versus 32.4%** (39.0%-46.7%) (29.2%-46.7%)	**43.5% versus 27.3%** (38.8%-48.2%) (23.7%-30.9%)

[a]Adjusted for age, gender, and propensity for sepsis, which includes age, race, ethnicity, gender, partnership, wealth, food stamp use, Charlson co-morbidity index, I/ADL limitations, self rating of health, body mass index, hospitalizations in the prior year, sepsis in the prior year, and residence in a nursing home.
Statistically significant results are presented in bold. Conceptually, this table reports the overall matched cohort's mortality if everyone had a sepsis hospitalization versus if everyone had the comparison condition.

Prescott et al, BMJ 2016

Ponovna hospitalizacija

- povprečna re-hospitalizacija preživelih po sepsi:
  - v prvih 30-ih dneh po odpustu - 19,9-32%:

    - starost, maligna bolezen, hospitalizacija v zadnjem letu pred sepso, nizke vrednosti Hb ob odpustu

    Jones et al. Ann Am Thorac Soc 2015; 12: 904-13

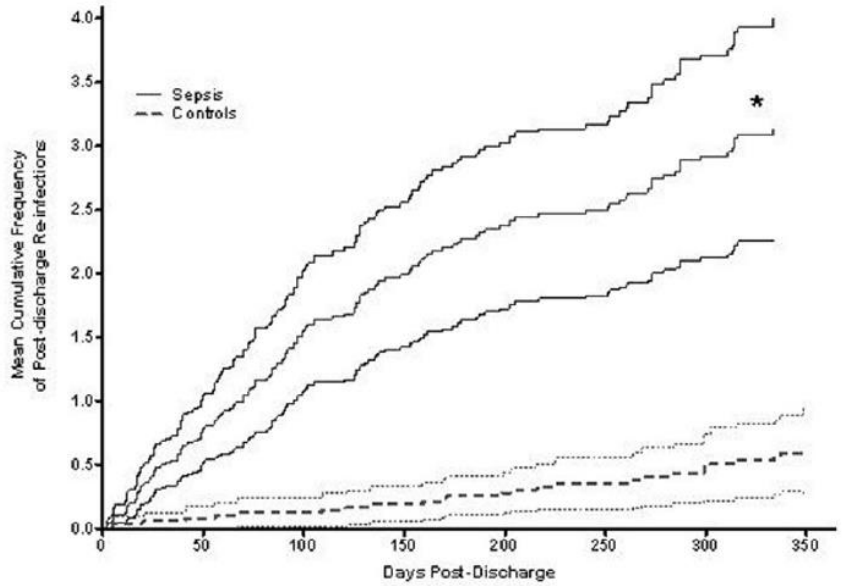
  - v prvih 90-ih dneh po odpustu – 40%
  - v enem letu po odpustu – 63%
- najpogostejši razlog za ponovni sprejem – okužba
  - pljučnica

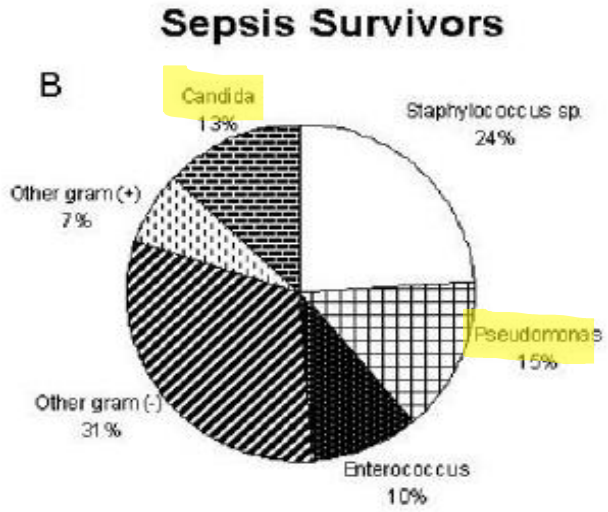
J Intensive Care Med. 2014 Mar-Apr;29(2):87-95. doi: 10.1177/0885066612467162. Epub 2012 Dec 26.

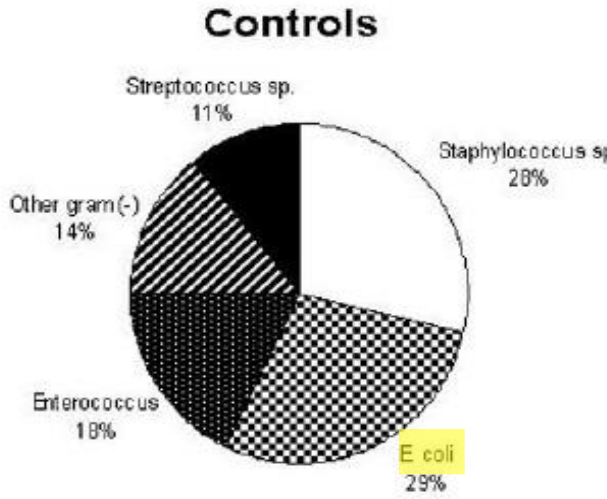
Subsequent infections in survivors of sepsis: epidemiology and outcomes.

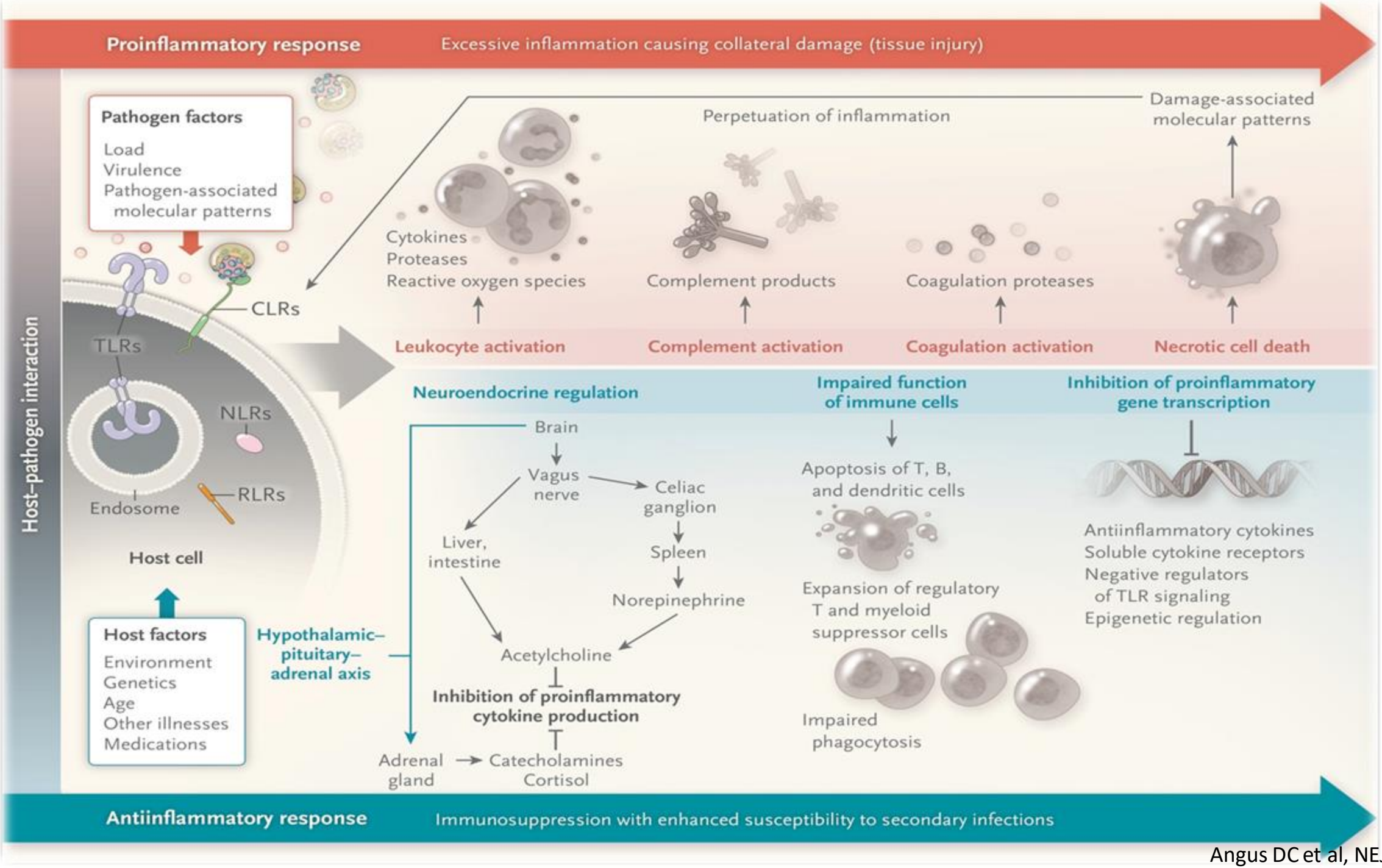
Wang T[1], Derhovanessian A, De Cruz S, Belperio JA, Deng JC, Hoo GS.

- bolniki v EIT s sepso/bolniki v EIT brez sepse
- ocenjevali pogostost in vrsto okužb po sepsi
- bolniki s sepso – 63% ponovna okužba v prvem letu!
  - starejši, DSO, hospitalizacija > 13 dni, kateter









Angus DC et al, NEJM 2013

Klinični dokazi imunske oslabljenosti pri sepsi

- okužbe z oportunističnimi patogeni
- nerazrešeno vnetno žarišče kljub ustreznem antibiotičnem zdravljenju
- reaktivacija latentnih virusov
- uspeh nekaterih učinkovin, ki spodbujajo vnetni odziv (GM CSF, IL7, IFNy) ?
- klinična ocena in trajanje imunske oslabelosti??

Am J Respir Crit Care Med. 2016 Jul 15;194(2):209-17. doi: 10.1164/rccm.201510-2023OC.

Long-Term Mortality and Major Adverse Cardiovascular Events in Sepsis Survivors. A Nationwide Population-based Study.

Ou SM[1,2,3], Chu H[2,4], Chao PW[5,6], Lee YJ[2,7], Kuo SC[8,2,9], Chen TJ[10], Tseng CM[2,11], Shih CJ[2,12,13], Chen YT[2,14].

Author information

Abstract

RATIONALE: Patients with sepsis who survive to hospital discharge may present with ongoing high morbidity and mortality. However, little is known about the risk of long-term, all-cause mortality and cardiovascular outcomes after sepsis.

OBJECTIVES: Our study aimed to investigate the long-term clinical outcomes in sepsis survivors.

METHODS: In this nationwide population-based study, data from patients with sepsis were retrieved from Taiwan's National Health Insurance Research Database between 2000 and 2002. Each sepsis survivor was 1:1 propensity-matched to control subjects from two different control populations: subjects who were in the general population and subjects who were hospitalized for a nonsepsis diagnosis. The primary outcomes were all-cause mortality, major adverse cardiovascular events, myocardial infarction, heart failure, stroke, and sudden cardiac death or ventricular arrhythmia.

MEASUREMENTS AND MAIN RESULTS: Compared with matched population control subjects, sepsis survivors had higher risks of all-cause mortality (hazard ratio [HR], 2.18; 95% confidence interval [CI], 2.14-2.22), major adverse cardiovascular events (HR, 1.37; 95% CI, 1.34-1.41), ischemic stroke (HR, 1.27; 95% CI, 1.23-1.32), hemorrhagic stroke (HR, 1.36; 95% CI, 1.26-1.46), myocardial infarction (HR, 1.22; 95% CI, 1.14-1.30), heart failure (HR, 1.48; 95% CI, 1.43-1.53), and sudden cardiac death or ventricular arrhythmia (HR, 1.65; 95% CI, 1.57-1.74). Similar results, although slightly attenuated risks, were found when comparisons were made with hospitalized control subjects without sepsis.

CONCLUSIONS: These data indicate that sepsis survivors had substantially increased risks of subsequent all-cause mortality and major adverse cardiovascular events at 1 year after discharge, which persisted for up to 5 years after discharge.

KEYWORDS: epidemiology; heart failure; major adverse cardiovascular events; mortality; sepsis

Kognitivni upad

- hospitalizacija vpliva na kognitivni upad
- sepsa je neodvisni dejavnik tveganja za kognitivni upad
  - 3× večje tveganje v primerjavi s kontrolno populacijo (OR 3,3 95% CI (1,5-7,3))
- pojav depresije
  - pogost pri preživelih po sepsi
  - dejavnik tveganja za pljučnico in sepso
  - signifikantno povezan s funkcionalnimi okvarami po sepsi

Shah et al. Am J Respir Crit Care Med 2013; 188: 586-92
Davydow DS et al. Am J Geriatr Psychiatry 2013; 21: 887-97

Kvaliteta življenja

- slabša kvaliteta življenja v primerjavi s splošno populacijo
- traja do 5 let po sprejemu
- podobne rezultate so dobili tudi pri drugih skupinah bolnikov po kritični bolezni
- kvaliteta življenja pred sprejemom vpliva tudi na kvaliteto življenja po odpustu

Winters BD et al. Crit Care Med 2010; 38: 1276-83.
Uthbertson BH et al. Crit Care 2013; 17: R70.

Long-term mortality and quality of life in intensive care patients treated for pneumonia and/or sepsis☆

Predictors of mortality and quality of life in patients with sepsis/pneumonia

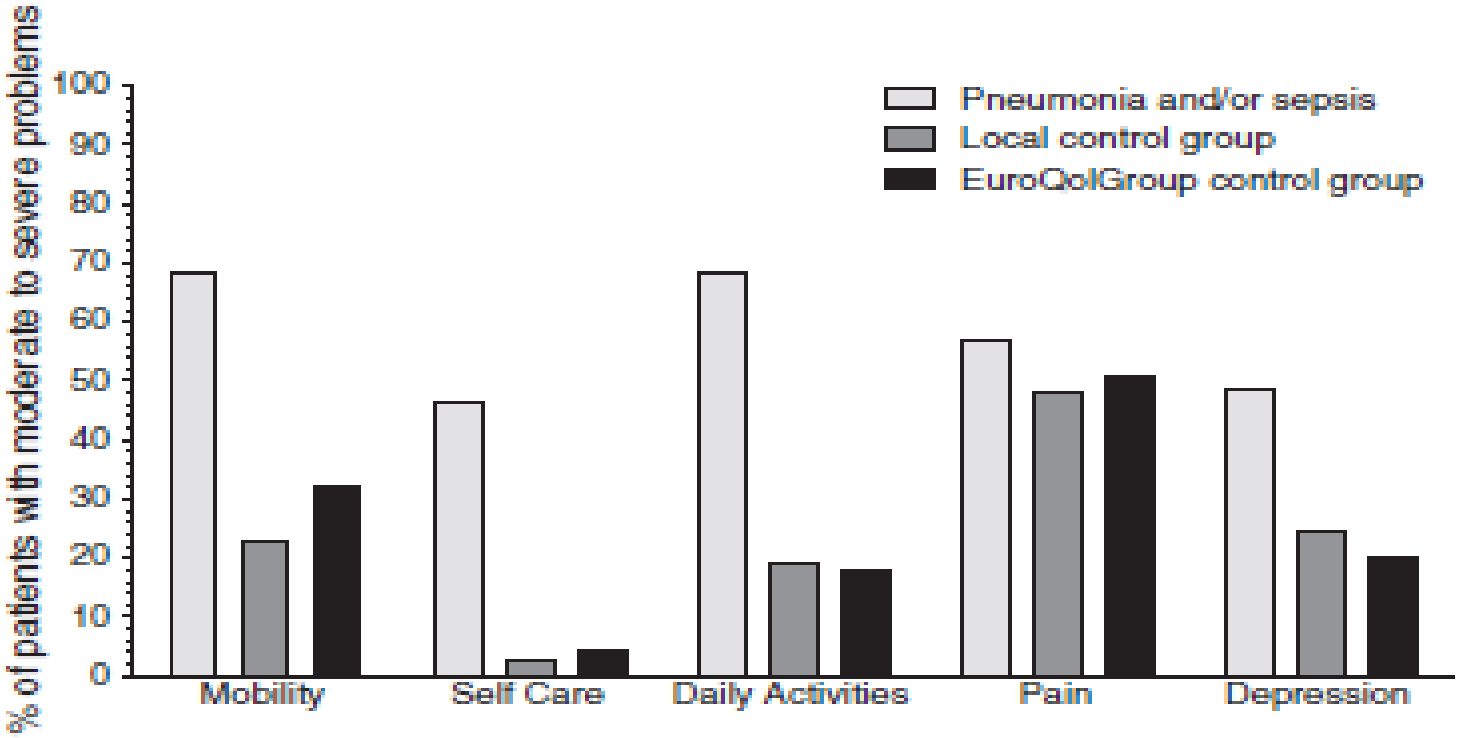


Fig. 3. The 5 dimensions of the EQ-5D in our cohort and 2 control groups. Percentage of patients reporting moderate-to-severe problems in the 5 dimensions of the EQ-5D questionnaire compared with answers of 2 control groups.

- Nemčija, 2008/2009
- bolnišnična smrtnost:
  - 17% pljučnica
  - 46% sepsa
- smrtnost po 1 letu:
  - 51% pljučnica
  - 65% sepsa

Honselmann KC et al Journal of Crit Care 2015; 30: 721-726

Dejavniki tveganja za slabši funkcionalni status bolnikov s sepso po odpustu
kronične bolezni
trajanje delirija v času hospitalizacije
naglušnost
nepokretnost
krhkost („frailty“)
samski zakonski stan
visoka starost
predhodno bivanje v domu starejših občanov
resnost akutne bolezni
slabovidnost
fizična/duševna prizadetost pred boleznijo

Rešitve - bolnišnica

Oddelek za intenzivno zdravljenje

- čimprejšnje antibiotično in podporno zdravljenje
- ocena, preprečevanje in zdravljenje bolečine
- izbor analgezije in sedacije
- spremljanje in zdravljenje delirija
- zgodnja fizioterapija
- vključevanje bolnikove družine

Bolnišnični oddelek

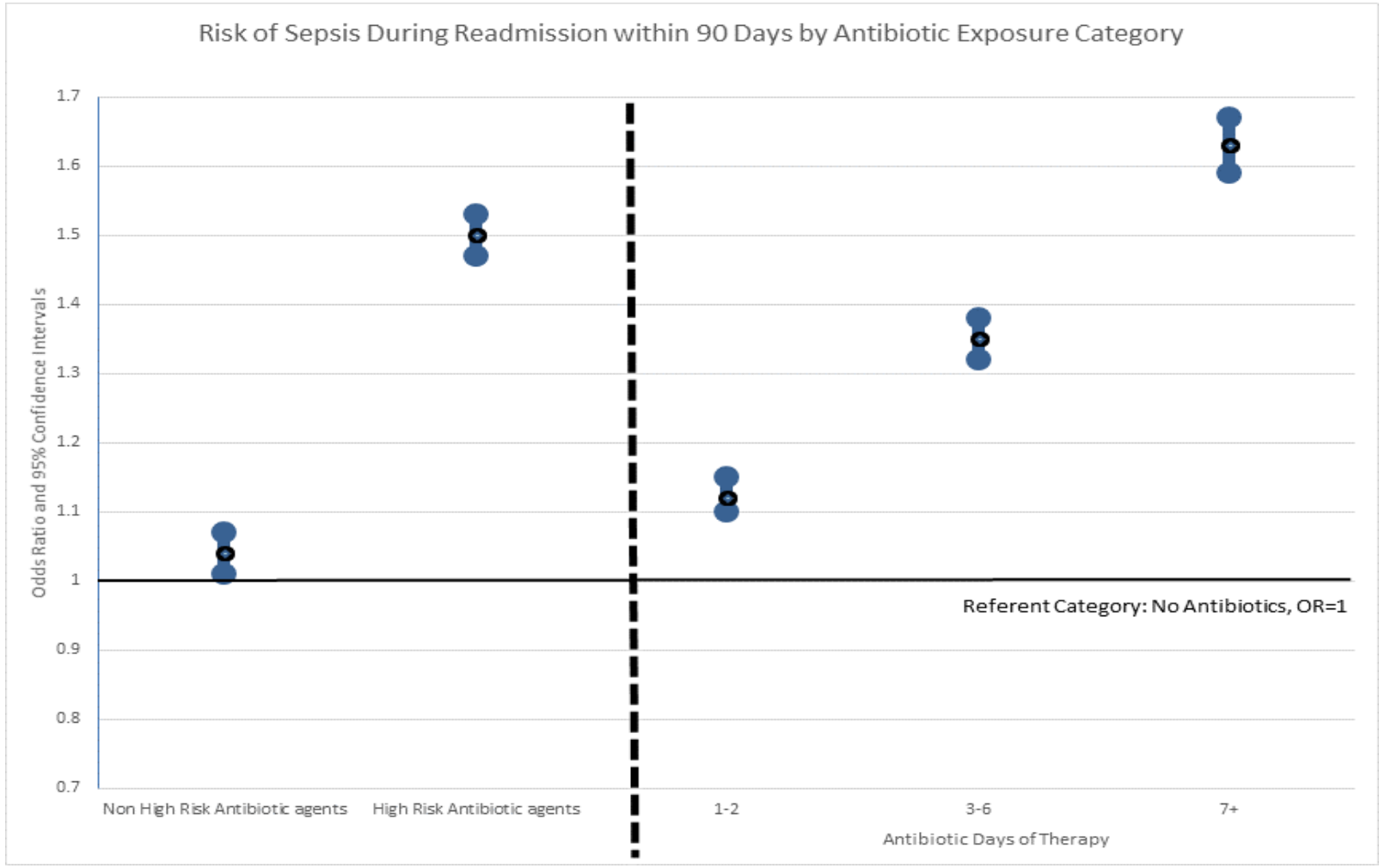
- fizioterapija!
- psiholog
- odpust v ustrezno okolje
- zdravila ob odpustu!
- razlaga bolezni in njenih dolgoročnih posledic bolniku in svojcem
- starejši bolniki + številne osnovne bolezni - pogovor o ponovnem intenzivnem zdravljenju

Rešitve - doma

Primarna preventiva:

- skrb za ustrezno vodenje osnovnih bolezni
- cepljenje (gripa, pnevmokok)
- higienski ukrepi
- antibiotična zaščita ob posegih (kadar je indicirana)
- osveščanje javnosti o sepsi in posledicah

Skrajšati čas protimikrobnega zdravljenja – vpliv na črevesno mikrobioto (disbioza)!



„high risk“ antibiotiki:

- 3. in 4. generacija cefalosporinov
- kinoloni
- beta laktam/zaviralec beta laktamaze
- karbapenemi
- vankomicin per os

Baggs J et al. https://idsa.confex.com/idsa/2016/webprogram/Paper58587.html

Imunomodulatorno zdravljenje?

- granulocite stimulirajoči rastni dejavniki (GM-CSF)
  - stimulira nastajanje nevtrofilcev, makrofagov, monocitov
  - visoko učinkovit pri preprečevanju sepse pri nevtropeničnih bolnikih
  - imunsko neoslabljeni – brez razlik v 28-dnevni smrtnosti – dolgoročno?
- IFN-γ
  - ključni aktivator makrofagov
  - reaktivacija anergičnih monocitov
- rekombinantni humani IL3, IL7, IL 15
  - zmanjšajo apoptozo limfocitov, povečajo limfopoezo
- pogoj: individualiziran pristop in ocena imunosupresije

Zaključki

- pozni zapleti sepse lahko pomembno poslabšajo bolnikovo življenje po odpustu iz bolnišnice
- podatki o poznih zapletih pri bolnikih s sepso so stari – trenutna situacija?
- zavedanje in preventivni ukrepi