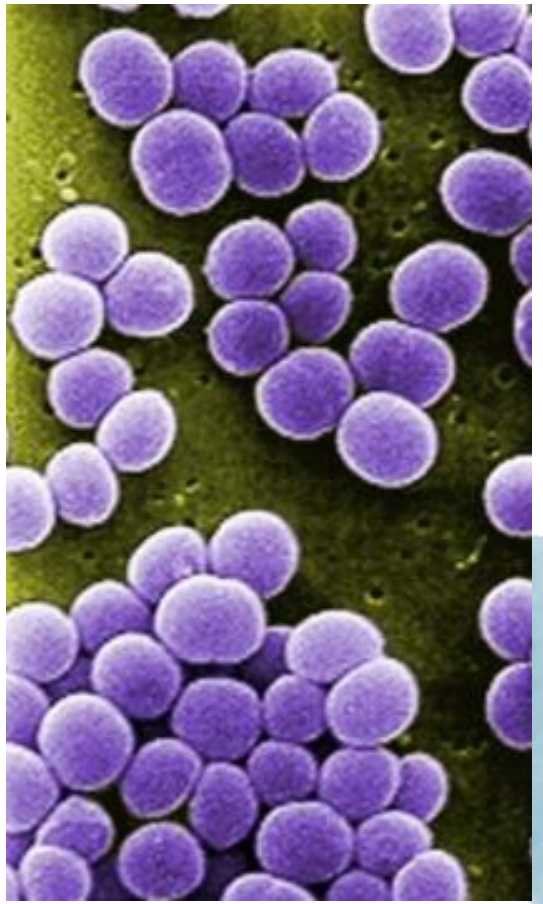
STAFILOKOKNA BAKTERIEMIJA - novosti

Manja Kordiš, dr.med.

26.6.2025

S.aureus bakteriemija



- Invazivna okužba
- Heterogena patologija
- Peristentna bakteriemija
- Metastatska okužba v 1/3
- Visoka smrtnost (15-30%), 300.000 smrti/leto

- Stare smernice, obravnava neenotna

JAMA | Review

Management of *Staphylococcus aureus* Bacteremia
A Review

April, 2025

Persistentna bakteriemija

- definicija: 2-4 dni?
- 90-dnevna smrtnost: 39% v. 22%
- Večje tveganje za novi metastaski fokus (1 dan: 6%, 2-4 dni:10 %, 5-7 dni: 22%)
- Kontrolne HK do negativizacije

Nezapletena bakteriemija (glede na IDSA)

- Izključitev endokarditisa,
- Brez umetnih materialov,
- Kontrolne HK po 2-4 dneh negativne,
- Brez vročine po 72h,
- Brez znakov metastatske okužbe

30%

Doma pridobljena (< 48h od sprejema), večje tveganje za zapleteno okužbo

JAMA | Review

Management of *Staphylococcus aureus* Bacteremia
A Review

Diagnostika metastatske okužbe

- Izključitev endokarditisa (12%)
  - TTE vsem, TEE glede na dejavnike tveganja
  - VIRSTA score <3

- MR
- CT
- PET-CT

} glede na klinično sliko /potek zdravljenja

Table 1. VIRSTA Score to Determine Priority of Transesophageal Echocardiography in Patients With *Staphylococcus aureus* Bacteremia

Clinical condition	Weight
Cerebral or peripheral emboli	5
Meningitis	5
Permanent intracardiac device or previous infective endocarditis	4
Intravenous drug use	4
Preexisting native valve disease	3
Persistent bacteremia (defined as positive follow-up blood culture result obtained 48 h after initial positive blood culture)	3
Vertebral osteomyelitis	2
Community or nonnosocomial health care–associated acquisition	2
Severe sepsis or shock	1
C-reactive protein >190 mg/L	1

Adapted from Tubiana et al, 2016.[37]

JAMA | Review

Management of *Staphylococcus aureus* Bacteremia
A Review

April, 2025

Table 2. Directed Intravenous Antibiotic Treatment Options for Patients With *Staphylococcus aureus* Bacteremia[a]

Drug	Recommended dose	Considerations	Common adverse effects (1%-10% incidence)
For methicillin-susceptible *S aureus*[b]			
Cefazolin	2 g every 8 h	Use 2 g every 6 h for critically unwell patients; may be used in most cases of nonsevere penicillin allergy Cefazolin associated with less toxicity and lower mortality than antistaphylococcal penicillins in observational studies	Gastrointestinal (diarrhea, nausea, vomiting)
Flucloxacillin	2 g every 6 h	Use 2 g every 4 h for critically unwell patients and for infective endocarditis	Gastrointestinal (diarrhea, nausea, vomiting), local injection site thrombophlebitis, acute kidney toxicity, drug allergy
Cloxacillin	2 g every 4 h		
Nafcillin	2 g every 4 h		
Oxacillin	2 g every 4 h		
Benzylpenicillin	2.4 g (4 million U) every 4 h	Only for *S aureus* isolates phenotypically confirmed as penicillin-susceptible with disk diffusion testing	Drug allergy

+ SOURCE CONTROL!

Trajanje zdravljenja?

Nezapletena: 2 tedna

Zapletena: 4-6 tednov

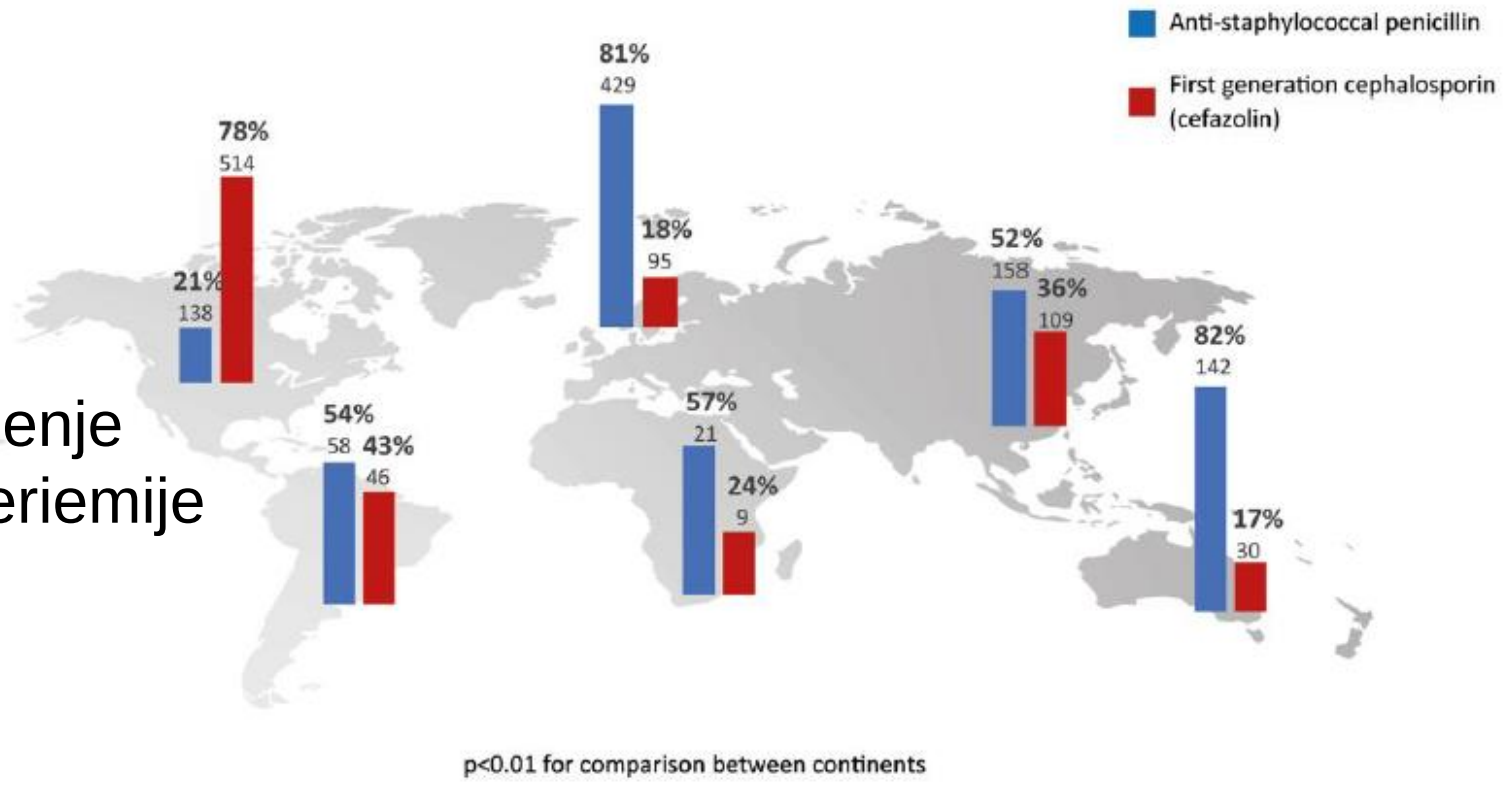
Terapija izbora pri MSSA?

Clinical Infectious Diseases
MAJOR ARTICLE

Global Differences in the Management of *Staphylococcus aureus* Bacteremia: No International Standard of Care

Annette C. Westgeest,[1,2] David T. P. Buis,[3] Kim C. E. Sigaloff,[3] Felicia Ruffin,[1] Leo G. Visser,[2] Yunsong Yu,[4] Emile F. Schippers,[2,5] Merel M. C. Lambregts,[2] Steven Y. C. Tong,[6,7] Mark G. J. de Boer,[2,8] and Vance G. Fowler Jr [1,9]

- **Razlike v terapiji izbora**
- Dodatek rifampicina
- Uporaba PET-CT
- Prehod na peroralno zdravljenje
- Definicija persistentne bakteriemije



Cefazolin- pomisleki pri uporabi

“Inoculum Effect”

- → Posledica penicilinaze (blaZ gen)
- → Okužbe z visokim bakterijskim bremenom (IE?)
- → V raziskavi prisoten pri 54.5%
- → Višja smrtnost?
  - → Pregledni članek JAC- Antimicrobial Resistance, Feb 2024¸23 raziskav: ni dokazov, testiranje se ne priporoča

Okužbe osrednjega živčevja

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Antibiotic Myths for the Infectious Diseases Clinician

Erin K. McCreary,[1] Melissa D. Johnson,[2] Travis M. Jones,[2] S. Shaefer Spires,[2] Angelina E. Davis,[2] April P. Dyer,[2] Elizabeth Dodds Ashley,[2] and Jason C. Gallagher[3]

Ni dovolj podatkov,
ne kot terapija izbora

PSP ali cefazolin?

SYSTEMATIC REVIEW · Articles in Press, May 09, 2025 · ***Open Access***

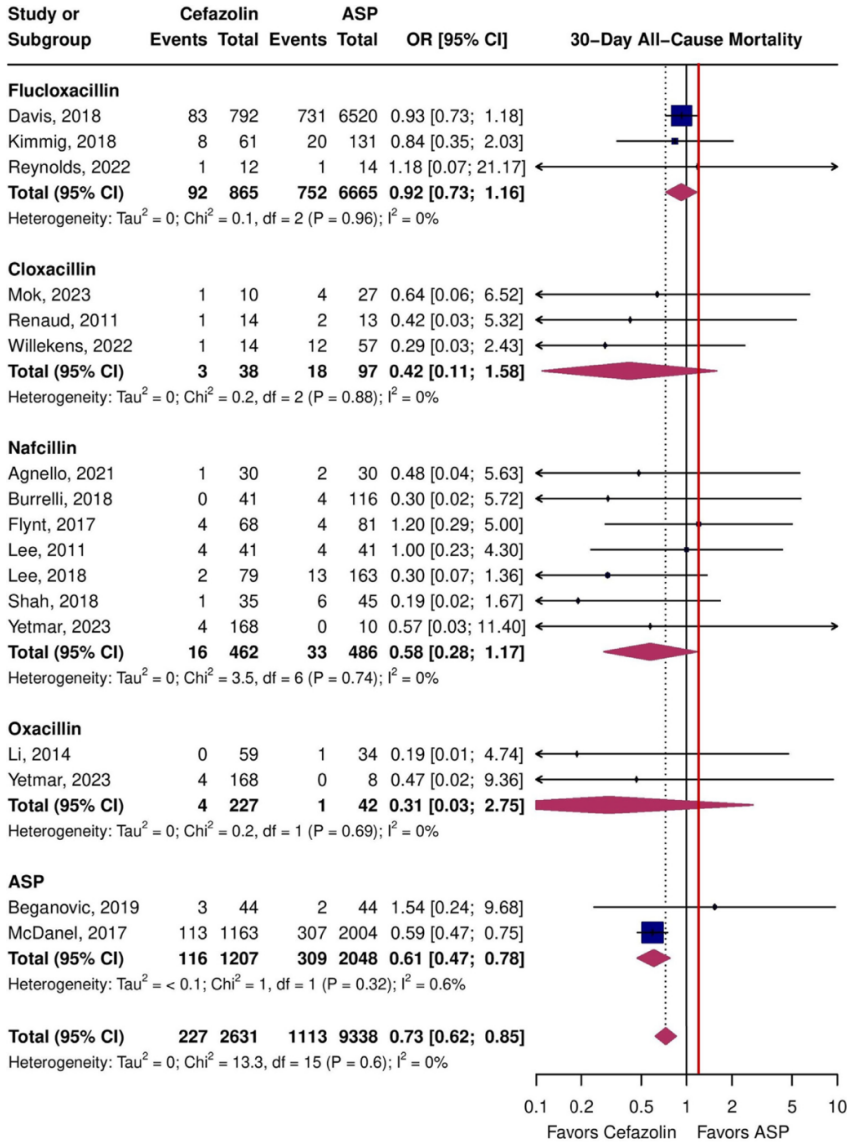
Cefazolin vs. antistaphylococcal penicillins for the treatment of methicillin-susceptible *Staphylococcus aureus* bacteraemia: a systematic review and meta-analysis

Connor Prosty [1),2)] · Dean Noutsios [1)] · Todd C. Lee [2),3),4)] · ... · Steven Y.C. Tong [17),18)] · Sean W.X. Ong [5),6),17),18)] o
Staphylococcus aureus Network Adaptive Platform MSSA/PSSA domain specific working group ... Show more

CMI CLINICAL MICROBIOLOGY AND INFECTION
ESCMID

Zaključki:

- Cefazolin neinferioren, 30-dnevna smrtnost nižja (RO 0.78)
- Cefazolin manj stranskih učinkov (11% v. 23.5%)
  - 7x manj prekinitev zdravljenja zaradi stranskih učinkov (2.1% v. 16.8%)
  - 3x manj nefrotoksičnosti (4.4 % v. 13.7%)



PSP ali cefazolin?

S.aureus Network Adaptive Platform (SNAP)

- Največja raziskava *S.aureus* bakteriemije
- Novi pristop pri raziskavi
- Več domen, sočasno odgovor na več vprašanj
- Malo izključitvenih kriterijev

	Domain		
Silo	**Backbone antibiotic**	**Adjunctive antibiotic**	**Early oral switch**
PSSA	(Flu)cloxacillin vs penicillin	No clindamycin vs clindamycin	Continued IV vs early oral switch at either day 7 (uncomplicated disease) or day 14 (complicated disease)
MSSA	(Flu)cloxacillin vs cefazolin		
MRSA	(Vancomycin/ daptomycin) vs (Vancomycin/ daptomycin) + cefazolin		

PSP ali cefazolin?

S.aureus Network Adaptive Platform (SNAP)

- N= 1341
- Cefazolin neinferioren PSP pri 90-dnevni smrtnosti: **15%** v. **17%**
- Menjava terapije zaradi stranskih učinkov: cefazolin **1.6%** v. PSP **9.1 %**
- Manj ALO pri cefazolinu: **13.7%** v. **19.1%**

PSSA- penicilin ali PSP?

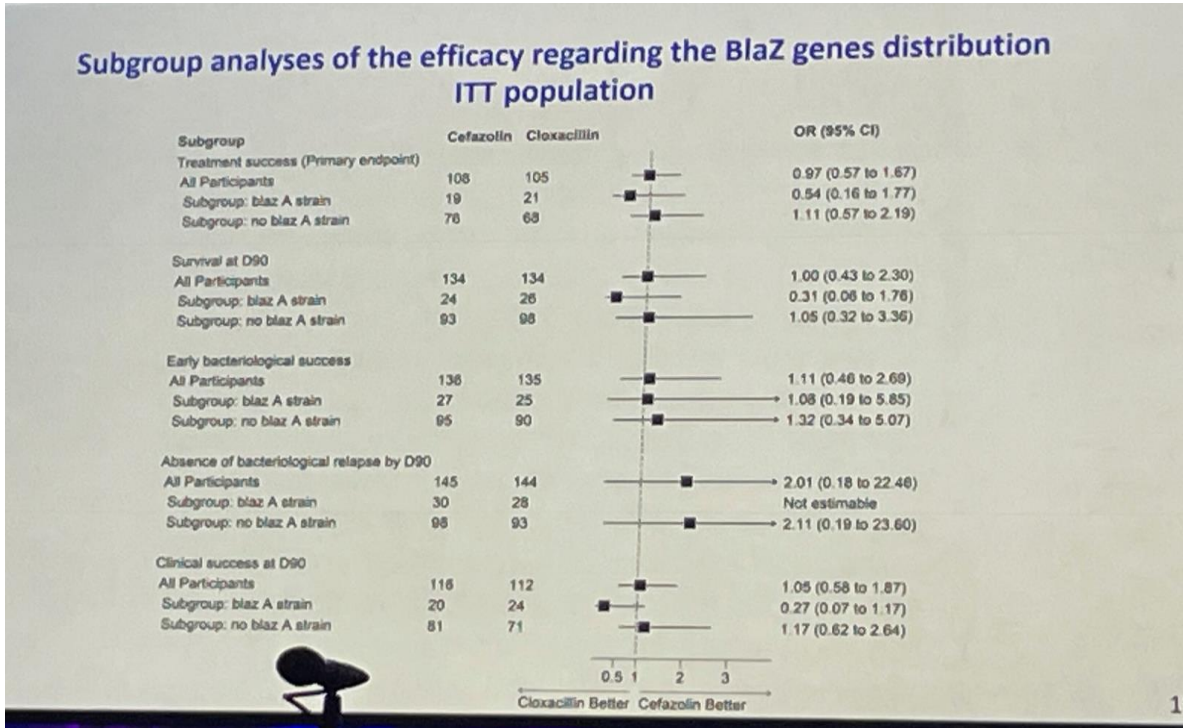
- Penicilin neinferioren PSP
  90-dnevna smrtnost: **13.8%** v. **21.5%**
  - trend k superiornosti

- Bistveno manj ALO (**21.6%** v **10.9%)**

- Testiranje občutljivosti na penicilin zanesljivo

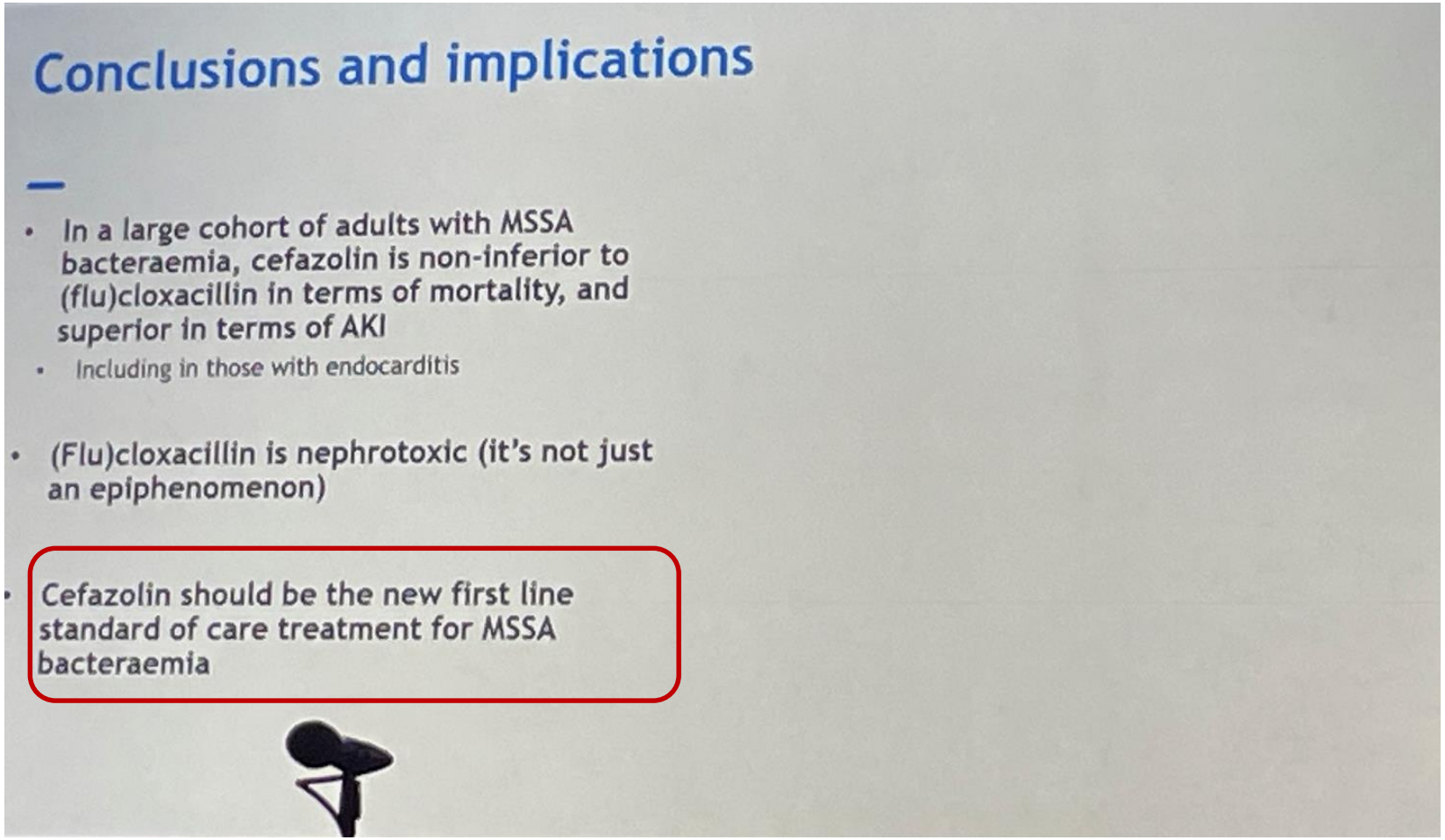
CloCeBa

- RCT, Francija
- kloksacilin v. cefazolin pri MSSA bakteriemiji (ne OŽ ali endovaskularni vsadek)
  a. Učinkovitost in varnost
  b. Epidemiologija blaZ beta-laktamaz
  c. Vpliv na intestinalno mikrobioto



ESCMID 2025

Zaključek ESCMID 2025



EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Guidance Document on Cephalosporins for *Staphylococcus aureus* Infection

24 February 2025

A recent EUCAST review of the pharmacokinetics and pharmacodynamics of the intravenous agents and subsequent consultation showed efficacy against wild-type *S. aureus* could be achieved with high-dosages of cefazolin (2 g x 3 iv), cefotaxime (2 g x 3-4 iv), and cefepime (2 g x 3 iv), but not with the highest dosages of ceftriaxone (2 g x 2 iv or 4 g x 1 iv) [See Appendix]. In the hollow fibre model, using a single strain of MSSA with a modal

IV cefalosporini pri bakteriemiji:

Cefazolin ✓

Cefuroksim ✗

Cefotaksim ✓

Ceftriakson ✓

Cefepim ✓

Terapija izbora pri MRSA?

IDSA smernice, 2011

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children

FREE

Catherine Liu , Arnold Bayer , Sara E. Cosgrove , Robert S. Daum , Scott K. Fridkin ,

Britanske smernice, 2021

JAC Antimicrob Resist
doi:10.1093/jacamr/dlaa114

JAC-Antimicrobial Resistance

Treatment of methicillin-resistant *Staphylococcus aureus* (MRSA): updated guidelines from the UK

Nicholas M. Brown[1]*, Anna L. Goodman[2,3], Carolyne Horner[4], Abi Jenkins[4] and Erwin M. Brown[4]

[1]*Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK;* [2]*Guy's and St Thomas' NHS Foundation Trust, London, UK;* [3]*MRC Clinical Trials Unit, University College London, London, UK;* [4]*British Society for Antimicrobial Chemotherapy, Birmingham, UK*

JAMA, 2025

For methicillin-resistant *S aureus*			
Vancomycin	Loading dose of 20-35 mg/kg (maximum, 3 g), then 15-20 mg/kg (maximum, 2 g) every 12 h[c]	AUC-guided dosing is recommended, aiming for an AUC of 400-600[d] When trough level-guided dosing is used, levels of 15-20 mg/L are effective but associated with increased kidney toxicity[d]	Vancomycin infusion reaction, acute kidney toxicity, ototoxicity
Daptomycin	6-10 mg/kg once daily	FDA-approved dose is 6 mg/kg once daily; however, many clinicians favor higher dosing of 8 to 10 mg/kg once daily because daptomycin exhibits concentration-dependent killing Do not use for methicillin-resistant *S aureus* pneumonia	Creatinine kinase elevation; eosinophilic pneumonia
Ceftobiprole	500 mg every 6 h for 8 d, then 500 mg every 8 h		Gastrointestinal (diarrhea, nausea, vomiting)

Izvid

Vzorec: **Kri - gojišče BACTEC - II. Periferna vena** (Odvzeto 08.04.2024 ob 13:15)

V direktnem preparatu iz pozitivne hemokulture, obarvanem po Gramu, smo videli po Gramu pozitivne koke v skupinah.

Aerobna hemokultura

Rezultat 1. *Staphylococcus aureus* - MRSA

V direktnem preparatu iz pozitivne hemokulture, obarvanem po Gramu, smo videli po Gramu pozitivne koke v skupinah.

Anaerobna hemokultura

Rezultat 2. *Staphylococcus aureus* - MRSA

Za pravilno interpretacijo rezultatov antibiograma je potrebno upoštevati komentarje pod tabelo in poznati osnovne opredelitve EUCAST.

	2.
penicilin	R
oksacilin	R
vankomicin	S 2
teikoplanin	S 1
gentamicin	(S)
eritromicin	R
klindamicin	R
tetraciklin	S
ciprofloksacin	R
trimetoprim+sulfametoksazol	S
rifampin	S
linezolid	S
mupirocin	S

Kaj bi uporabili?

S.aureus bakteriemija

UKC Ljubljana, 1.1.2024- 1.1.2025

- n= 192
- PSSA= 32 (17%)
- MRSA= 10/192 (5%)
  - → smrtnost: 5/10 (50%)
  - → MIC vanko 2 = 5/10 (50%)

1 smrt
3 najprej vankomicin, nato daptomicin
1 + kontrolne hemokulture

S.aureus; EUCAST clinical breakpoints, 1.1.2025

Glycopeptides and lipoglycopeptides[1]	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
Dalbavancin[2]	0.25[3]	0.25[3]			Note[A]	Note[A]		**1.** Glycopeptide MICs are method dependent and should be determined by broth microdilution (ISO standard 20776-1).
Oritavancin[2], *S. aureus*	0.125[3]	0.125[3]			Note[A]	Note[A]		*S. aureus* with vancomycin MIC values of 2 mg/L are on the border of the wild-type distribution and there may be an impaired clinical response.
Teicoplanin[2], *S. aureus*	2	2			Note[A]	Note[A]		~~**2.** Resistant isolates are rare or not yet reported. The identification and antimicrobial susceptibility test result on any such~~ isolate must be confirmed and the isolate sent to a reference laboratory.
Teicoplanin, Coagulase-negative staphylococci	4	4			Note[A]	Note[A]		**3.** MICs must be determined in the presence of polysorbate-80 (0.002% in the medium for broth dilution methods; agar dilution methods have not been validated). Follow the manufacturers' instructions for commercial systems.
Telavancin[2], MRSA	0.125[3]	0.125[3]			Note[A]	Note[A]		~~**4.** Coagulase-negative staphylococci susceptible to both vancomycin and teicoplanin can be reported susceptible to dalbavancin.~~
Vancomycin[2], *S. aureus*	2	2			Note[A]	Note[A]		~~**5.** *S. aureus* isolates susceptible to vancomycin can be reported susceptible to dalbavancin and oritavancin.~~
Vancomycin[2], Coagulase-negative staphylococci	4	4			Note[A]	Note[A]		~~**6.** MRSA isolates susceptible to vancomycin can be reported susceptible to telavancin.~~
								A. Disk diffusion is unreliable and cannot distinguish between wild-type isolates and those with non-*vanA*-mediated glycopeptide resistance.

Metode testiranja občutljivosti:

- mikrodilucija (zlati standard)
- Etest
- avtomatizirane metode (Vitek)

visoka vrednost:

≥ 1.5 mg/L

Vankomicin "MIC creep" po letu 2000

JOURNAL ARTICLE

Vancomycin MIC creep in non-vancomycin-intermediate *Staphylococcus aureus* (VISA), vancomycin-susceptible clinical methicillin-resistant *S. aureus* (MRSA) blood isolates from 2001–05 Get access >

Gregory Steinkraus ✉ , Roger White , Lawrence Friedrich

Journal of Antimicrobial Chemotherapy, Volume 60, Issue 4, October 2007, Pages 788–794,

Razlike v raziskavah:
- lokacija,
- metoda testiranja,
- MSSA/MRSA,
- mesto okužbe.

Ni prepričljivih dokazov za "MIC creep"

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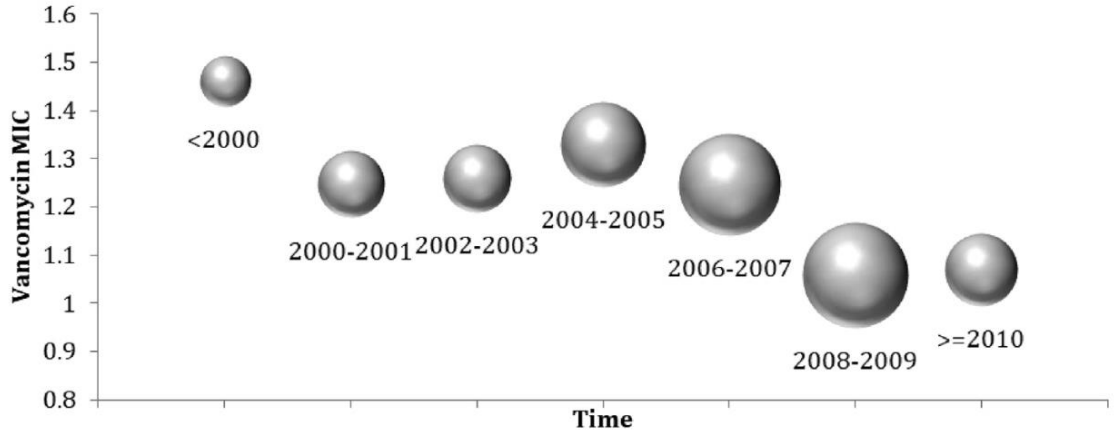

Fig. 2. Pooled mean of vancomycin MIC determined by the broth microdilution method over time. The bubble size represents the meta-analysis sub-group weight.

Diaz et al. CMI 2018.

Raznoliki rezultati vpliva VAN-MIK na uspeh zdravljenja.

VPLIV JE…

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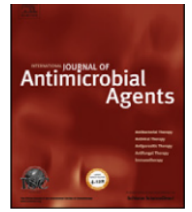


Review

Impact of vancomycin minimum inhibitory concentration on clinical outcomes of patients with vancomycin-susceptible *Staphylococcus aureus* infections: a meta-analysis and meta-regression

Michael N. Mavros[a,b], Giannoula S. Tansarli[a], Konstantinos Z. Vardakas[a,c], Petros I. Rafailidis[a,d], Drosos E. Karageorgopoulos[a,e], Matthew E. Falagas[a,c,f,*]

- Meta-analiza 33 raziskav (>5000)
- Zaključek: skupina z visokim VAN-MIK ima 1.2 x višjo umrljivost, 1.7x višji neuspeh zdravljenja
- Pomanjkljivost: vpliv drugih dejavnikov

...VPLIVA NI

- prospektivna raziskava, n=1027, invazivna *S.aureus* okužba (66% MRSA)

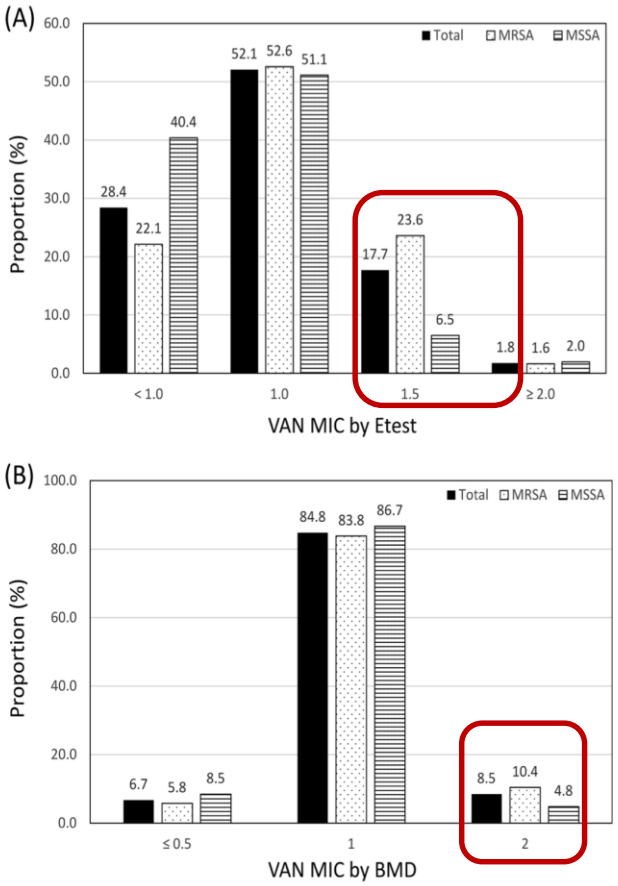


TABLE 2 All-cause 30-day mortality rates of patients with invasive *Staphylococcus aureus* infections according to vancomycin MIC and patient subgroup[a]

MIC methodology subgroup	Mortality rate (no. of 30-day mortality cases/total no. of patients)	Etest			Broth microdilution		
		Low MIC	High MIC	*P* value	Low MIC	High MIC	*P* value
Total	27.4 (281/1,027)	26.7 (221/827)	30.0 (60/200)	0.351	26.7 (251/940)	34.5 (30/87)	0.119
MRSA infection	29.4 (198/673)	28.4 (143/503)	32.4 (55/170)	0.332	28.7 (173/603)	35.7 (25/70)	0.222
MSSA infection	23.4 (83/354)	24.1 (78/324)	16.7 (5/30)	0.360	23.1 (78/337)	29.4 (5/17)	0.561
Bloodstream infection	28.6 (272/950)	28.2 (216/766)	30.4 (56/184)	0.547	28.0 (244/870)	35.0 (28/80)	0.188
MRSA infection	30.7 (189/616)	30.1 (138/459)	32.5 (51/157)	0.571	30.1 (166/551)	35.4 (23/65)	0.385
MSSA infection	24.9 (83/334)	25.4 (78/307)	18.5 (5/27)	0.427	24.5 (78/319)	33.3 (5/15)	0.540

[a]High vancomycin MIC was defined as ≥1.5 mg/liter. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*. Values in MIC columns are mortality rates (no. of 30-day mortality cases/total no. of patients).

- van-MIK ≥1.5 mg/L ni povezan z 30-dnevno smrtnostjo

Multivariatna analiza, vpliv na 30-dnevno smrtnostjo:

- metastatska okužba, bakteriemija, starost, huda sepsa/šok, huda pridružena bolezen, imunosupresivna terapija, MRSA

Povzetek raziskav

- rezultati raznoliki
- vpliv metode testiranja
- vpliv drugih dejavnikov bolj pomemben (metastatska okužba, nerazrešen fokus, nivoji vankomicina, pridružene bolezni)
- vpliv pri okužbah z visokim bremenom, npr. IE?

IX. How should results of vancomycin susceptibility testing be used to guide therapy?

69. For isolates with a vancomycin minimum inhibitory concentration (MIC) ≤2 μg/mL (eg, susceptible according to Clinical and Laboratory Standards Institute [CLSI] breakpoints), the patient's clinical response should determine the continued use of vancomycin, independent of the MIC **(A-III).**

IDSA 2011

Peroralno zdravljenje

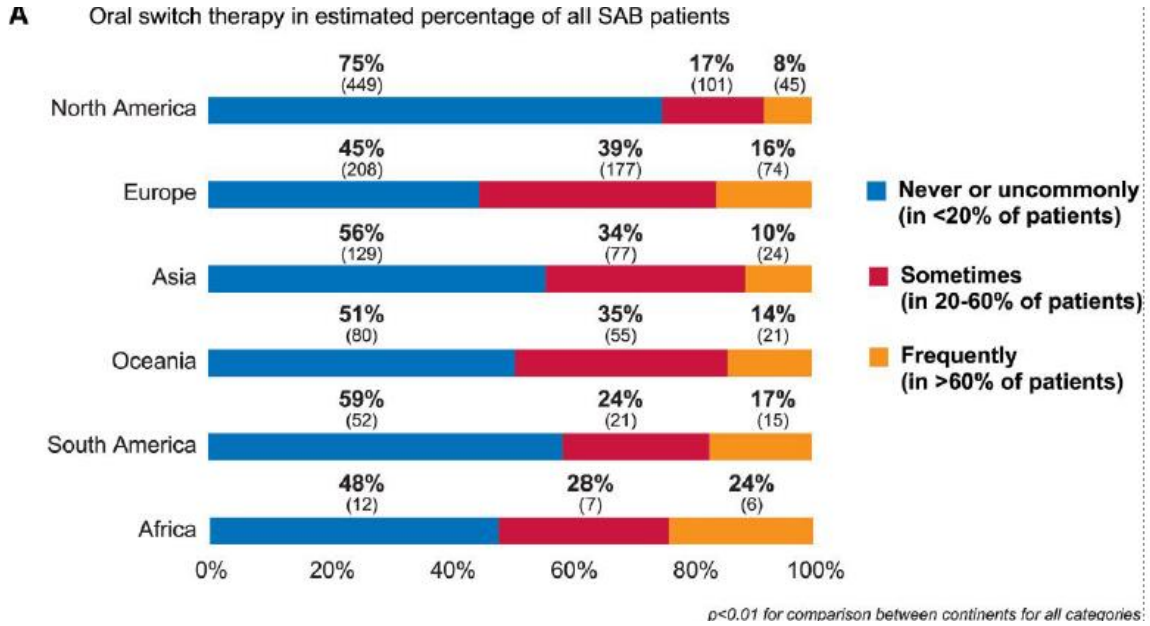
POET trial, NEJM 2019

- N=400, levostranski IE, PO v IV terapija, vsaj 10 dni iv terapije, klinično stabilni
- PO kombinacija dveh antibiotikov
- MSSA: 87 oseb→ smrtnost, nepredvidena KV operacija, embolizacija, relaps bakteriemije: **IV 7.5%** vs **PO 6.4%**

SABATO trial, Lancet ID 2024

- Multicentrična raziskava, 31 centrov, RCT
- delno zdravljenje nezapletene bakteriemije PO (PO po 5-7 dneh vs IV 14 dni)
- TMP/SMX, klindamicin, linezolid
- N= 213 (od 5063)→ ponovitev bakteriemije, smrtnost po 90 dneh: **IV 12% v. PO 13%**

Razlike v prehodu na peroralno terapijo



CID, 2023

- Najmanj prehoda na po zdravljenje v ZDA (MRSA, OPAT)

Kombinirana terapija

- **Ni dokazov za boljši klinični izhod, lahko skrajša trajanje bakteriemije**
  + fosfomicin
  + daptomicin
  + BL (predvsem ceftarolin) pri MRSA

- **Stranski učinki**
  CAMERA 2 študija: vpliv kombinirane terapije vankomicina/daptomicina z BL na 90 dnevno smrtnost → predčasno zaključena zaradi stranskih učinkov!

- **Persistentna bakteriemija (30%)**
  Cefazolin+ ertapenem
  MRSA: vankomicin/daptomicin+ cefazolin/fosfomicin/ceftarolin, ceftobiprole

Zaključek

- Razlike v obravnavi *S.aureus* bakteriemije, potrebne smernice
- Ali bi morali spremeniti terapijo izbora pri zdravljenju MSSA bakteriemije? (PSP, cefazolin, penicilin)
- Vloga VAN-MIK 2 pri zdravljenju MRSA bakteriemije?
- Vloga peroralne terapije?
- Vloga kombinirane terapije?

Hvala za pozornost!

Cephalosporins	Standard dosage	High dosage	Uncomplicated UTI	Special situations
Cefaclor	0.25-0.5 g x 3 oral depending on species and/or infection type	1 g x 3 oral		***Staphylococcus* spp.:** Minimum dose 0.5 g x 3 oral
Cefadroxil	0.5-1 g x 2 oral	None	0.5-1 g x 2 oral	
Cefalexin	0.25-1 g x 2-3 oral	None	0.25-1 g x 2-3 oral	
Cefazolin	1 g x 3 iv	2 g x 3 iv		
Cefepime	1 g x 3 iv or 2 g x 2 iv	2 g x 3 iv		
Cefiderocol	2 g x 3 iv over 3 hours	None		
Cefixime	0.2-0.4 g x 2 oral	None	0.2-0.4 g x 2 oral	**Uncomplicated gonorrhoea:** 0.4 g oral as a single dose
Cefotaxime	1 g x 3 iv	2 g x 3 iv		**Meningitis:** 2 g x 4 iv ***S. aureus:*** High dose only
Cefpodoxime	0.1-0.2 g x 2 oral	None	0.1-0.2 g x 2 oral	
Ceftaroline	0.6 g x 2 iv over 1 hour	0.6 g x 3 iv over 2 hours		***S. aureus* in complicated skin and skin structure infections:** There is some PK-PD evidence to suggest that isolates with MICs of 4 mg/L could be treated with high dose.
Ceftazidime	1 g x 3 iv	2 g x 3 iv or 1 g x 6 iv		
Ceftazidime-avibactam	(2 g ceftazidime + 0.5 g avibactam) x 3 iv over 2 hours			
Ceftibuten	0.4 g x 1 oral	None		
Ceftobiprole	0.5 g x 3 iv over 2 hours	None		
Ceftolozane-tazobactam (intra-abdominal infections and UTI)	(1 g ceftolozane + 0.5 g tazobactam) x 3 iv over 1 hour	None		
Ceftolozane-tazobactam (hospital acquired pneumonia, including ventilator associated pneumonia)	(2 g ceftolozane + 1 g tazobactam) x 3 iv over 1 hour	None		
Ceftriaxone	2 g x 1 iv	2 g x 2 iv or 4 g x 1 iv		**Meningitis:** 2 g x 2 iv or 4 g x 1 iv ***S. aureus:*** High dose only **Uncomplicated gonorrhoea:** 0.5-1 g im as a single dose
Cefuroxime iv	0.75 g x 3 iv	1.5 g x 3 iv		
Cefuroxime oral	0.25 g x 2 oral	0.5 g x 2 oral	0.25 g x 2 oral	