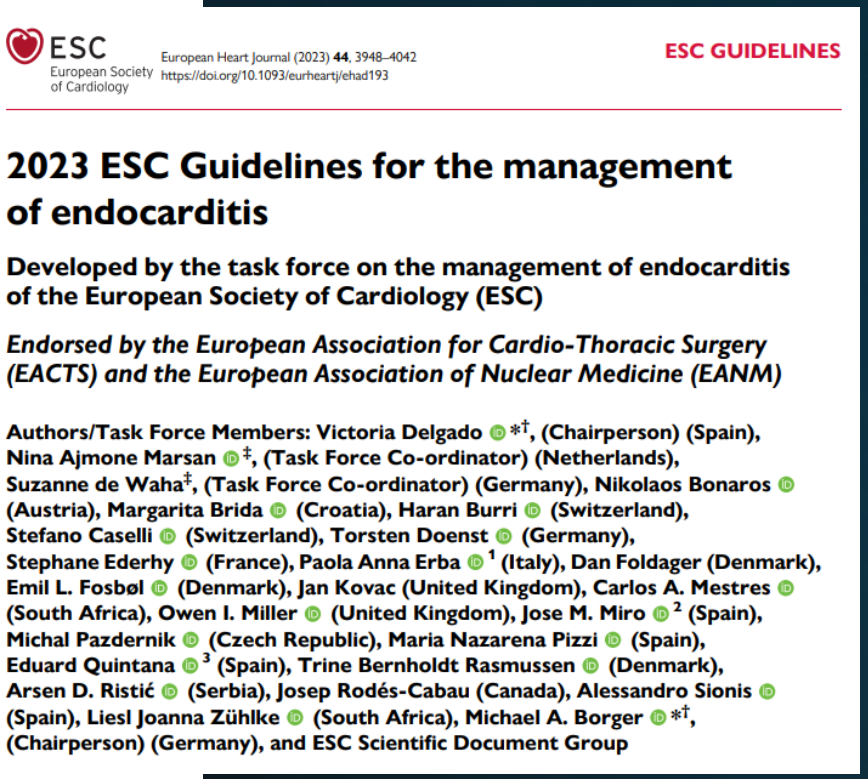
Využití fosfomycinu v léčbě infekční endokarditidy

A. Myjavec[1], P. Paterová[2], Z. Turek[3], J. Střítеská[3], J. Samek[3]

[1]Kardiochirurgická klinika FN a LF UK v Hradci Králové,
[2]Ústav klinické mikrobiologie FN a LF UK v Hradci Králové
[3]KARIM FN a LF UK v Hradci Králové

Infekční endokarditida

- Odhadovaná incidence onemocnění v roce 2019: 13,8 případů na 100 000 obyvatel
- Vysoká mortalita a morbidita postižených pacientů
- Celosvětově příčina 66 300 úmrtí pacientů
- Základní pilíře léčby: antibiotika a kardiochirurgie



ESC European Society of Cardiology

European Heart Journal (2023) **44**, 3948–4042
https://doi.org/10.1093/eurheartj/ehad193

ESC GUIDELINES

2023 ESC Guidelines for the management of endocarditis

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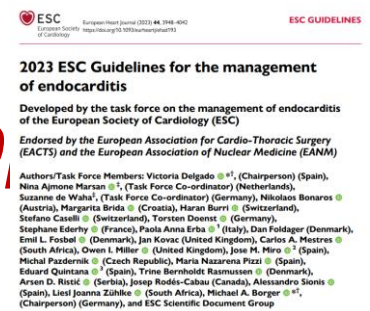
Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Nuclear Medicine (EANM)

Authors/Task Force Members: Victoria Delgado *†, (Chairperson) (Spain), Nina Ajmone Marsan ‡, (Task Force Co-ordinator) (Netherlands), Suzanne de Waha‡, (Task Force Co-ordinator) (Germany), Nikolaos Bonaros (Austria), Margarita Brida (Croatia), Haran Burri (Switzerland), Stefano Caselli (Switzerland), Torsten Doenst (Germany), Stephane Ederhy (France), Paola Anna Erba [1] (Italy), Dan Foldager (Denmark), Emil L. Fosbøl (Denmark), Jan Kovac (United Kingdom), Carlos A. Mestres (South Africa), Owen I. Miller (United Kingdom), Jose M. Miro [2] (Spain), Michal Pazdernik (Czech Republic), Maria Nazarena Pizzi (Spain), Eduard Quintana [3] (Spain), Trine Bernholdt Rasmussen (Denmark), Arsen D. Ristić (Serbia), Josep Rodés-Cabau (Canada), Alessandro Sionis (Spain), Liesl Joanna Zühlke (South Africa), Michael A. Borger *†, (Chairperson) (Germany), and ESC Scientific Document Group

Doporučení pro antibiotickou léčbu infekční endokarditidy způsobené *Staphylococcus sp.*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Recommendations		Class[a]	Level[b]
IE caused by methicillin-susceptible staphylococci			
In patients with NVE due to methicillin-susceptible staphylococci, (flu)cloxacillin or cefazolin is recommended for 4–6 weeks using the following doses:[264,314,316–318]		I	B
Adult antibiotic dosage and route			
(Flu)cloxacillin[c]	12 g/day i.v. in 4–6 doses		
Cefazolin[e]	6 g/day i.v. in 3 doses		
Paediatric antibiotic dosage and route			
(Flu)cloxacillin[c]	200–300 mg/kg/day i.v. in 4–6 equally divided doses		
Cefazolin[e]	300–600 mg/kg/day in 3–4 doses		
In patients with PVE due to methicillin-susceptible staphylococci, (flu)cloxacillin or cefazolin with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:[264,314,316–318,320]		I	B
Adult antibiotic dosage and route			
(Flu)cloxacillin[c]	12 g/day i.v. in 4–6 doses		
Cefazolin	6 g/day i.v. in 3 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
(Flu)cloxacillin[c]	200–300 mg/kg/day i.v. in 4–6 equally divided doses		
Cefazolin	300–600 mg/kg/day in 3–4 doses		
Rifampin	20 mg/kg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Allergy to beta-lactams			
In patients with NVE due to methicillin-susceptible staphylococci who are allergic to penicillin, cefazolin for 4–6 weeks is recommended using the following doses:[322–327]		I	B
Adult antibiotic dosage and route			
Cefazolin[e]	6 g/day i.v. in 3 doses		
Paediatric antibiotic dosage and route			
Cefazolin[e]	300–600 mg/kg/day in 3–4 doses		
In patients with PVE due to methicillin-susceptible staphylococci who are allergic to penicillin, cefazolin combined with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:[344]		I	B
Adult antibiotic dosage and route			
Cefazolin[e]	6 g/day i.v. in 3 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
Cefazolin[e]	300–600 mg/kg/day in 3–4 doses		
Rifampin	20 mg/kg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
In patients with NVE due to methicillin-susceptible staphylococci who are allergic to penicillin, daptomycin combined with ceftaroline or fosfomycin may be considered.[322–327]		IIb	C
Adult antibiotic dosage and route			
Daptomycin	10 mg/kg/day i.v. in 1 dose		
Ceftaroline[f]	1800 mg/day i.v. in 3 doses		
OR	OR		
Fosfomycin[g]	8–12 g/day i.v. in 4 doses		
In patients with PVE due to methicillin-susceptible staphylococci who are allergic to penicillin, daptomycin combined with ceftaroline or fosfomycin or gentamicin with rifampin for at least 6 weeks and gentamicin for 2 weeks may be considered using the following doses:[344]		IIb	C
Adult antibiotic dosage and route			
Daptomycin	10 mg/kg/day i.v. in 1 dose		
Ceftaroline[f]	1800 mg/day i.v. in 3 doses		
OR	OR		
Fosfomycin[g]	8–12 g/day i.v. in 4 doses		
Rifampin	900 mg/day i.v. or orally in 3 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
IE caused by methicillin-resistant staphylococci			
In patients with NVE due to methicillin-resistant staphylococci, vancomycin is recommended for 4–6 weeks using the following doses:[345]		I	B
Adult antibiotic dosage and route			
Vancomycin[h]	30–60 mg/kg/day i.v. in 2–3 doses		
Paediatric antibiotic dosage and route			
Vancomycin[h]	30 mg/kg/day i.v. in 2–3 equally divided doses		
In patients with PVE due to methicillin-resistant staphylococci, vancomycin with rifampin for at least 6 weeks and gentamicin for 2 weeks is recommended using the following doses:		I	B
Adult antibiotic dosage and route			
Vancomycin[h]	30–60 mg/kg/day i.v. in 2–3 doses		
Rifampin	900–1200 mg/day i.v. or orally in 2 or 3 divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
Paediatric antibiotic dosage and route			
Vancomycin[h]	30 mg/kg/day i.v. in 2–3 equally divided doses		
Rifampin	20 mg/kg/day i.v. or orally in 2 or 3 divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 (preferred) or 2 doses		
In patients with NVE due to methicillin-resistant staphylococci, daptomycin combined with cloxacillin, ceftaroline or fosfomycin may be considered using the following doses:[335,345–349]		IIb	C
Adult antibiotic dosage and route			
Daptomycin	10 mg/kg/day i.v. in 1 dose		
Cloxacillin[c]	12 g/day i.v. in 6 doses		
OR	OR		
Ceftaroline[f]	1800 mg/day i.v. in 3 doses		
OR	OR		
Fosfomycin[g]	8–12 g/day i.v. in 4 doses		

NVE, PVE

NVE

Doporučení pro antibiotickou léčbu infekční endokarditidy způsobené *Enterococcus spp.*

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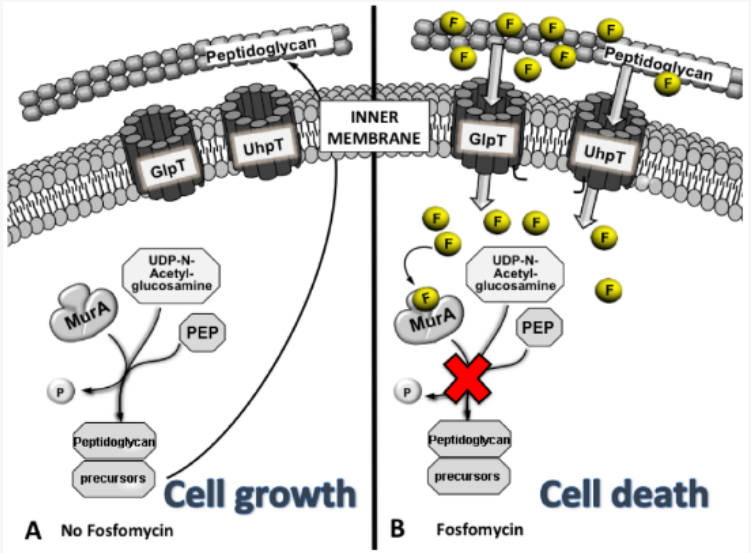
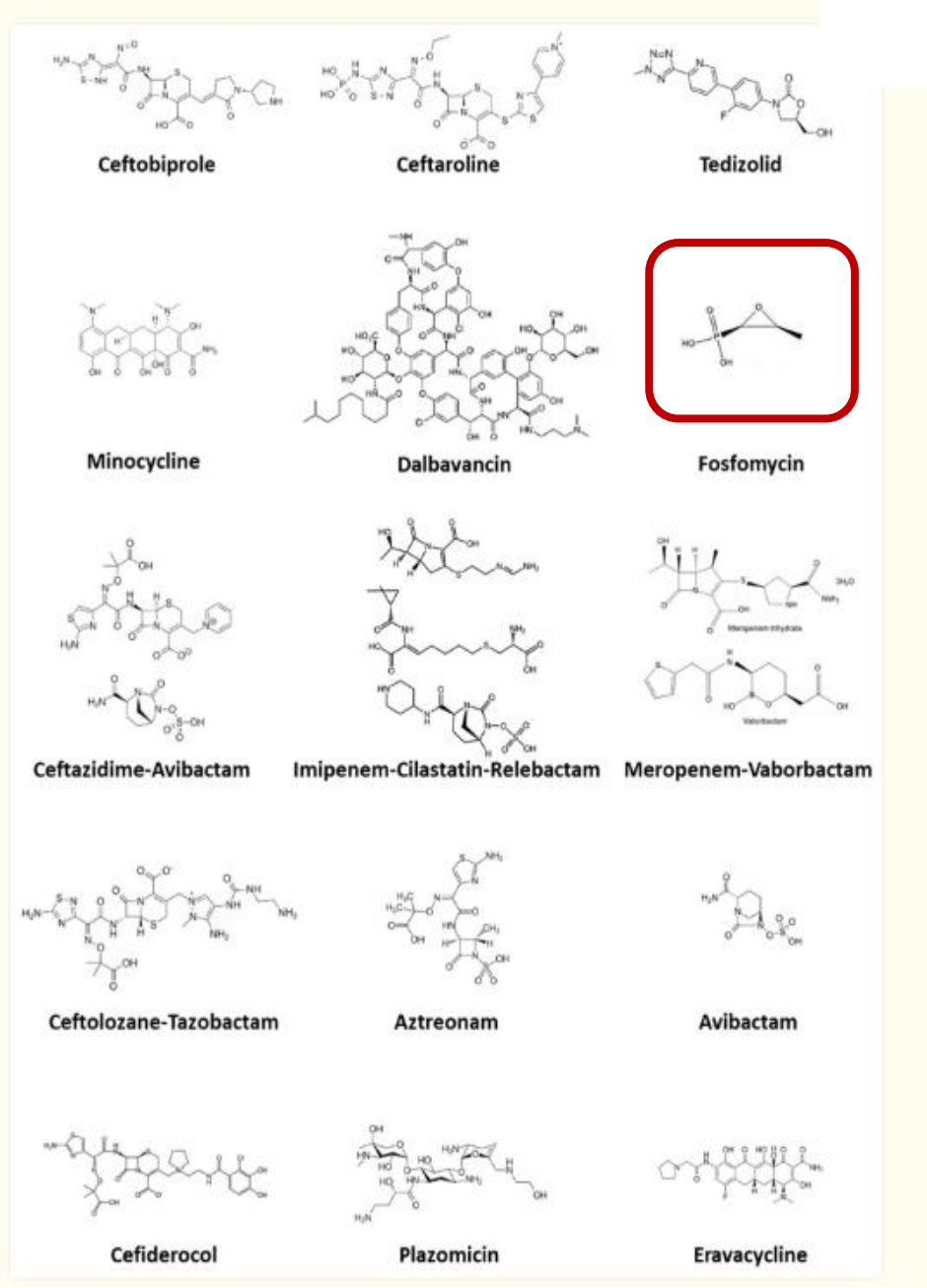
High-level aminoglycoside resistance[d]			
In patients with NVE or PVE due to HLAR *Enterococcus* spp., the combination of ampicillin or amoxicillin and ceftriaxone for 6 weeks is recommended using the following doses:[355,360,361]		I	B
Adult antibiotic dosage and route			
Ampicillin	12 g/day i.v. in 4–6 doses		
Amoxicillin	200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. or i.m. in 2 doses		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg i.v. or i.m. in 2 doses		
Beta-lactam resistant *Enterococcus* spp. (*E. faecium*)[e]			
In patients with IE due to beta-lactam resistant *Enterococcus* spp. (*E. faecium*), vancomycin for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:[358,359,369]		I	C
Adult antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2 doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Vancomycin	30 mg/kg/day i.v. in 2–3 equally divided doses		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose		
Vancomycin-resistant *Enterococcus* spp.[f]			
In patients with IE due to vancomycin-resistant *Enterococcus* spp., daptomycin combined with beta-lactams (ampicillin, ertapenem, or ceftaroline) or fosfomycin is recommended using the following doses:[369]		I	C
Adult antibiotic dosage and route			
Daptomycin	10–12 mg/kg/day i.v. in 1 dose		
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Fosfomycin	12 g/day i.v. in 4 doses		
Ceftaroline	1800 mg/day i.v. in 3 doses		
Ertapenem[g]	2 g/day i.v. or i.m. in 1 dose		

Figure 2. Although transporters are usually very selective, the chemical structure of fosfomycin mimics both glycerol-3-P (G3P) and glucose-6-P (G6P), which are transported under normal conditions. MurA catalyses the formation of UDP-GlcNac-3-O-enolpyruvate, a peptidoglycan precursor, from UDP-GlcNAc and PEP during the first step of peptidoglycan biosynthesis, allowing cell growth (**A**). In contrast, when fosfomycin (F) is present, it is transported inside the cell by GlpT and UhpT, blocking the UDP-GlcNac-3-O-enolpyruvate synthesis by mimicking the original substrate of MurA, PEP, avoiding cell wall synthesis and leading to cell death (**B**). For simplicity, only peptidoglycan and the inner membrane are shown.





Molecular Mechanisms and Clinical Impact of Acquired and Intrinsic Fosfomycin Resistance
Review Article
Castañeda-García A, Blázquez J, Rodríguez-Rojas A
Antibiotiscs 2013, 2, 217-236; doi:10.3390/antibiotics2020217

Emerging Treatment Options for Multi-Drug-Resistant Bacterial Infections
Giurazza R, Mazza MC, Andini R et al
Life (Basel), 2021 Jun; 11(6): 519
Published online 2021 Jun 3. doi:10.3390/life11060519

Fosfomycin i.v. – spektrum účinku

- **G-** enterobakterie (*Klebsiella spp., E coli spp.* včetně ESBL+), *P. aeruginosa, A. baumannii*
- **G+** (*S. aureus*, enterokoky)
- **MRSA, VRE, CRE, CCRE**
- **Riziko vzniku rezistence *intra terapiam* → kombinační léčba !!!**
- **Imunomodulační efekt (lymfocyty, monocyty, neutrofily, inflamatorní cytokiny**

Obvykle citlivé jsou:
Staphylococcus aureus, *Citrobacter freundii, Citrobacter koseri, Escherichia coli, Haemophilus influenzae, Neisseria meningitidis, Salmonella enterica, anaerobní Fusobacterium spp., Peptococcus spp., Peptostreptococcus spp.*

Druhy, u nichž může být problém získaná rezistence:
Staphylococcus epidermidis, Streptococcus pneumoniae, Enterococcus spp., *Enterobacter cloacae, Klebsiella aerogenes, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcescens, Clostridium spp.*

Přirozeně rezistentní jsou:
Staphylococcus saprophyticus, Streptococcus pyogenes, ***Legionella pneumophila****, Morganella morganii, Stenotrophomonas maltophilia, Bacteroides spp., Chlamydia spp., Chlamydophila spp.,* ***Mycoplasma spp.***

Emerging Treatment Options for Multi-Drug-Resistant Bacterial Infections
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New evidence on the use of fosfomycin for bacteremia and infectious endocardits
Vengazones J, Montero A, Maseda E
Rev Esp Quimioter 2019; 32 (Suppl. 1): 25-29

Fosfomycin i.v. – kombinace s jinými atb

- cloxacillin, daptomycin
- cefotaxim, ceftriaxon, ceftazidim (-avibactam), cefepim, ceftaroline, ceftobiprole
- meropenem, imipenem
- amikacin, gentamicin
- ciprofloxacin
- aztreonam
- colistin
- tigecykline

Fosfomycin: the characteristics, aktivity and use in critical care
Hashemian SMR, Farhadi Z, Farhadi T
Therapeutics and Clinical Risk Management 2109:15; 525-530

New evidence on the use of fosfomycin for bacteremia and infectious endocardits
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Rev Esp Quimioter 2019; 32 (Suppl. 1): 25-29

Fosfomycin a renální insuficience (SPC)

Tabulka 2 – Úpravy dávky pro pacienty s hodnotou CrCL nižší než 40 ml/min

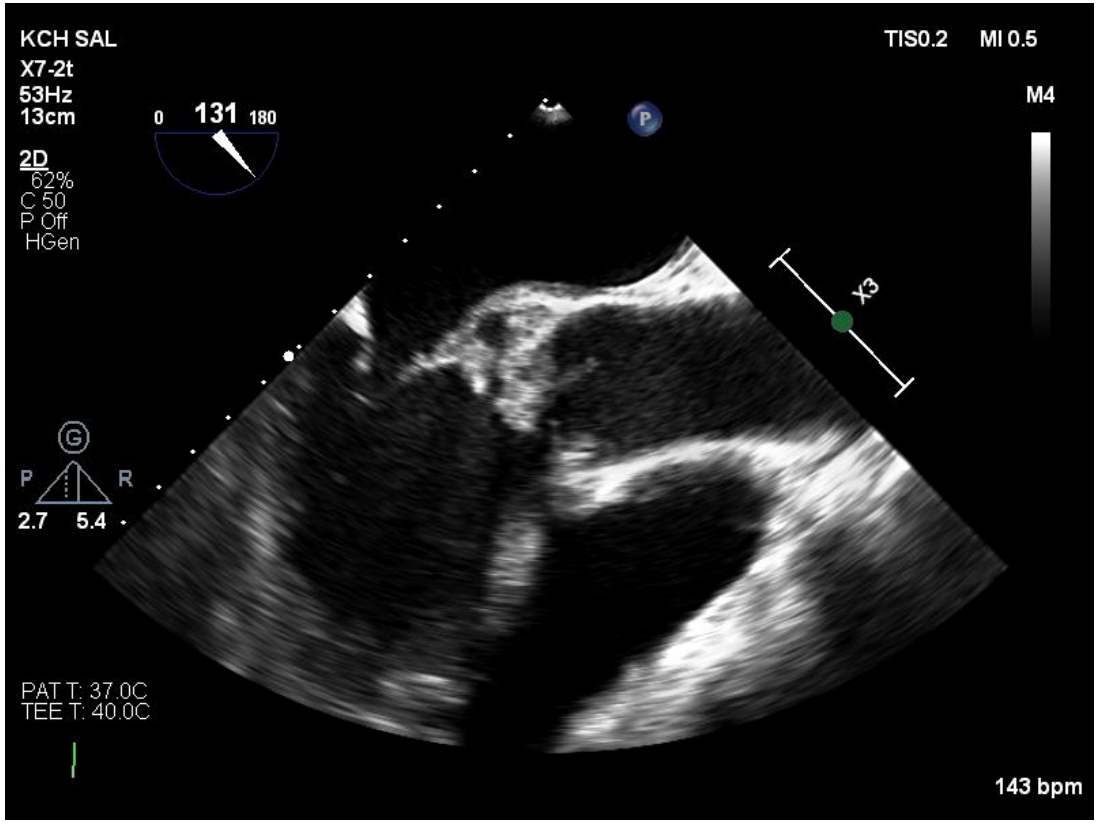
$CL_{CR\ pacienta}$	$CL_{CR\ pacienta}$ / $CL_{CR\ normální}$	Doporučená denní dávka[a]
40 ml/min	0,333	70 % (ve 2–3 dílčích dávkách)
30 ml/min	0,250	60 % (ve 2–3 dílčích dávkách)
20 ml/min	0,167	40 % (ve 2–3 dílčích dávkách)
10 ml/min	0,083	20 % (v 1–2 dílčích dávkách)

[a] Dávka je vyjádřena jako podíl dávky, která by se považovala za odpovídající, pokud by pacientova funkce ledvin byla normální na základě výpočtu podle Cockroftova-Gaultova vzorce.

První (nasycovací) dávka má být zvýšena o 100 %, ale nesmí překročit 8 g.

Naše zkušenosti – NVE, MSSA

- 29 letý pacient, NVIE BAV, septický šok
- **Hospitalizace: 27.8. – 19.12.2023**
- Etiologie: MSSA
  (meropenem 3x2g, vankomycin 3x1g, gentamicin 3mg/kg, linezolid 2x600mg)
- **Commando procedure**
  (AVR bio + MVR bio + Ao-Mi kontinuita) 27.8.2023
- **HMK + chlopeň: MSSA**
  → oxacillin 6x3g + fosfomycin 4x4g 29.8.2023
- **4.10.2023:**
  daptomycin (750mg/48h + fosfomycin 2x4mg)
- **Nežádoucí účinky při léčbě fosfomycinem:**
  - opakované zvracení → změna dávkovacího režimu
  - známky srdečního selhávání (dušnost, otoky DKK - nárty, bérce)
  - hypokalémie



Naše zkušenosti – pozdní PVE, HACEK

- **Stp. Rossově operaci 2017**

- **Pozdní PVE**
  - vlající echogenita v oblasti předního cípu homograftu
  - hyperechogení ložisko ve stěně autograftu v aortální pozici

- **HMK:**
  - 16.2.2024 - 3+3 - *Aggregatibacter actinomycetemcomitans*

- **Spádová nemocnice**
  - hospitalizace 16.2. – 21.3.2024

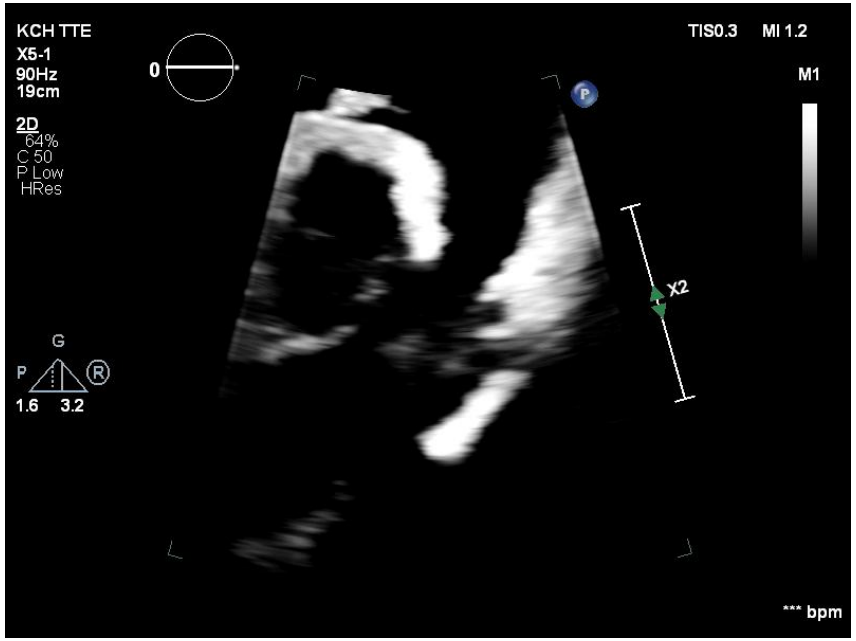
- **ATB ve spádu**
  - 16.-20.2.2024: ampicillin + gentamicin + ceftriaxon
  - 20.-29.2.2024: ampicillin + gentamicin
  - 29.2.-18.3.2024 ampicillin monoterapie
  - 18.-21.3.2024 ampicillin + ceftriaxon

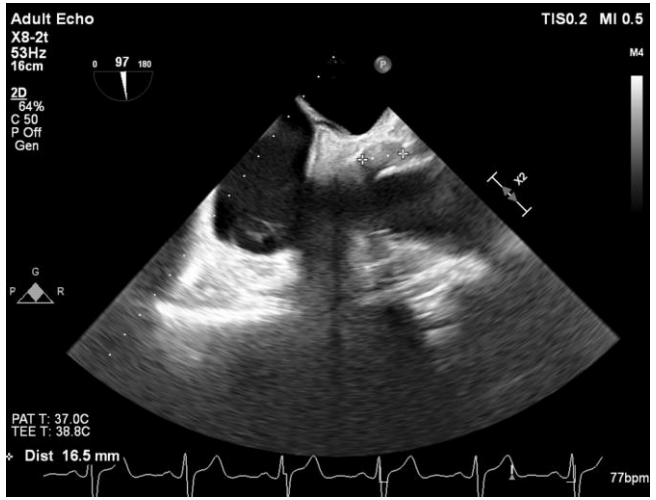
- **17.3.2024:** febrílie, zimnice, třesavka

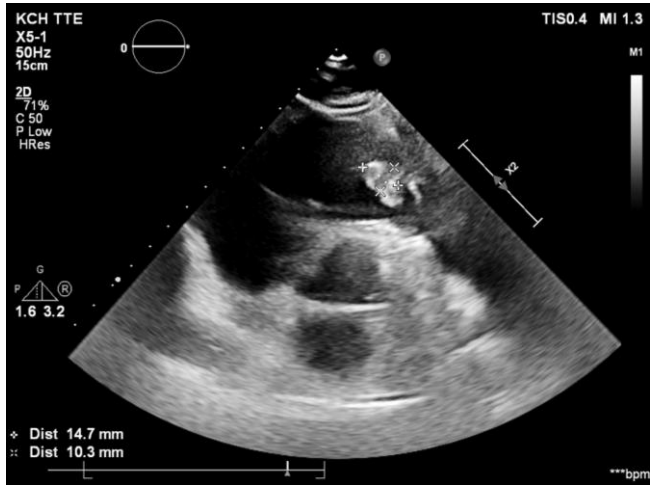
- **18.3.2024:** ***CRP 48,7, leu 15,4***
  UZ TEE bez progrese

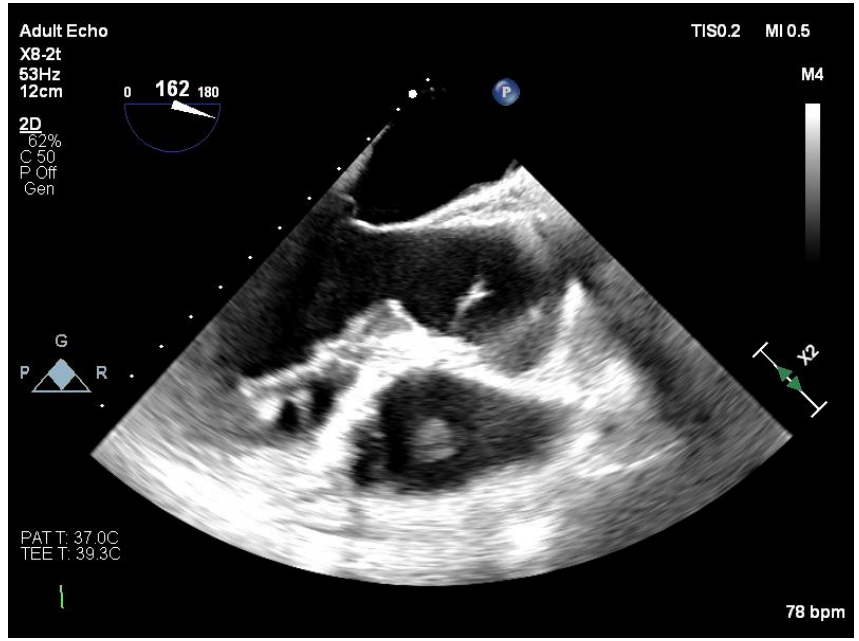
- **21.3.2024:** překlad ad KCH FN HK

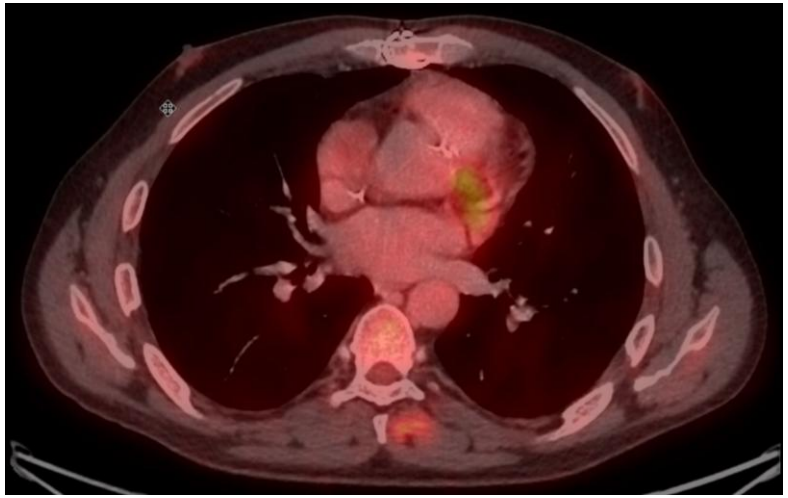
Naše zkušenosti – pozdní PVE, HACEK

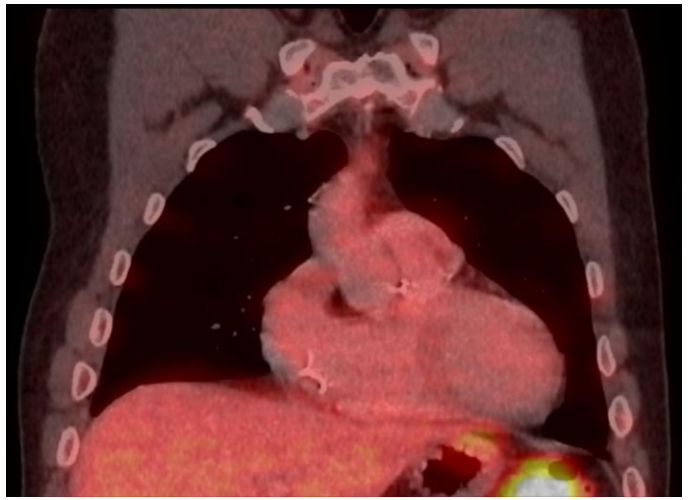


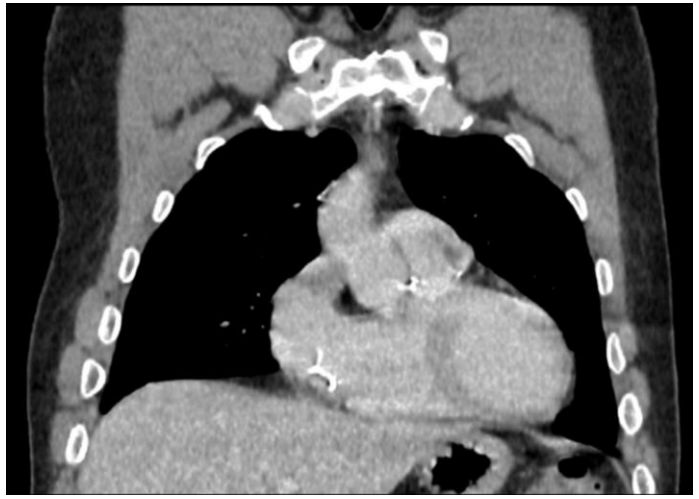












Vlevo: Fúze PET/CT a samostatný PET): vidět proužek akumulace glukózy dorzálně od aorty, odpovídá aortální chlopni při posunu fúze během srdeční činnosti.
Mírně nehomogenně prsténčitě zvýšený metabolismus FDG v oblasti aortální chlopně, zde nelze jednoznačně infekční endokarditidu vyloučit.
Vpravo: Trombus v truncus pulmonalis bez zvýšeného metabolismu FDG (v.s. se nejedná o infikovaný trombus).

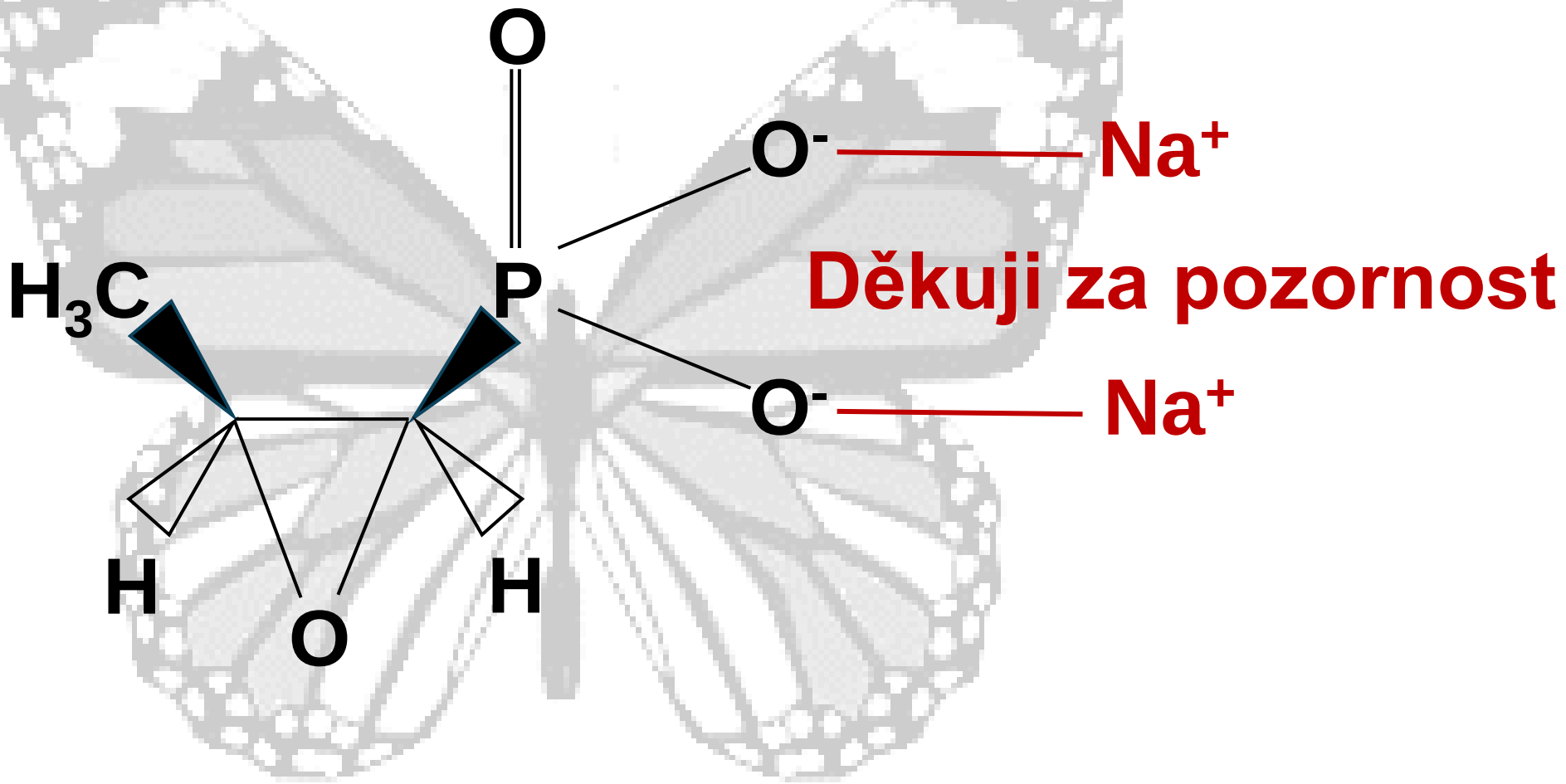
Laskavostí MUDr. M.Slaniny, PhD . a MUDr. G.Beladové (oddělení nukleární medicíny FN HK)

Naše zkušenosti – pozdní PVE, HACEK

- **Na KCH FN HK:**
  - 21.3.2024: ceftriaxon 1x2g + fosfomycin 4x4 g (180min)
  - léčba plánována na **8 týdnů**

Fosfomycin v léčbě (nejen) IE – kam patří?

- Rychlý a výborný průnik do většiny tkání těla
  V kombinaci **cílená terapie** závažných infekcí a infekcí v obtížně dostupném terénu (klouby, kosti, oči, svaly, kůže, podkoží, plíce, žluč, likvor, chlopně)
- Průnik do **biofilmu**
- Účinek **v log fázi**
- **Empirická <u>kombinační</u>** terapie závažných G+ infekcí → MDR enterobakterie, MRSA, …
- Salvage terapie multirezistentních kmenů (*P. aeruginosa*)
- Snížení rizika vzniku rezistence (daptomycin)
- **MSSA při alergii na PNC** **II B** **(NVE, PVE)**
  MRSA **II B** **(NVE)**
  VRE **I** **(NVE, PVE)**
- **HEART TEAM**


O
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Děkuji za pozornost
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Na+
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H