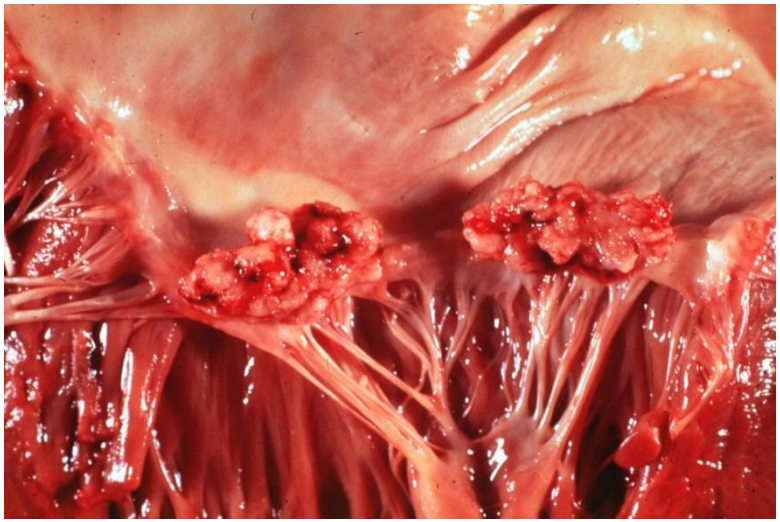
Kontroverze ATB terapie infekční endokarditidy



Jiří Beneš
Klinika infekčních nemocí 3. LF UK
FN Bulovka, Praha

Brno, 6.5.2024

ESC European Society of Cardiology

European Heart Journal (2023) **44**, 3948–4042
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ESC GUIDELINES

2023 ESC Guidelines for the management of endocarditis

Developed by the task force on the management of endocarditis of the European Society of Cardiology (ESC)

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

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† The two Chairpersons contributed equally to the document and are joint corresponding authors.

‡ The two Task Force Co-ordinators contributed equally to the document.

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[3] Representing the European Association for Cardio-Thoracic Surgery (EACTS)

Aktuální doporučené postupy

Delgado V, Marsan NA, de Waha S, Bonaros N, Brida M, Burri H, Caselli S, Doenst T, Ederhy S, Erba PA, Foldager D, Fosbø EL, Kovac J, Mestres CA, Miller OI, Miro JM, Pazdernik M, Pizzi MN, Quintana E, Rasmussen TB, Ristić AD, Rodés-Cabau J, Sionis A, Zühlke LJ, Borger MA, ESC Scientific Document Group.

2023 ESC Guidelines for the management of endocarditis.

European Heart Journal 2023 Oct 14; 44(39):3948-4042.

Victoria Delgado. Head of the department of Cardiovascular Imaging. Barcelona, Cataluña, España

Preamble: *Členové této pracovní skupiny byli vybráni ESC, aby zastupovali lékaře zabývající se problematikou IE. Cílem výběrového řízení bylo zahrnout členy z celého regionu ESC, kteří se specializují (publikují) o IE. Pozornost byla věnována diverzitě, zejména s ohledem na pohlaví a zemi původu.*

Aktuální doporučené postupy

*Delgado V, Marsan NA, de Waha S, Bonaros N, Brida M, Burri H, Caselli S, Doenst T, Ederhy S, Erba PA, Foldager D, Fosbø EL, Kovac J, Mestres CA, Miller OI, **Miro JM**, Pazdernik M, Pizzi MN, Quintana E, Rasmussen TB, Ristić AD, Rodés-Cabau J, Sionis A, Zühlke LJ, Borger MA, ESC Scientific Document Group.*

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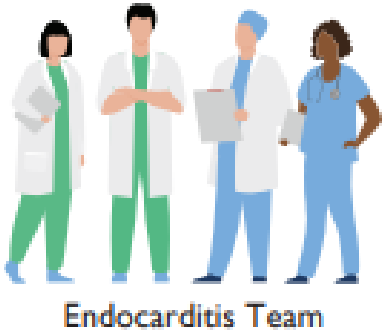
Table 7: Members of the Endocarditis Team

Core members
- Cardiologists
- Cardiac imaging experts
- Cardiovascular surgeons
- Infectious disease specialist
- Microbiologist
- Specialist in outpatient parenteral antibiotic treatment

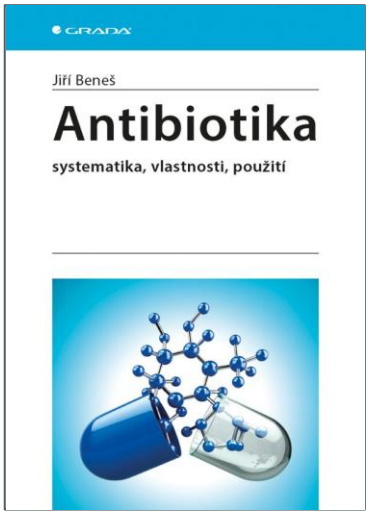


Professor Jose Maria Miró, M.D., Barcelona
He has two research lines: HIV/AIDS and IE

Kontroverze

ATB profylaxe i léčba, výběr přípravků i dávkování

- Stovky případů IE (hlavně NVE, vč. IVDA) léčeny na naší klinice.
- 2000: Doporučené postupy v diagnostice a léčbě IE.
  Beneš J, Kvasnička J. Cor Vasa 2000;42(2):K21-8.
- 2007: Infekční endokarditida. Doporučené postupy diagnostiky, léčby, dispenzarizace a profylaxe.
  Beneš J, Gregor P, Mokráček A. Cor Vasa 2007;49(9):157-171.
- 2016: Doporučení ESC pro diagnostiku a léčbu infekční endokarditidy.
  Linhartová K, Beneš J, Gregor P. Cor Vasa 2016;58(1):e107-128.
- Incidence, predisposing factors, and aetiology of infective endocarditis in the Czech Republic.
  Džupová O, Machala L, Baloun R, Malý M, Beneš J. doi: 10.3109/00365548.2011.632643.



Jiří Beneš
Antibiotika: systematika, vlastnosti, použití
Grada, 2018, 600 stran

ATB profylaxe u zubolékařských výkonů

Table 6: Prophylactic antibiotic regime for high-risk dental procedures

	Single-dose 30–60 min before procedure	
	Adults	**Children**
No allergy to penicillin or ampicillin		
Amoxicillin	2 g orally	50 mg/kg orally
Ampicillin	2 g i.m. or i.v.	50 mg/kg i.v. or i.m.
Cefazolin or ceftriaxone	1 g i.m. or i.v.	50 mg/kg i.v. or i.m.
Allergy to penicillin or ampicillin		
Cephalexin[a,b]	2 g orally	50 mg/kg orally
Azithromycin or clarithromycin	500 mg orally	15 mg/kg orally
Doxycycline	100 mg orally	<45 kg, 2.2 mg/kg orally >45 kg, 100 mg orally
Cefazolin or ceftriaxone	1 g i.m. or i.v.	50 mg/kg i.v. or i.m.

Azitromycin a klaritromycin v pokusech na zvířatech lepší než placebo.
Účinnost vzhledem k jiným ATB ověřena jen u klaritromycinu. *doi: 10.1128/AAC.40.3.809*

Doxycyklin není spolehlivý proti orálním streptokokům. *doi: 10.1093/infdis/146.6.806*

Klindamycin zavržen kvůli riziku CDI (studie z počátku století).

Recommendation Table 7

Recommendations for antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus gallolyticus* group

Recommendations		Class[a]	Level[b]
Penicillin-susceptible oral streptococci and *Streptococcus gallolyticus* group			
Standard treatment: 4-week duration in NVE or 6-week duration in PVE			
In patients with IE due to oral streptococci and *S. gallolyticus* group, penicillin G, amoxicillin, or ceftriaxone are recommended for 4 (in NVE) or 6 weeks (in PVE), using the following doses:[277,278]		I	B
Adult antibiotic dosage and route			
Penicillin G	12–18 million[c] U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Paediatric antibiotic dosage and route			
Penicillin G	200 000 U/kg/day i.v. in 4–6 divided doses		
Amoxicillin	100–200[c] mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg/day i.v. in 1 dose		
Standard treatment: 2-week duration (not applicable to PVE)			
2-week treatment with penicillin G, amoxicillin, ceftriaxone combined with gentamicin is recommended only for the treatment of non-complicated NVE due to oral streptococci and *S. gallolyticus* in patients with normal renal function using the following doses:[277,278]		I	B
Adult antibiotic dosage and route			
Penicillin G	12–18 million[c] U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	100–200 mg/kg/day i.v. in 4–6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose[d]		

Paediatric antibiotic dosage and route			
Penicillin G	200 000 U/kg/day i.v. in 4–6 divided doses		
Amoxicillin	100–200 mg/kg/day[c] i.v. in 4–6 doses		
Ceftriaxone	100 mg/kg i.v. in 1 dose		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose or 3 equally divided doses[d]		
Allergy to beta-lactams			
In patients allergic to beta-lactams and with IE due to oral streptococci and *S. gallolyticus*, vancomycin for 4 weeks in NVE or for 6 weeks in PVE is recommended using the following doses:[292]		I	C
Adult antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
Paediatric antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 or 3 equally divided doses[e]		
Oral streptococci and *Streptococcus gallolyticus* group susceptible, increased exposure or resistant to penicillin			
In patients with NVE due to oral streptococci and *S. gallolyticus*, penicillin G, amoxicillin, or ceftriaxone for 4 weeks in combination with gentamicin for 2 weeks is recommended using the following doses:[285–290]		I	B
Adult antibiotic dosage and route			
Penicillin G	24 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	12 g/day i.v. in 6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin	3 mg/kg/day i.v. or i.m. in 1 dose[d]		
In patients with PVE due to oral streptococci and *S. gallolyticus*, penicillin G, amoxicillin, or ceftriaxone for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:[285–290]		I	B
Adult antibiotic dosage and route			
Penicillin G	24 million U/day i.v. either in 4–6 doses or continuously		
Amoxicillin	12 g/day i.v. in 6 doses		
Ceftriaxone	2 g/day i.v. in 1 dose		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose[d]		
Allergy to beta-lactams			
In patients with NVE due to oral streptococci and *S. gallolyticus* and who are allergic to beta-lactams, vancomycin for 4 weeks is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
Paediatric antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
In patients with PVE due to oral streptococci and *S. gallolyticus* and who are allergic to beta-lactams, vancomycin for 6 weeks combined with gentamicin for 2 weeks is recommended using the following doses:		I	C
Adult antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose[d]		
Paediatric antibiotic dosage and route			
Vancomycin[e]	30 mg/kg/day i.v. in 2 doses[e]		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose[d]		

Kde je hranice mezi „S“, „I“ a „R“?
Původně tu bylo číslo (hodnota MIC).
Při skutečné rezistenci nelze PEN použít !!!

Proč není zmíněno dávkování u dětí?
Redakční chyba?

Měření hladin je nutné a dostupné!
Nasycovací dávka?

Recommendation Table 8

Recommendations for antibiotic treatment of infective endocarditis due to *Staphylococcus* spp.

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		

Nalačno?

Recommendation Table 8

Recommendations for antibiotic treatment of infective endocarditis due to *Staphylococcus* spp.

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		

For penicillin-allergic patients with MSSA IE, penicillin desensitization can be attempted or cefazolin can be used since vancomycin is inferior to beta-lactams.[309]

Riziko desenzibilizace a/nebo zkřížené alergie je menší zlo než vankomycin?

Recommendation Table 10

Antibiotic regimens for initial empirical treatment of IE

Recommendations		Class[b]	Level[c]
In patients with community-acquired NVE or late PVE (≥12 months post-surgery), ampicillin in combination with ceftriaxone or with (flu)cloxacillin and gentamicin should be considered using the following doses:[255]		IIa	C
Adult antibiotic dosage and route			
Ampicillin	12 g/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. or i.m. in 2 doses		
(Flu)cloxacillin	12 g/day i.v. in 4–6 doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Ceftriaxone	100 mg/kg i.v. or i.m. in 1 dose		
(Flu)cloxacillin	200–300 mg/kg/day i.v. in 4–6 equally divided doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 3 equally divided doses		

AMP + CTR
nebo
AMP+FLC+GEN

Jak to, že iniciální empirická ATB léčba nepostihuje stafylokoky?

HRUBÁ CHYBA !!

(*S. aureus* je častý původce NVE a IE mívá akutní průběh)

Ambulantní doléčení IE orálními antibiotiky

Možnost přechodu na ambulantní léčbu po 10 dnech účinné ATB léčby

Podmínky ze strany pacienta:

- původce dobře citlivý k ATB
- pacient klinicky stabilní
- pacient dobře toleruje léčbu (včetně event. antikoagulační th)
- dobré sociální zázemí (…. IVDA je kontraindikace)

Podmínky ze strany ZZ:

- ambulantní ATB léčbu zajišťuje vycvičený tým
- rozpis klinických kontrol
- možnost konzultací kdykoli
- psaná pravidla, jasné kompetence

léčbu vede nemocniční tým, nikoli praktický lékař!

- zpětné kontroly, vyhodnocování účinnosti léčby

Norris AH, et al. 2018 Infectious Diseases Society of America Clinical Practice Guideline for the Management of Outpatient Parenteral Antimicrobial Therapy. Clin Infect Dis. 2019 Jan 1;68(1):1-4. doi: 10.1093/cid/ciy867.

Ambulantní doléčení IE orálními antibiotiky

Table S9 Combinations of antibiotics for oral step-down treatment

Penicillin-and methicillin-susceptible *S. aureus* & CoNS	Methicillin-susceptible *S. aureus* & CoNS	Methicillin-resistant CoNS	*E. faecalis*	Penicillin-susceptible streptococci	Penicillin-resistant streptococci
Amoxicillin 1 g × 4 Rifampin 600 mg × 2	Dicloxacillin 1 g × 4 Rifampin 600 mg × 2	Linezolid 600 mg × 2 Fusidic acid 750 mg × 2	Amoxicillin 1 g × 4 Moxifloxacin 400 mg × 1	Amoxicillin 1 g × 4 Rifampin 600 mg × 2	Linezolid 600 mg × 2 Rifampin 600 mg × 2
Amoxicillin 1 g × 4 Fusidic acid 750 mg × 2	Dicloxacillin 1 g × 4 Fusidic acid 750 mg × 2	Linezolid 600 mg × 2 Rifampin 600 mg × 2	Amoxicillin 1 g × 4 Linezolid 600 mg × 2	Amoxicillin 1 g × 4 Moxifloxacin 400 mg × 1	Moxifloxacin 400 mg × 1 Rifampin 600 mg × 2
Moxifloxacin 400 mg × 1 Rifampin 600 mg × 2	Moxifloxacin 400 mg × 1 Rifampin 600 mg × 2		Amoxicillin 1 g × 4 Rifampin 600 mg × 2	Amoxicillin 1 g × 4 Linezolid 600 mg × 2	Linezolid 600 mg × 2 Moxifloxacin 400 mg × 1
Linezolid 600 mg × 2 Rifampin 600 mg × 2	Linezolid 600 mg × 2 Rifampin 600 mg × 2		Linezolid 600 mg × 2 Moxifloxacin 400 mg × 1	Linezolid 600 mg × 2 Rifampin 600 mg × 2	
Linezolid 600 mg × 2 Fusidic acid 750 mg × 2	Linezolid 600 mg × 2 Fusidic acid 750 mg × 2		Linezolid 600 mg × 2 Rifampin 600 mg × 2	Linezolid 600 mg × 2 Moxifloxacin 400 mg × 1	

Dikloxacilin, kyselina fusidová: nejsou v ČR registrovány
AMO, DIC/FLC: 4x denně: adherence k několikatýdenní léčbě?
Rifampicin: přísně nalačno, riziko lékových interakcí
Linezolid: jednotné dávkování není vhodné pro léčbu IE
Linezolid + rifampicin: farmakologický antagonismus
Není zmíněn COT (COT + RIF je účinné proti *S. aureus*)

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Prosím, nepřebírejte doporučené ATB režimy, aniž byste se poradili se svým klinickým mikrobiologem, infektologem, farmakologem !