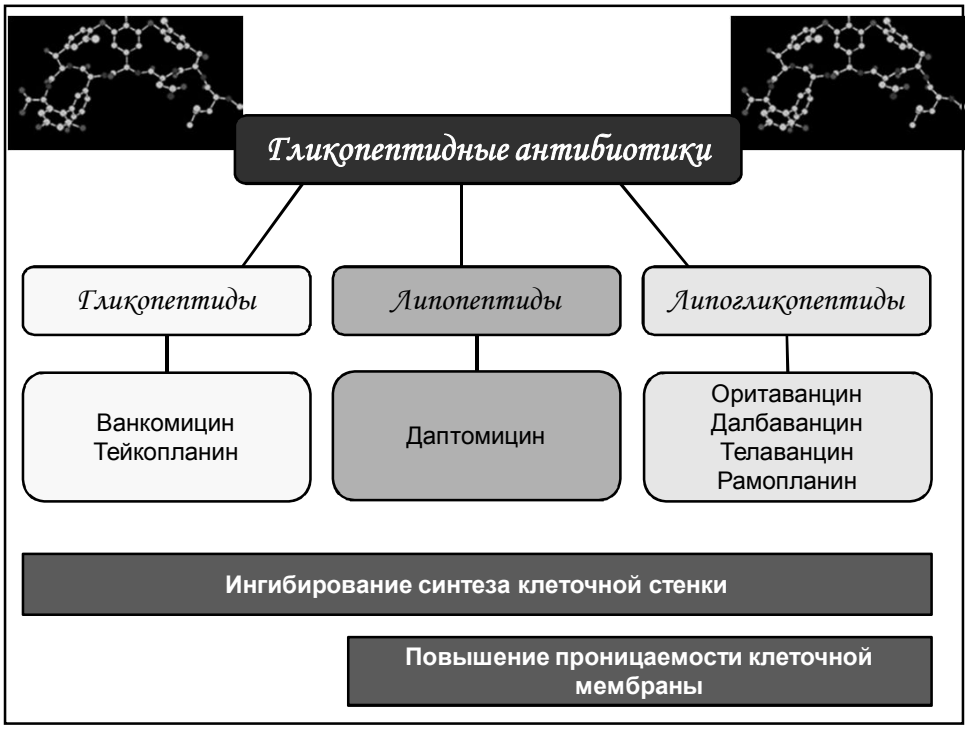
Белорусский государственный медицинский университет
Кафедра инфекционных болезней

Гликопептиды: особенности применения в клинической практике

доцент, к.м.н. Горбич Юрий Леонидович



Спектр активности

Грам (+) возбудители:

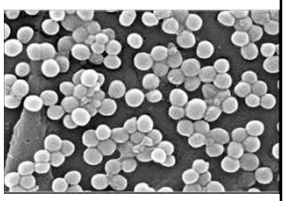
Staphylococcus spp. (включая MRSA),
Streptococcus spp.,
Enterococcus spp.,
Arcanobacter spp.

Анаэробы:

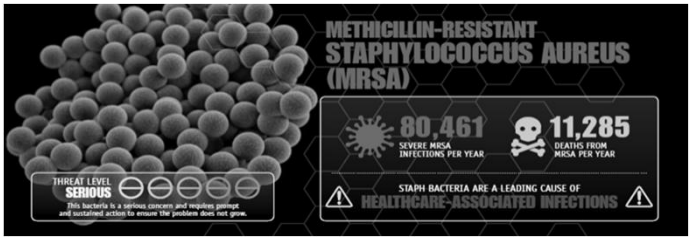
Clostridium spp.,
Propionibacterium acnes,
Peptostreptococci

Грам (-) возбудители:

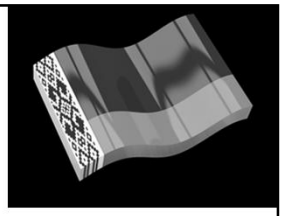
НЕ АКТИВЕН

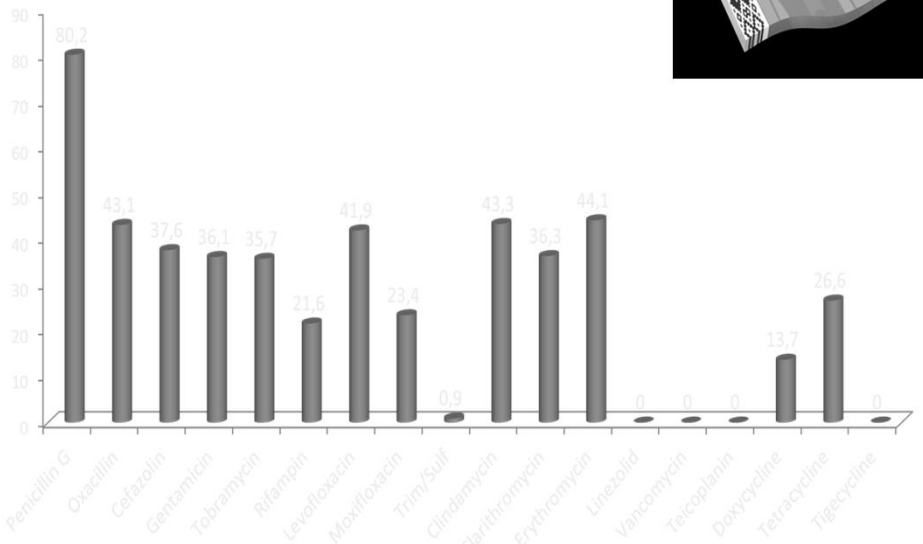


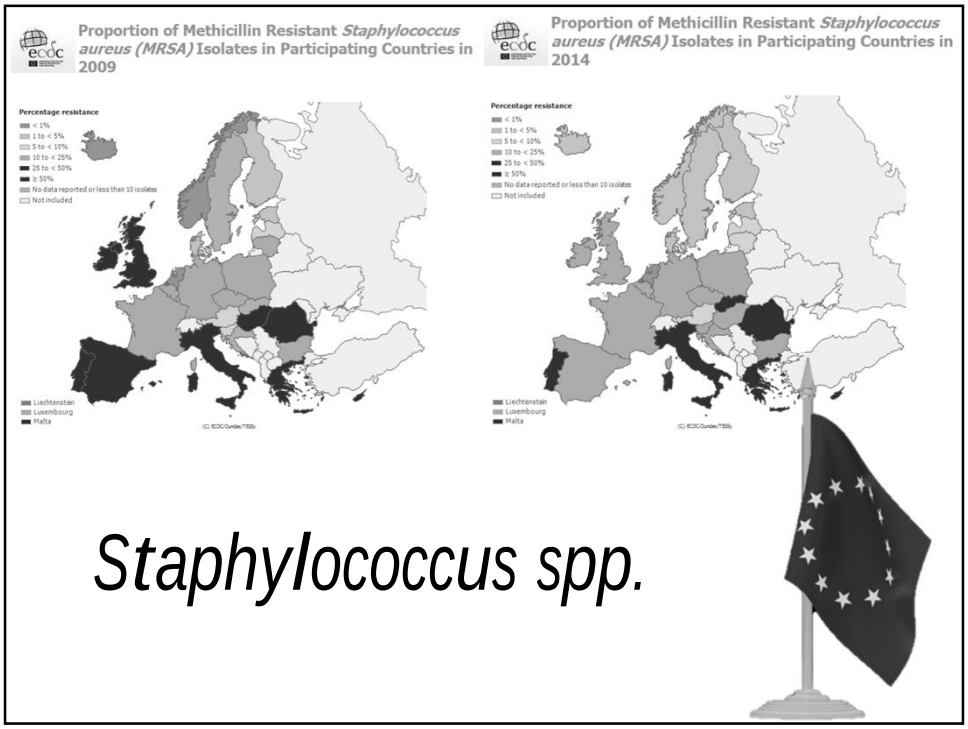
Наиболее проблемные Грам(+) микроорганизмы



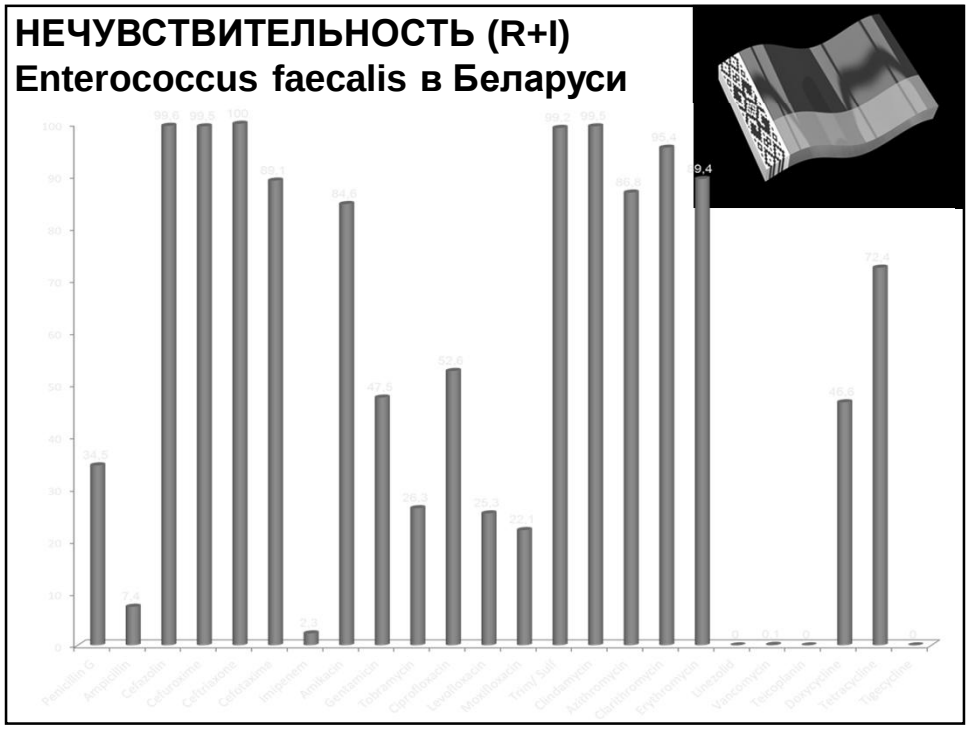
НЕЧУВСТВИТЕЛЬНОСТЬ (R+I)
Staphylococcus aureus в Беларуси



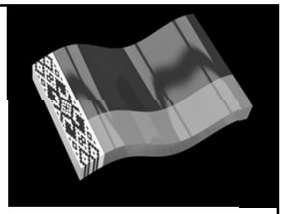


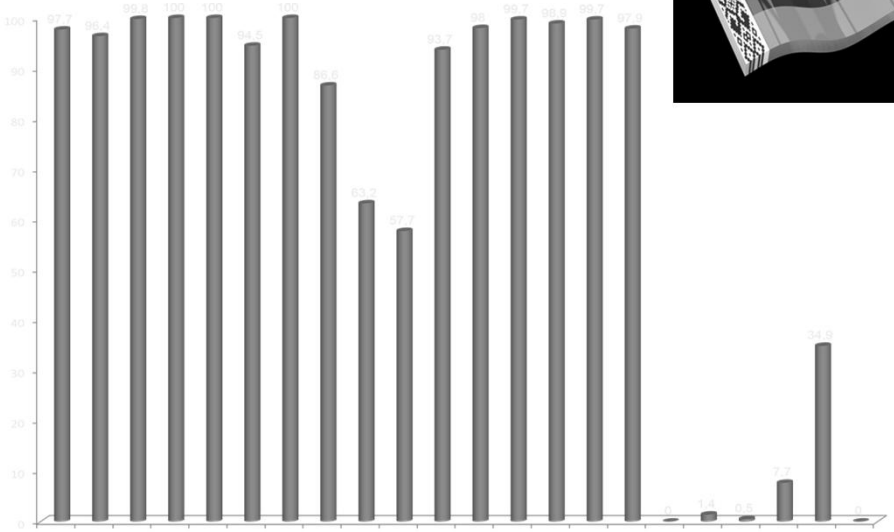


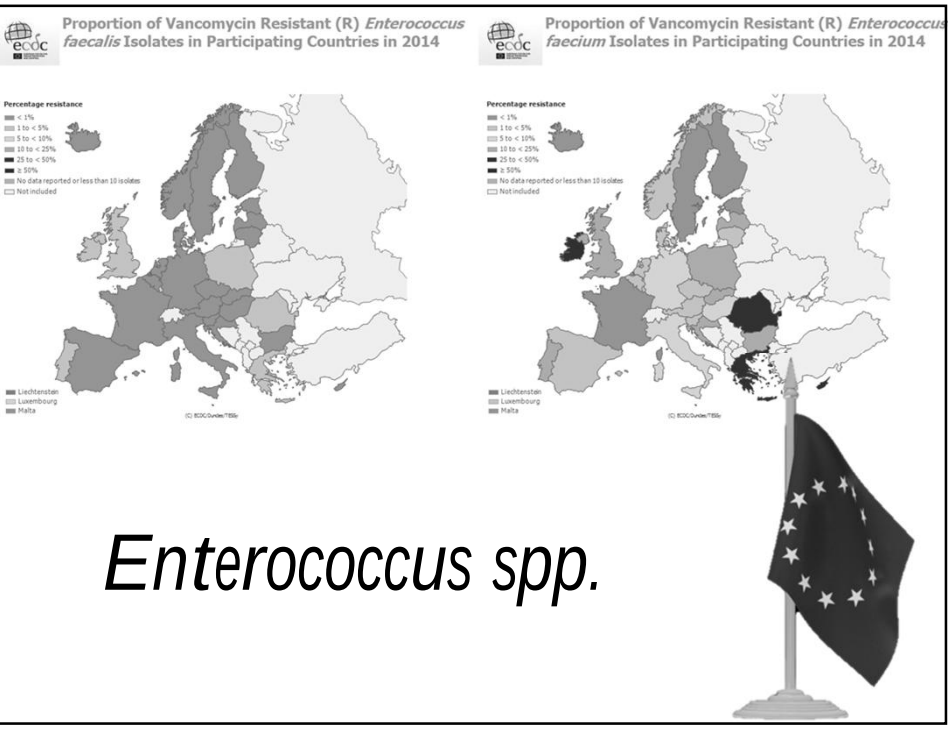

РЕЗИСТЕНТНОСТЬ S. AUREUS К МЕТИЦИЛЛИНУ
У+Р, %
0-5
5-15
15-25
25-50
50-75
75-100
Нет данных


НЕЧУВСТВИТЕЛЬНОСТЬ (R+I)
Enterococcus faecalis в Беларуси
Penicillin G
Ampicillin
Cefazolin
Cefuroxime
Ceftriaxone
Cefotaxime
Imipenem
Amikacin
Gentamicin
Tobramycin
Ciprofloxacin
Levofloxacin
Moxifloxacin
Trimy Sulf
Clindamycin
Azithromycin
Clarithromycin
Erythromycin
Linezolid
Vancomycin
Teicoplanin
Doxycycline
Tetracycline
Tigecycline

НЕЧУВСТВИТЕЛЬНОСТЬ (R+I)
Enterococcus faecium в Беларуси

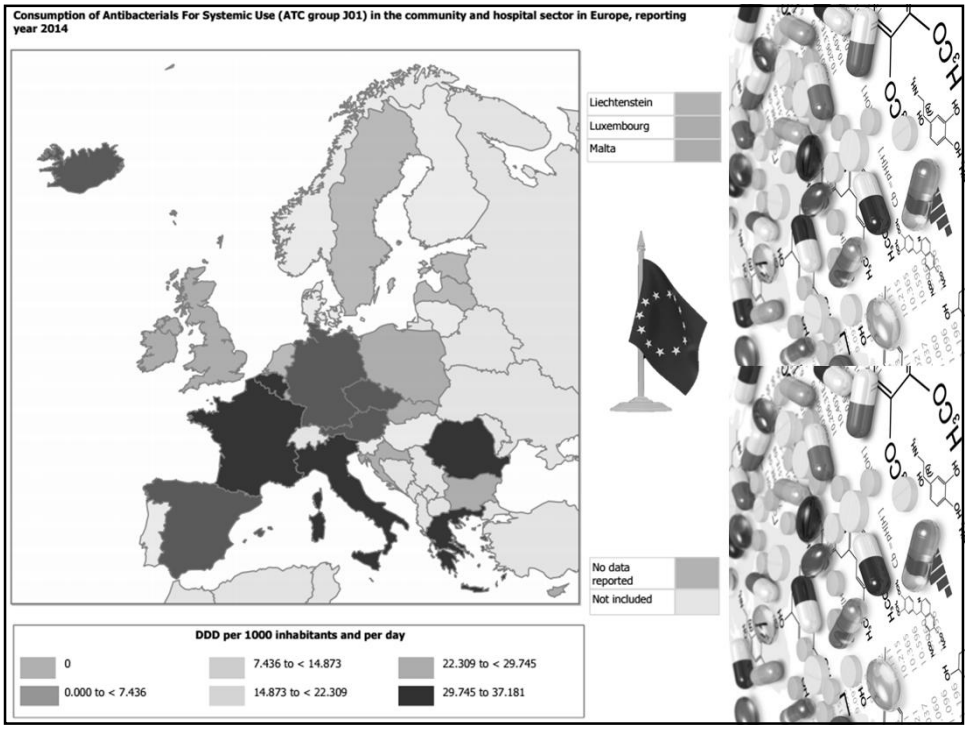




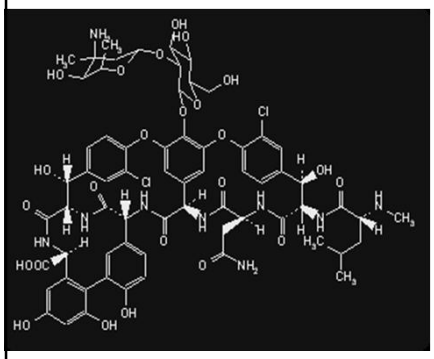


АМП, активные в отношении Грам(+) инфекций

- Ванкомицин
- Тейкопланин
- Линезолид
- Даптомицин
- Тигециклин
- Телаванцин



Ванкомицин



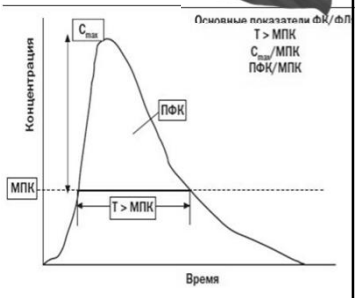
Antimicrob Agents Chemother. 2016 Apr 22;60(5):2601-9. doi: 10.1128/AAC.03147-14. Print 2016 May.

Optimizing the Clinical Use of Vancomycin.

Álvarez R[1], López Cortés LE[1], Molina J[1], Cisneros JM[1], Pachón J[2].

Эффективность ванкомицина:

- ✓ AUC/MIC ≥400
- ✓ Подбор дозы исходя из массы тела и концентрации в плазме крови
- ✓ Концентрация в плазме крови: 15 – 20 мг/л для MIC ≤1 мг/л
- ✓ Нефротоксичность – при целевых концентрациях в плазме крови >15 мг/л
- ✓ Staphylococcus aureus (MIC >1 мг/л) – **АЛЬТЕРНАТИВНАЯ ТЕРАПИЯ**



MRSA

Minsk GCGE

bioMerieux Customer:

Microbiology Chart Report

Printed Apr 19, 2010 09:18 CDT

Patient Name: [redacted]
Location: 4 GKB
Lab ID: 28064/12

Patient ID: 28064/12
Physician:
Isolate Number: 1

Selected Organism : Staphylococcus aureus

Source: KROV

Collected: Apr 5, 2010

Comments:	

Susceptibility Information	Analysis Time: 8.25 hours			Status: Final	
Antimicrobial	MIC	Interpretation	Antimicrobial	MIC	Interpretation
Cefoxitin Screen	POS	+	Teicoplanin	<= 0.5	S
Benzylpenicillin	>= 0.5	R	Vancomycin	1	S
Oxacillin	>= 4	R	Tetracycline	>= 16	R
Gentamicin	>= 16	R	Tigecycline	0.25	S
Tobramycin	>= 16	R	Fosfomycin	32	S
Levofloxacin	>= 8	R	Nitrofurantoin	<= 16	S
Moxifloxacin	4	I	Fusidic Acid	<= 0.5	S
Inducible Clindamycin Resistance	NEG	-	Mupirocin	<= 2	S
Erythromycin	>= 8	R	Rifampicin	>= 32	R
Clindamycin	>= 8	R	Trimethoprim/Sulfamethoxazole	<= 10	S
Linezolid	2	S			

+= Deduced drug *= AES modified **= User modified

AES Findings		
Confidence:	Consistent	
Phenotype:	BETA-LACTAMS	MODIFICATION OF PBP (mecA)
	MACROLIDES/LINCOSAMIDES/STREPTOGRAMINS	MLSB+SA CONSTITUTIVE

ORIGINAL ARTICLE — BACTERIOLOGY

Vancomycin minimum inhibitory concentration, host comorbidities and mortality in *Staphylococcus aureus* bacteraemia

N. E. Holmes[1,2], J. D. Turnidge[3,4], W. J. Munckhof[5,6], J. O. Robinson[7], T. M. Korman[8,9], M. V. N. O'Sullivan[10,11], T. L. Anderson[12,13], S. A. Roberts[14], S. J. C. Warren[12,13], W. Gao[1,15], P. D. R. Johnson[1,2,16,†] and B. P. Howden[1,15,16,17,†]

TABLE 2. Univariable and multivariable logistic regression analysis for associations with 30-day mortality (n = 410)

Variable[a]	Univariable p value	Multivariable OR	Multivariable 95% CI	Multivariable p value
Age ≥70 years	<0.001	3.73	2.14–6.51	<0.001
Elevated vancomycin MIC[b]	<0.001	2.59	1.49–4.51	0.001
Pitt score ≥4	<0.001	2.79	1.54–5.06	0.001
Sepsis syndrome	<0.001	3.28	1.53–7.03	0.002
CCI	0.003			NS
ICU admission	0.010			NS
Active injecting drug use	0.012			NS
Hospital onset	0.020			NS

CCI, Charlson Comorbidity Index; NS, not significant (p ≥0.05).
[a]As discussed in Results section, variables that were significant on univariable analysis that were not considered for multivariable analysis were presence of a Do not resuscitate order (direct effect on outcome due to treatment modification), APACHE II score ≥18 and SAPS II score (collinearity with age), heart disease and malignancy (collinearity with CCI).
[b]Elevated vancomycin MIC defined as Etest® >1.5 mg/L.

Clinical Microbiology and Infection, Volume 19 Number 12, December 2013

Clin Infect Dis. 2011 Apr 15;52(8):975-81. doi: 10.1093/cid/cir124.

Impact of vancomycin exposure on outcomes in patients with methicillin-resistant Staphylococcus aureus bacteremia: support for consensus guidelines suggested targets.

Kullar R[1], Davis SL, Levine DP, Rybak MJ.

Table 2.
Vancomycin Trough Concentrations and Poor Outcomes

Characteristic N = 308[a]	Vancomycin failure n (%)	P (vs reference category)	Nephrotoxicity[b] n (%)	P (vs reference category)
Trough <10 mg/L (n=70)	46 (65.7%)	0.001	10/65 (15.4%)	.682
Trough 10–14.9 mg/L(n=90)	52 (57.8%)	0.016	13/76 (17.1%)	.476
Trough 15–20 mg/L(n=86)	34 (39.5%)	REF	10/77 (13.0%)	REF
Trough >20 mg/L(n=62)	31 (50.0%)	0.206	17/62 (27.4%)	.032

- ✓ 320 пациентов

Независимые предикторы неудачи терапии:

- ✓ Инфекционный эндокардит (AOR, 4.55; 95% CI, 2.26-9.15)
- ✓ ИСМП (AOR, 2.19; 95% CI, 1.21-3.97)
- ✓ Концентрация ванкомицина в плазме <15 мг/л (AOR, 2.00; 95% CI, 1.25-3.22)
- ✓ МПК ванкомицина (Etest) >1 мг/л (AOR, 1.52; 95% CI, 1.09-2.49)

РЕКОМЕНДАЦИИ IDSA ПО ПРИМЕНЕНИЮ ВАНКОМИЦИНА В КЛИНИЧЕСКОЙ ПРАКТИКЕ

- **При остаточной к-ции <10 мг/л высока вероятность формирования штаммов со сниженной чувствительностью к ванкомицину**
- **При МПК штамма <1 мг/л для достижения ПФК/МК>400 рекомендовано поддержание остаточного уровня ванкомицина 15-20 мг/л**
- **Для более быстрого достижения равновесной к-ции рекомендована вводная доза** 25-30 **мг/кг**
- **При МПК ≥2 мг/л невозможно достижение ПФК/МПК>400 без риска развития токсических эффектов**
- **Рекомендован индивидуальный подбор дозы на основе мониторинга остаточной к-ции**
- **Для достижения рекомендуемого значения остаточной сывороточной концентрации в случае, если МПК <1 мг/л, большинство пациентов с нормальной функцией почек должны получать ванкомицин в дозе** 15-20 **мг/кг в расчёте на действительную массу тела каждые 12 ч. Длительность инфузии должна быть увеличена с 1,5 до 2 ч в случае, если рассчитанная разовая доза ванкомицина превышает 1 г**

Clin Infect Dis 2009; 49:325-7

Acad Emerg Med. 2016 Jun;23(6):744-6. doi: 10.1111/acem.12934. Epub 2016 May 14.

High Single-dose Vancomycin Loading Is Not Associated With Increased Nephrotoxicity in Emergency Department Sepsis Patients.

Rosini JM[1], Davis JJ[2], Muenzer J[2], Levine BJ[2], Papas MA[3], Comer D[4], Arnold R[2,4].

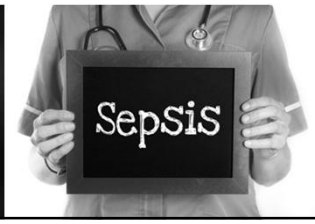
Ретроспективное когортное исследование

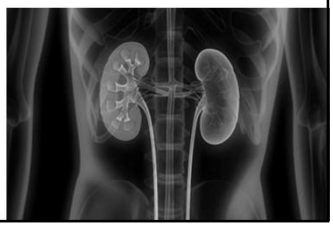
3 университетских госпиталя

2 131 взрослый пациент с сепсисом

Ванкомицин в дозе >20 **мг/кг** vs. ≤20 mg/kg

Нефротоксичность – 5.8% vs. 11.1% (RR = 0.60; 95% CI = 0.44 to 0.82)





Antimicrob Agents Chemother. 2013 Feb;57(2):734-44. doi: 10.1128/AAC.01568-12. Epub 2012 Nov 19.

Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter.

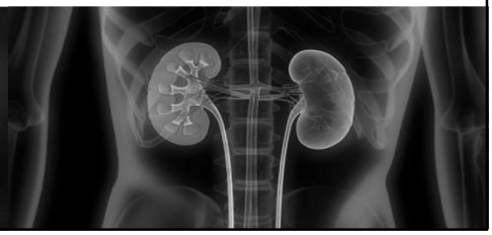
van Hal SJ[1], Paterson DL, Lodise TP.

Study or Subgroup	High troughs ≥15mg/L Events	Total	Low trough <15mg/L Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosso et al. (21)	42	142	13	146	9.8%	4.30 [2.19, 8.43]
Cano et al. (22)	22	89	7	99	7.2%	4.32 [1.74, 10.69]
Chung et al. (23)	12	25	16	48	6.5%	1.85 [0.69, 4.96]
Hermsen et al. (30)	5	16	4	39	3.6%	3.98 [0.91, 17.46]
Hidayat et al. (13)	11	63	0	32	1.1%	14.24 [0.81, 249.87]
Jeffres et al. (15)	27	49	13	45	7.7%	3.02 [1.28, 7.11]
Kralovicova et al. (31)	21	60	29	138	9.8%	2.02 [1.04, 3.96]
Kullar et al. (32)	8	116	1	84	2.0%	6.15 [0.75, 50.13]
Kullar et al. (8)	27	139	23	141	10.6%	1.24 [0.67, 2.28]
Lodise et al. (36)	7	27	14	139	6.2%	3.13 [1.12, 8.69]
McKamy et al. (38)	16	57	8	110	7.0%	4.98 [1.98, 12.52]
Minejima et al. (39)	17	72	25	155	9.6%	1.61 [0.80, 3.21]
Prabaker et al. (43)	7	54	24	294	7.3%	1.68 [0.68, 4.11]
Wunderink et al. (50)	26	118	24	215	10.7%	2.25 [1.22, 4.13]
Zimmermann et al. (51)	8	12	0	33	1.0%	126.56 [6.19, 2585.90]
Total (95% CI)		**1039**		**1718**	**100.0%**	**2.67 [1.95, 3.65]**
Total events	256		201			

Heterogeneity: Tau² = 0.14; Chi² = 23.89, df = 14 (P = 0.05); I² = 41%
Test for overall effect: Z = 6.13 (P < 0.00001)

Odds Ratio M-H, Random, 95% CI

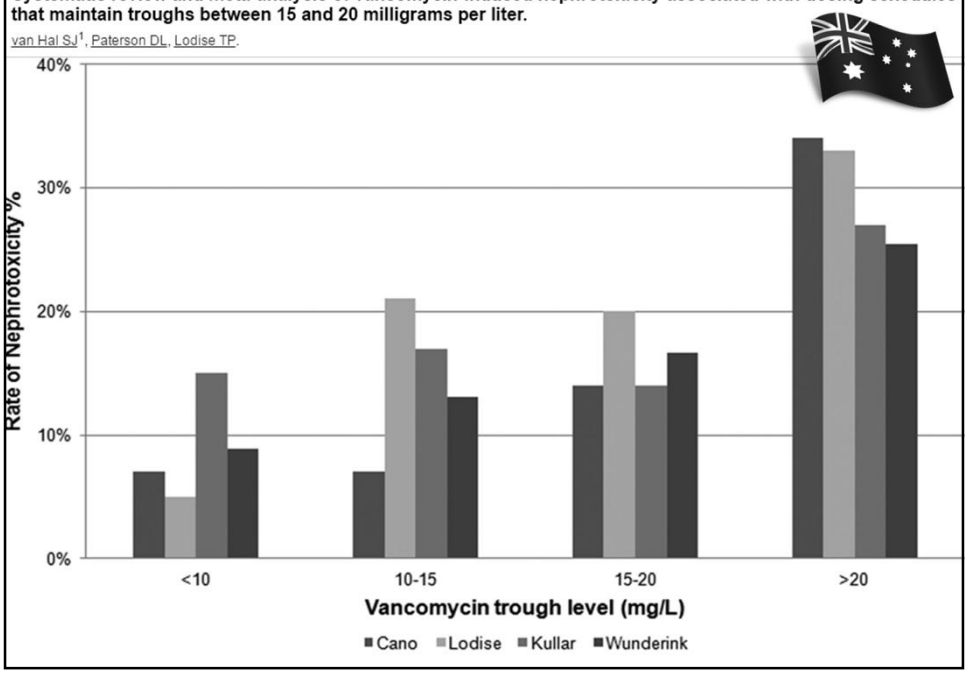
0.01 0.1 1 10 100
Low troughs <15mg/L High troughs ≥15mg/L



Antimicrob Agents Chemother. 2013 Feb;57(2):734-44. doi: 10.1128/AAC.01568-12. Epub 2012 Nov 19.

Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter.

van Hal SJ[1], Paterson DL, Lodise TP.



Antimicrob Agents Chemother. 2013 Feb;57(2):734-44. doi: 10.1128/AAC.01568-12. Epub 2012 Nov 19.

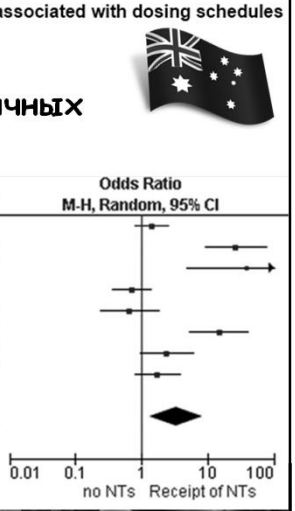
Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter.

van Hal SJ[1], Paterson DL, Lodise TP.

Сопутствующий прием иных нефротоксичных препаратов:

Study or Subgroup	Receipt of NTs Events	Total	no NTs Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosso et al. (21)	26	55	90	233	14.0%	1.42 [0.79, 2.57]
Cano et al. (22)	16	29	7	159	12.4%	26.73 [9.32, 76.63]
Hidayat et al. (13)	10	11	17	84	8.4%	39.41 [4.71, 329.47]
Kralovicova et al. (31)	31	134	19	64	13.7%	0.71 [0.36, 1.39]
Lodise et al. (36)	6	21	55	145	12.6%	0.65 [0.24, 1.79]
McKamy et al. (38)	18	24	24	143	12.6%	14.88 [5.35, 41.36]
Minejima et al. (39)	37	169	6	58	12.9%	2.43 [0.97, 6.10]
Prabaker et al. (43)	21	31	174	317	13.4%	1.73 [0.79, 3.78]
Total (95% CI)		**474**		**1203**	**100.0%**	**3.30 [1.30, 8.39]**
Total events	165		392			

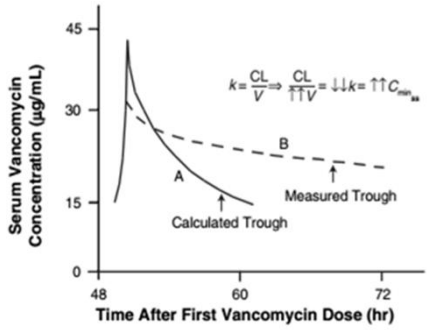
Heterogeneity: Tau² = 1.54; Chi² = 60.99, df = 7 (P < 0.00001); I² = 89%
Test for overall effect: Z = 2.50 (P = 0.01)



Am J Health Syst Pharm. 2012 Jun 1;69(11):944-50. doi: 10.2146/ajhp110324.

Performance of a vancomycin dosage regimen developed for obese patients.

Reynolds DC[1], Waite LH, Alexander DP, DeRyke CA.



- ✓ Пациенты с избытком массы тела (вес ≥ 100 кг и ≥ 140% от идеального)
- ✓ 15 мг/кг через 8-12 часов vs. 10 мг/кг через 12 часов (или 15 мг/кг через 24 часа)
- ✓ 74 и 68 пациентов, соответственно
- ✓ Средняя поддерживающая доза – 34 ± 7 мг/кг/сут и 19 ± 2 мг/кг/сут ($p < 0.001$)
- ✓ Достижение целевой концентрации в плазме – 36% vs. 59% ($p = 0.006$)
- ✓ Нефротоксичность – NS

Clin Infect Dis. 2011 Jul 15;53(2):124-9. doi: 10.1093/cid/cir337.

Implementation of a dose calculator for vancomycin to achieve target trough levels of 15-20 microg/mL in persons undergoing hemodialysis.

Vandecasteele SJ[1], De Bacquer D, De Vriese AS.

Пациенты на гемодиализе:

- ✓ До следующего сеанса
  - 1 день – 15 мг/кг
  - 2 дня – 25 мг/кг
  - 3 дня – 35 мг/кг
- ✓ В конце процедуры
- ✓ Скорость введения 15 мг/мин
- ✓ В течение последних 120 минут диализа

Burns. 2011 May;37(3):406-14. doi: 10.1016/j.burns.2010.06.005. Epub 2010 Nov 20.

Optimizing initial vancomycin dosing in burn patients.

Elliqsen M[1], Walker SA, Walker SE, Simor A.

Ретроспективное исследование

49 ожоговых пациентов

Фармакокинетика ванкомицина меняется в зависимости от времени, прошедшего после ожоговой травмы (до и после 14 дней ($p < 0.05$)

Достижение целевых концентраций:

- Стандартная доза 1г в/в через 12 часов - <10%
- 20-25%:
  - ✓ 48 часов – 14 дней - 1.5 г ч/з 8 часов, 1.75 г ч/з 8 часов, 1 г ч/з 6 часов, 1.25 г ч/з 6 часов или 750 ч/з 4 часа
  - ✓ >14 дней – 1-1.25 г ч/з 8 часов или 500 мг ч/з 4 часа

ТЕРАПЕВТИЧЕСКИЙ ЛЕКАРСТВЕННЫЙ МОНИТОРИНГ !

J Antimicrob Chemother. 2012 Jan;67(1):17-24. doi: 10.1093/jac/dkr442. Epub 2011 Oct 25.

Continuous versus intermittent infusion of vancomycin for the treatment of Gram-positive infections: systematic review and meta-analysis.

Cataldo MA[1], Tacconelli E, Grilli E, Pea F, Petrosillo N.

1 рандомизированное клиническое и 5 описательных исследований

MEDLINE U.S. National Library of Medicine

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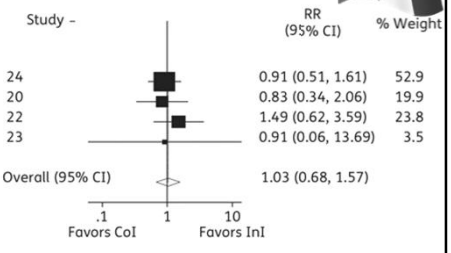
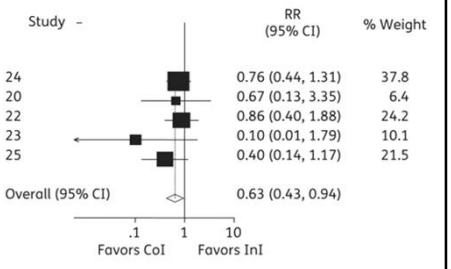


Летальность



Нефротоксичность

J Antimicrob Chemother. 2012 Mar;67(3):727-35. doi: 10.1093/jac/dkr522. Epub 2011 Dec 15.

A comparative evaluation of adverse platelet outcomes among Veterans' Affairs patients receiving linezolid or vancomycin.

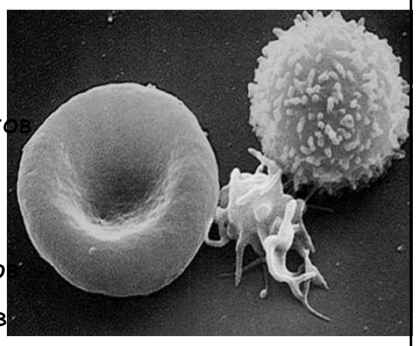
Patel N[1], VanDeWall H, Tristani L, Rivera A, Woo B, Dihmess A, Li HK, Smith R, Lodise TP.

✓ *Ванкомицин vs. Линезолид*

- ✓ январь 2005 – февраль 2008
- ✓ 502 пациента (1:1)
- ✓ Частота регистрации уровня тромбоцитов ≤50 и ≤20×10^9/л не отличалась
- ✓ ≥50% снижение уровня тромбоцитов –

  ванкомицин – 78 (31.1%) пациентов

  линезолид – 43 (17.1%) пациентов



(*OP* 0.55; 95% ДИ 0.40-0.77)

Ann Pharmacother. 2011 May;45(5):629-38. doi: 10.1345/aph.1P583. Epub 2011 Apr 26.

Vancomycin-induced neutropenia: is it dose- or duration-related?

Black E[1], Lau TT, Ensom MH.

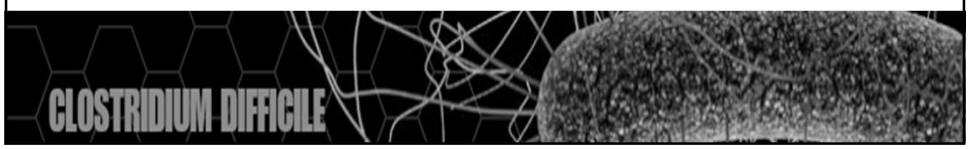
Clostridium difficile:

1935

1935 г. - Hall and O'Toole впервые описали "Bacillus difficilis" (лат: difficilis - сложный)

1970-е гг. - "Clostridium difficile" (C. difficile)

"Kloster" (греч.) - веретено



CLOSTRIDIUM DIFFICILE

- **МЕТРОНИДАЗОЛ**
- **ВАНКОМИЦИН**
- **ТЕЙКОПЛАНИН**
- **ФИДАКСОМИЦИН**
- **РИФАКСИМИН**
- **ТИГЕЦИКЛИН**
- **РАМОПЛАНИН**
- **НИТАЗОКСАНИД**
- **ОРИТАВАНЦИН**
- **РИФАЛАЗИЛ**

ORIGINAL ARTICLE 10.1111/1469-0691.12418

European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection

S. B. Debast[1], M. P. Bauer[2], E. J. Kuijper[3], on behalf of the Committee*

1) Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, Departments of 2) Infectious Diseases and 3) Medical Microbiology, Centre for Infectious Diseases, Leiden University Medical Centre, Leiden, the Netherlands

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)

Stuart H. Cohen, MD; Dale N. Gerding, MD; Stuart Johnson, MD; Ciaran P. Kelly, MD; Vivian G. Loo, MD; L. Clifford McDonald, MD; Jacques Pepin, MD; Mark H. Wilcox, MD

Lancet. 1983 Nov 5;2(8358):1043-6.

Prospective randomised trial of metronidazole versus vancomycin for Clostridium-difficile-associated diarrhoea and colitis.

Teasley DG, Gerding DN, Olson MM, Peterson LR, Gebhard RL, Schwartz MJ, Lee JT Jr.

94 пациента с диареей и колитом, вызванными C. difficile

Клиническая эффективность: **метронидазол** – 95%,
ванкомицин – 100%

(p=0,20)

Clin Infect Dis. 1996 May;22(5):813-8.

Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of Clostridium difficile-associated diarrhea.

Wenisch C[1], Parschalk B, Hasenhündl M, Hirschl AM, Graninger W.

119 пациентов с диареей, вызванной C. difficile

Клиническая эффективность: **метронидазол** – 94%,
ванкомицин – 94%

(p>0,8)

CLOSTRIDIUM DIFFICILE

Clin Infect Dis. 2007 Aug 1;45(3):302-7. Epub 2007 Jun 19.

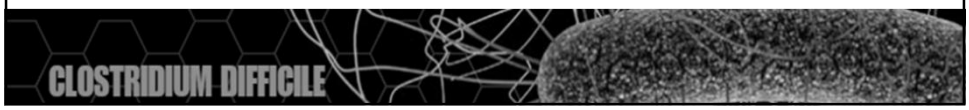
A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity.

Zar FA[1], Bakkanagari SR, Moorthi KM, Davis MB.

Тяжесть заболевания	Количество вылеченных пациентов / Количество пролеченных пациентов: Метронидазол	Ванкомицин	Всего	P^a
Не тяжелая	37/41 (90)	39/40 (98)	76/81 (94)	.36
Тяжелая	29/38 (76)	30/31 (97)	59/69 (86)	.02
Всего	66/79 (84)	69/71 (97)	135/150 (90)	

NOTE. Mtz, metronidazole; Vm, vancomycin.

[a] *P* values were calculated using Fisher's exact test.



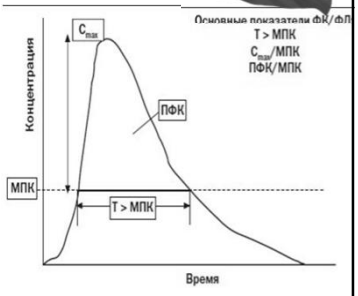
Antimicrob Agents Chemother. 2016 Apr 22;60(5):2601-9. doi: 10.1128/AAC.03147-14. Print 2016 May.

Optimizing the Clinical Use of Vancomycin.

Álvarez R[1], López Cortés LE[1], Molina J[1], Cisneros JM[1], Pachón J[2].

Эффективность ванкомицина:

- ✓ AUC/MIC ≥400
- ✓ Подбор дозы исходя из массы тела и концентрации в плазме крови
- ✓ Концентрация в плазме крови: 15 – 20 мг/л для MIC ≤1 мг/л
- ✓ Нефротоксичность – при целевых концентрациях в плазме крови >15 мг/л
- ✓ Staphylococcus aureus (MIC >1 мг/л) – **АЛЬТЕРНАТИВНАЯ ТЕРАПИЯ**

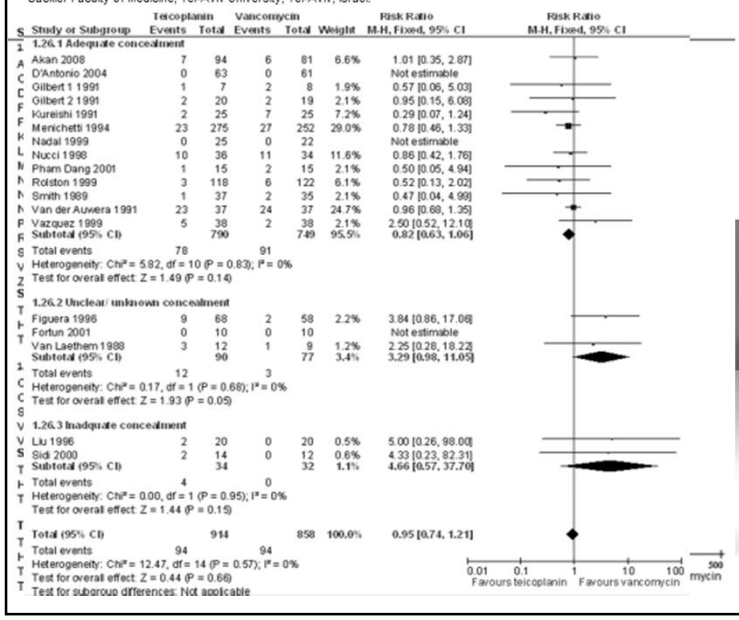


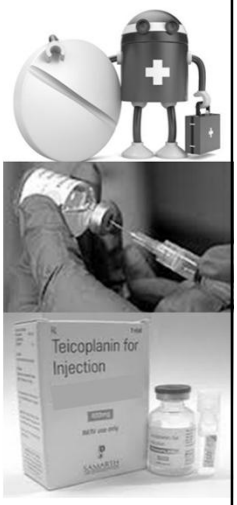
Antimicrob Agents Chemother. 2009 Oct;53(10):4069-79. doi: 10.1128/AAC.00341-09. Epub 2009 Jul 13.

Comparative efficacy and safety of vancomycin versus teicoplanin: systematic review and meta-analysis.

Svetitsky S, Leibovici L, Paul M.

Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.

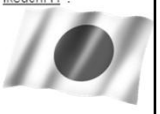




J Infect Chemother. 2014 Jan;20(1):43-7. doi: 10.1016/j.jiac.2013.08.006. Epub 2013 Dec 12.

High-dose regimen to achieve novel target trough concentration in teicoplanin.

Ueda T[1], Takesue Y[2], Nakajima K[2], Ichki K[2], Wada Y[2], Komatsu M[2], Tsuchida T[2], Takahashi Y[3], Ishihara M[3], Kimura T[3], Uchino M[4], Ikeuchi H[4].



Целевая концентрация в плазме – 15-30 мг/л

138 пациентов без нарушения функции почек:

- Режим A – 6 мг/кг через 12 часов первые 2 дня
- Режим B – 10-12 мг/кг ч/з 12 часов первые 3 дня, затем 6 мг/кг ч/з 24 часа

Средняя C(min) в плазме на 4-й день:

A - 13.7 ± 5.3 **мг/л** B - 20.0 ± 6.6 mg/L (P < 0.001)

Клиническая эффективность - 66.7% vs. 85.0% (

Нежелательные лекарственные реакции:

- ✓ нефротоксичность – 1.3% vs 3.3% (P = 0.413)
- ✓ гепатотоксичность – 5.1% vs 3.3% (P = 0.608)

Int J Clin Pharm. 2016 Aug;38(4):908-14. doi: 10.1007/s11096-016-0308-3. Epub 2016 Apr 28.

Change of teicoplanin loading dose requirement for incremental increases of systemic inflammatory response syndrome score in the setting of sepsis.

Nakano T[1,2], Nakamura Y[3], Takata T[4], Irie K[5], Sano K[5], Imakyure O[6], Mishima K[5], Futagami K[6].

Ретроспективное когортное исследование

Fukuoka University Hospital

апрель 2012 – март 2015

133 пациента (83 пациента с *CCBO*)

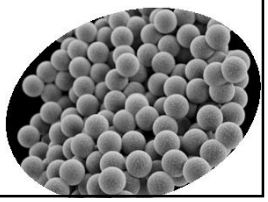
Концентрация в плазме при одинаковой дозе:

сепсис vs. не-сепсис – 15.7 ± 7.1 vs. 20.1 ± 8.6 мг/л (P < 0.01)

***Для достижения целевой концентрации** (15-30 **мг/л**) **в первые** 48 **часов**:*

не-сепсис – 12-24 мг/кг/сут.

сепсис – 18-30 мг/кг/сут.



Clin Infect Dis. 2013 Jun;56(11):1562-9. doi: 10.1093/cid/cit112. Epub 2013 Feb 28.

Early use of daptomycin versus vancomycin for methicillin-resistant Staphylococcus aureus bacteremia with vancomycin minimum inhibitory concentration >1 mg/L: a matched cohort study.

Murray KP[1], Zhao JJ, Davis SL, Kullar R, Kaye KS, Lephart P, Rybak MJ.

170 пациентов (1:1)

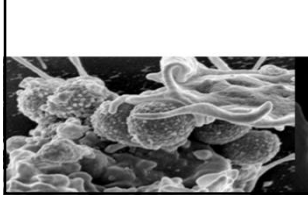
Даптомицин vs. **Ванкомицин**

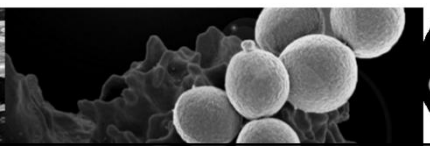
Клиническая неэффективность в течение 30 дней – 20.0% vs 48.2% (P < 0.001)

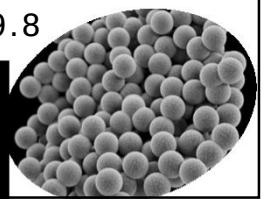
30-дневная летальность – 3.5% vs. 12.9% (P = .047)

персистирующая бактериемия – 18.8% vs. 42.4% (P = .001)

LR (ванкомицин и клиническая неэффективность) – aOR=4.5; 95% CI, 2.1-9.8



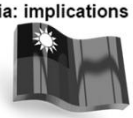




Clin Microbiol Infect. 2016 Jul 27. pii: S1198-743X(16)30242-7. doi: 10.1016/j.cmi.2016.07.018. [Epub ahead of print]

Daptomycin versus linezolid for the treatment of vancomycin-resistant enterococcal bacteraemia: implications of daptomycin dose.

Chuang YC[1], Lin HY[2], Chen PY[3], Lin CY[4], Wang JT[5], Chang SC[6].



Ванкомицин-резистентные энтерококки (VRE)

Даптомицин vs. линезолид

Мультицентровое проспективное когортное исследование

212 пациентов (141 vs. 71)

14-дневная летальность - 36.9% vs. 21.1% (p 0.03)

Факторы снижающие летальность:

- терапия линезолидом (aOR, 0.36; 95% CI, 0.17-0.79; p 0.01)
- терапия даптомицином в дозе ≥9 мг/кг (aOR, 0.26; 95% CI, 0.09-0.74; p 0.01)

Летальность:

Линезолид vs. даптомицин ≥ 9 мг/кг - NS (aOR, 1.40; 95% CI, 0.45-4.37; p 0.57).

Даптомицин

Когда нужна бактерицидная активнос

!!! Эндокардит и сепсис

? Менингит

? Остеомиелит

? Инфек

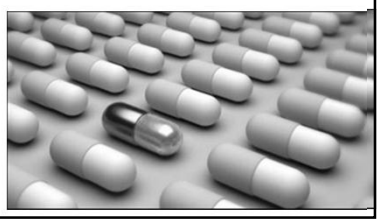
?

ORIGINAL ARTICLE

Daptomycin non-susceptible Staphylococcus aureus at a US medical centre

A. Velazquez[1], C. A. DeRyke[2], R. Goering[3], V. Hoover[4] and M. R. Wallace[1]
1) Infectious Disease, Orlando Health, 2) Pharmacy, Orlando Health, Orlando, FL, 3) Medical Microbiology and Immunology, School of Medicine, Creighton University, Omaha, NE and 4) Microbiology, Orlando Health, Orlando, FL, USA

Clinical Microbiology and Infection, Volume 19 Number 12, December 2013
1170

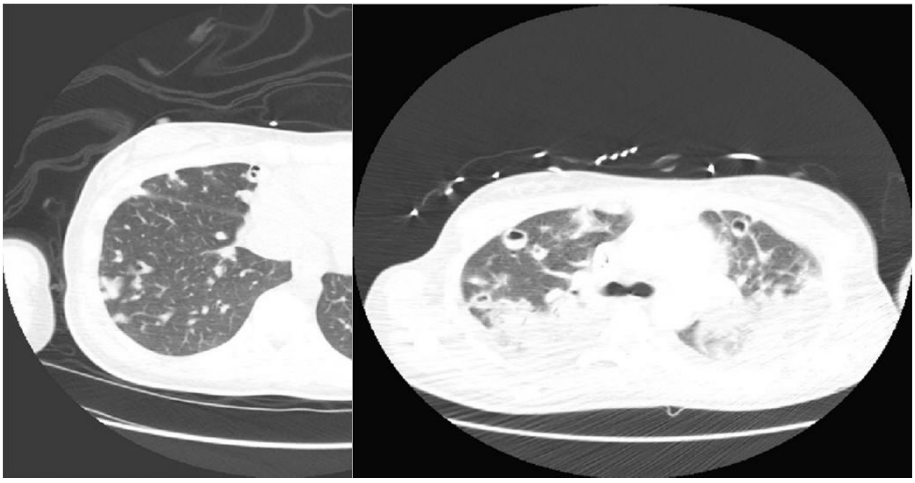


[1]LaPlante, acother 2004;5:2321–2331
[2]Silverman e gents Chemother 2003;47:2538–2544

Case Rep Infect Dis. 2013;2013:653582. doi: 10.1155/2013/653582. Epub 2013 Nov 25.

Daptomycin Failure for Treatment of Pulmonary Septic Emboli in Native Tricuspid and Mitral Valve Methicillin-Resistant Staphylococcus aureus Endocarditis.

Zainah H, Zervos M, Stephane W, Chamas Alhelo S, Alkhoury G, Weinmann A.



Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections

G. Ralph Corey, M.D., Heidi Kabler, M.D., Purvi Mehra, M.D., Sandeep Gupta, M.D., J. Scott Overcash, M.D., Ashwin Porwal, M.D., Philip Giordano, M.D., Christopher Lucasti, M.D., Antonio Perez, M.D., Samantha Good, Ph.D., Hai Jiang, Ph.D., Greg Moeck, Ph.D., and William O'Riordan, M.D., for the SOLO I Investigators*

ABSTRACT

BACKGROUND

Oritavancin is a lipoglycopeptide with bactericidal activity against gram-positive bacteria. Its concentration-dependent activity and prolonged half-life allow for single-dose treatment.

METHODS

We conducted a randomized, double-blind trial in which adults with acute bacterial skin and skin-structure infections received either a single intravenous dose of 1200 mg of oritavancin or a regimen of intravenous vancomycin twice daily for 7 to 10 days. Three efficacy end points were tested for noninferiority. The primary composite end point was defined as cessation of spreading or reduction in lesion size, absence of fever, and no need for administration of a rescue antibiotic 48 to 72 hours after administration of oritavancin. Secondary end points were clinical cure 7 to 14 days after the end of treatment, as determined by a study investigator, and a reduction in lesion size of 20% or more 48 to 72 hours after administration of oritavancin.

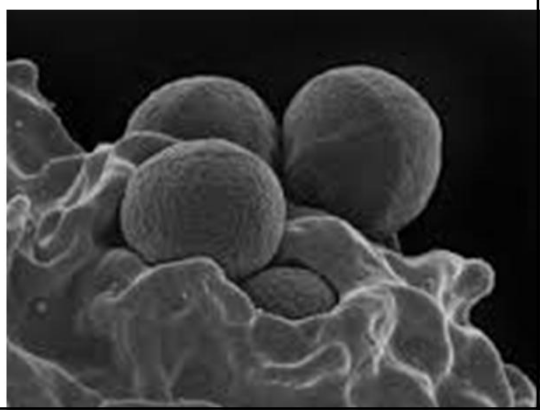
RESULTS

The modified intention-to-treat population comprised 475 patients who received oritavancin and 479 patients who received vancomycin. All three efficacy end points met the prespecified noninferiority margin of 10 percentage points for oritavancin versus vancomycin: primary end point, 82.3% versus 78.9% (95% confidence interval [CI] for the difference, −1.6 to 8.4 percentage points); investigator-assessed clinical cure, 79.6% versus 80.0% (95% CI for the difference, −5.5 to 4.7 percentage points); and proportion of patients with a reduction in lesion area of 20% or more, 86.9% versus 82.9% (95% CI for the difference, −0.5 to 8.6 percentage points). Efficacy outcomes measured according to type of pathogen, including methicillin-resistant *Staphylococcus aureus*, were similar in the two treatment groups. The overall frequency of adverse events was also similar, although nausea was more common among those treated with oritavancin.

CONCLUSIONS

A single dose of oritavancin was noninferior to twice-daily vancomycin administered for 7 to 10 days for the treatment of acute bacterial skin and skin-structure infections caused by gram-positive pathogens. (Funded by the Medicines Company; SOLO I ClinicalTrials.gov number, NCT01252719.)

N ENGL J MED 370;23 NEJM.ORG JUNE 5, 2014



Clin Infect Dis. 2015 Jan 15;60(2):254-62. doi: 10.1093/cid/ciu778. Epub 2014 Oct 6.

Single-dose oritavancin versus 7-10 days of vancomycin in the treatment of gram-positive acute bacterial skin and skin structure infections: the SOLO II noninferiority study.

Corey GR[1], Good S[2], Jiang H[2], Moeck G[2], Wikler M[2], Green S[3], Manos P[4], Keech R[5], Singh R[6], Heller B[7], Bubnova N[8], O'Riordan W[9]; SOLO II Investigators.

Рандомизированное двойное слепое исследование

Оритаванцин *VS.* **Ванкомицин**

Острые бактериальные инфекции кожи и мягких тканей

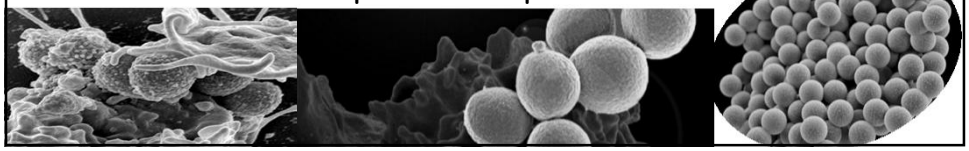
1005 пациентов (503 vs. 502)

Клиническая эффективность – 82.7% vs. 80.5% (95% CI, -2.6-7.0)

Уменьшение зоны поражения ≥ 20% – 85.9% vs 85.3%

(95% CI, -3.7-5.0)

Нежелательные лекарственные реакции - NS



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 5, 2014 VOL. 370 NO. 23

Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection

Helen W. Boucher, M.D., Mark Wilcox, M.D., George H. Talbot, M.D., Sailaja Puttagunta, M.D., Anita F. Das, Ph.D., and Michael W. Dunne, M.D.

ABSTRACT

BACKGROUND

Dalbavancin, a lipoglycopeptide antibiotic agent that is active against gram-positive pathogens, has a long plasma half-life, allowing for once-weekly dosing. DISCOVER 1 and DISCOVER 2 were identically designed noninferiority trials of dalbavancin for the treatment of acute bacterial skin and skin-structure infection.

METHODS

We randomly assigned patients to receive dalbavancin intravenously on days 1 and 8 or vancomycin intravenously for at least 3 days with the option to switch to oral linezolid to complete 10 to 14 days of therapy. The primary end point, early clinical response, required the cessation of spread of infection-related erythema and the absence of fever at 48 to 72 hours. Secondary end points at the end of therapy included clinical status and investigator's assessment of outcome.

RESULTS

Analysis of the primary end point showed noninferiority of dalbavancin in both DISCOVER 1 and DISCOVER 2. In the pooled analysis, 525 of 659 patients (79.7%) in the dalbavancin group and 521 of 653 (79.8%) in the vancomycin–linezolid group had an early clinical response indicating treatment success (weighted difference, −0.1 percentage point; 95% confidence interval, −4.5 to 4.2). The outcomes were similar in the analyses by study and the pooled analyses of clinical status at the end of therapy and the investigator's assessment of outcome. For patients infected with *Staphylococcus aureus*, including methicillin-resistant *S. aureus*, clinical success was seen in 90.6% of the patients treated with dalbavancin and 93.8% of those treated with vancomycin–linezolid. Adverse events and study days with an adverse event were less frequent in the dalbavancin group than in the vancomycin–linezolid group. The most common treatment-related adverse events in either group were nausea, diarrhea, and pruritus.

CONCLUSIONS

Once-weekly intravenous dalbavancin was not inferior to twice-daily intravenous vancomycin followed by oral linezolid for the treatment of acute bacterial skin and skin-structure infection. (Funded by Durata Therapeutics; DISCOVER 1 and DISCOVER 2 ClinicalTrials.gov numbers, NCT01339091 and NCT01431339.)

From the Division of Infectious Diseases and Geographic Medicine, Tufts Medical Center and Tufts University School of Medicine, Boston (H.W.B.); the Department of Microbiology, Leeds Teaching Hospital and University of Leeds, Old Medical School, Leeds, United Kingdom (M.W.); Talbot Advisors, Anna Maria, FL (G.H.T.); Durata Therapeutics, Branford, CT (S.P., M.W.D.); and InClin, San Mateo, CA (A.F.D.). Address reprint requests to Dr. Boucher at Tufts Medical Center, 800 Washington St., Box 238, Boston, MA 02111, or at hboucher@tuftsmedicalcenter.org.

N Engl J Med 2014;370:2169-79.
DOI: 10.1056/NEJMoa1310480

FDA MAY 2014

Dalbavancin

CAS# 171500-79-1

FDA Approves Dalbavancin for the Treatment of Acute Skin Infections

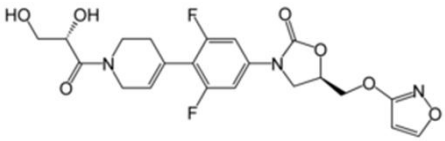
IGM

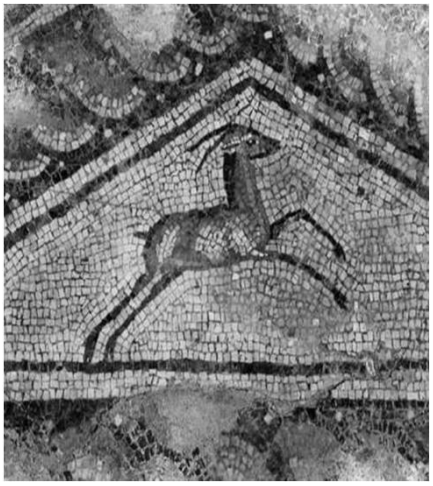
Новые препараты…

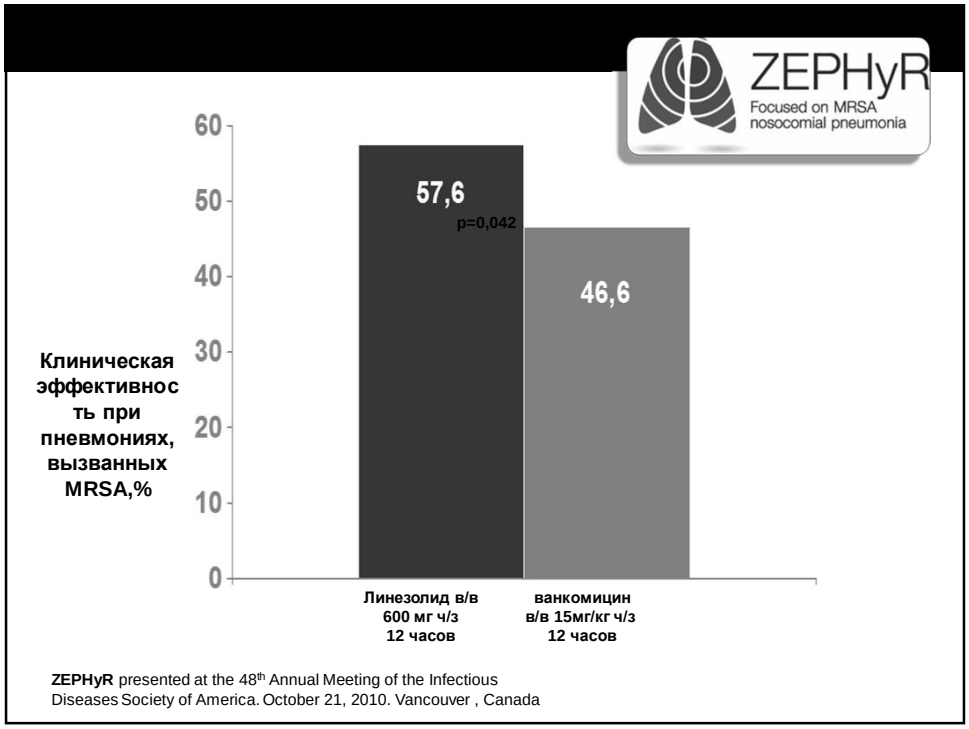
- **Телаванцин:**

- Липопептид; ингибирует синтез бактериальной стенки.
- Ноябрь 2012 года (FDA) - нозокомиальная пневмония, вызванная MRSA при отсутствии других препаратов.
- 2 исследования (1532 пациента) – телаванцин превосходит ванкомицин по эффективности при нозокомиальной пневмонии, вызванной *S.aureus.*

Линезолид







ZEPHyR presented at the 48th Annual Meeting of the Infectious Diseases Society of America. October 21, 2010. Vancouver , Canada

1. Cottagnound et al. *J Antimicrob Chemother.* 2000;46:981-985; 2. ZYVOX® (linezolid injection, tablets, and oral suspension) [package insert]. Kalamazoo, Mich: Pharmacia & Upjohn, a Pfizer Company; revised 2003; 3. Lovering AM et al. *J Antimicrob Chemother.* 2002, 50:73-77; 4. Conte JE et al. *Antimicrob Agents Chemother.* 2002;46:1475-1480; 5. Gee T. *Antimicrob Agents Chemother.* 2001;45:1843-1846.

Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial

Gregory J Moran, Edward Fang, G Ralph Corey, Anita F Das, Carisa De Anda, Philippe Prokocimer

Summary

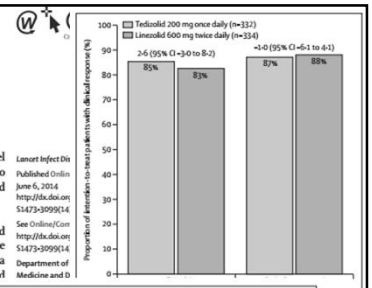
Background New antibiotics are needed to treat infections caused by drug-resistant bacteria. Tedizolid is a novel oxazolidinone antibacterial drug designed to provide enhanced activity against Gram-positive pathogens. We aimed to assess the efficacy and safety of intravenous to oral tedizolid for treatment of patients with acute bacterial skin and skin-structure infections.

Methods ESTABLISH-2 was a randomised, double-blind, phase 3, non-inferiority trial done between Sept 28, 2011, and Jan 10, 2013, at 58 centres in nine countries. Patients (aged ≥12 years) with acute bacterial skin and skin-structure infections (cellulitis or erysipelas, major cutaneous abscess, or wound infection) that had a minimum lesion area of 75 cm² and were suspected or documented to be associated with a Gram-positive pathogen, were randomly assigned (1:1), via an interactive voice-response system with block ra (200 mg for 6 days) or twice-daily linezolid (600 mg for 10 stratified by geographic region and type of acute bacterial skin early clinical response (≥20% reduction in lesion area at 48–72 of −10%. Analysis was by intention to treat. This study is regis

Findings 666 patients were randomly assigned to receive tedi the tedizolid group and 276 (83%) in the linezolid group ac −3·0 to 8·2), meeting the prespecified non-inferiority margir tedizolid than linezolid, taking place in 52 (16%) of 331 patie Treatment-emergent adverse events leading to discontinuati the tedizolid group and four (1%) patients in the linezolid gr

Interpretation Intravenous to oral once-daily tedizolid 200 600 mg for 10 days for treatment of patients with acute bact become a useful option for the treatment of acute bacteria outpatient settings.

Funding Cubist Pharmaceuticals



	Tedizolid phosphate (n=332)	Linezolid (n=334)	Absolute percent difference (95% CI)
Cellulitis or erysipelas	134/166 (81%)	135/168 (80%)	0·3% (−8·2 to 8·9)
Major cutaneous abscess	59/68 (87%)	61/68 (90%)	−2·9% (−14·5 to 8·4)
Wound infection	90/98 (92%)	80/98 (82%)	10·2% (0·7 to 20·1)
ABSSSI on leg and foot	109/132 (83%)	109/137 (80%)	3·0% (−5·5 to 12·5)
Antibacterial use in previous 7 days	7/10 (70%)	5/6 (83%)	−13·3% (ND)
Patients with bacteraemia	7/7 (100%)	9/12 (75%)	25·0% (ND)
Presence of baseline fever	96/103 (93%)	89/97 (92%)	1·4% (−6·3 to 9·5)
Absence of baseline fever	187/229 (82%)	187/237 (79%)	2·8% (−4·5 to 10·0)
MRSA	44/53 (83%)	44/56 (79%)	4·4% (−10·8 to 19·5)
MSSA	97/105 (92%)	94/111 (85%)	7·7% (−0·9 to 16·6)
Other baseline pathogen identified	50/59 (85%)	47/59 (80%)	5·0% (−9·1 to 19·3)
No baseline pathogen identified	109/135 (81%)	110/132 (83%)	−2·6% (−11·9 to 6·7)
Received intravenous study drug on day 1 only then switched to oral	133/150 (89%)	139/159 (87%)	1·3% (−6·2 to 8·6)
USA	128/156 (82%)	131/158 (83%)	−0·8% (−9·4 to 7·6)
Europe	104/112 (93%)	99/111 (89%)	3·7% (−4·1 to 11·7)
Other geographies	51/64 (80%)	46/65 (71%)	8·9% (−6·1 to 23·7)

−20 −10 0 10 20 30
Linezolid better Tedizolid better

Figure 3: **Early clinical response at the 48–72 h visit by subgroup in the intention-to-treat population**
Data are n/N (%), unless otherwise indicated. Percent difference is response rate for the tedizolid group minus linezolid group. Some patients had more than one baseline pathogen identified. ABSSSI= acute bacterial skin and skin-structure infection. MRSA=meticillin-resistant *Staphylococcus aureus*. MSSA=meticillin-susceptible *Staphylococcus aureus*. ND=not determinable.

Цефтаролин:

Clin Ther. 2012 Apr;34(4):743-65. doi: 10.1016/j.clinthera.2012.02.025. Epub 2012 Mar 22.

Ceftaroline fosamil: a cephalosporin with activity against methicillin-resistant Staphylococcus aureus.

Poon H[1], Chang MH, Fung HB.

Expert Rev Anti Infect Ther. 2014 Jul;12(7):727-9. doi: 10.1586/14787210.2014.908118. Epub 2014 Jun 5.

A novel treatment option for MRSA pneumonia: ceftaroline fosamil-yielding new hope in the fight against a persistent infection.

Arshad S[1], Hartman P, Zervos MJ.

Diagn Microbiol Infect Dis. 2014 Apr;78(4):422-8. doi: 10.1016/j.diagmicrobio.2013.08.027. Epub 2014 Jan 18.

Ceftaroline activity against bacterial organisms isolated from acute bacterial skin and skin structure infections in United States medical centers (2009-2011).

Pfaller MA[1], Flamm RK[1], Sader HS[2], Jones RN[1].

- **Осложненные инфекции кожи и мягких тканей** (CANVAS I и CANVAS II)
- **Внебольничная пневмония** (FOCUS I и FOCUS II)

J Antimicrob Chemother. 2014 Jul;69(7):2010-3. doi: 10.1093/jac/dku085. Epub 2014 Mar 28.

Salvage treatment of methicillin-resistant staphylococcal endocarditis with ceftaroline: a multicentre observational study.

Tattevin P[1], Boutoille D[2], Vitrat V[3], Van Grunderbeeck N[4], Revest M[5], Dupont M[6], Alfandari S[7], Stahl JP[8].

J Chemother. 2015 Feb;27(1):29-34. doi: 10.1179/1973947813Y.0000000156. Epub 2013 Dec 19.

Methicillin-resistant Staphylococcus aureus nosocomial pneumonia patients treated with ceftaroline: retrospective case series of 10 patients.

Pasquale TR, Tan MJ, Trienski TL, File TM Jr.

Int J Antimicrob Agents. 2013 Nov;42(5):450-5. doi: 10.1016/j.ijantimicag.2013.07.005. Epub 2013 Aug 11.

Ceftaroline for meticillin-resistant Staphylococcus aureus bacteraemia: case series and review of the literature.

Polenakovik HM[1], Pleiman CM.

Streptococcus spp.
Staphylococcus spp.
(MRSA, VISA, VRSA, DRSA)
H. influenzae
M. catarrhalis
Neisseria spp.
Enterobacteriaceae spp.
Aeromonas spp.
Pasteurella spp.
Peptostreptococcus spp.
P.aeruginosa (?)

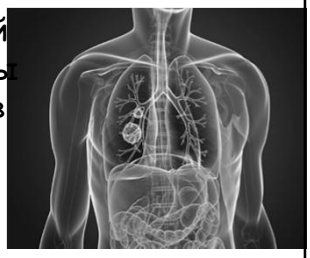
Цефтаролин:

J Antimicrob Chemother. 2015 Dec 24. pii: dkv415. [Epub ahead of print]

Ceftaroline fosamil versus ceftriaxone for the treatment of community-acquired pneumonia: individual patient data meta-analysis of randomized controlled trials.

Taboada M[1], Melnick D[2], Iaconis JP[3], Sun F[4], Zhong NS[5], File TM[6], Llorens L[7], Friedland HD[7], Wilson D[8].

- Цефтаролин vs. цефтриаксон 5-7 дней
- 3 клинических исследования III фазы
- 1916 госпитализированных пациентов с ВП



Цефтаролин > цефтриаксон

(1.65; 95% ДИ 1.26, 2.16; P<0.001)

АБТ в предшествующие 96 часов снижает различия между препаратами

Цефтобипрол:

Int J Antimicrob Agents. 2012 Mar;39(3):240-6. doi: 10.1016/j.ijantimicag.2011.11.005. Epub 2012 Jan 9.

A randomised, double-blind trial comparing ceftobiprole medocaril with ceftriaxone with or without linezolid for the treatment of patients with community-acquired pneumonia requiring hospitalisation.

Nicholson SC[1], Welte T, File TM Jr, Strauss RS, Michiels B, Kaul P, Balis D, Arbit D, Amsler K, Noel GJ.

Clin Infect Dis. 2014 Jul 1;59(1):51-61. doi: 10.1093/cid/ciu219. Epub 2014 Apr 9.

A phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia.

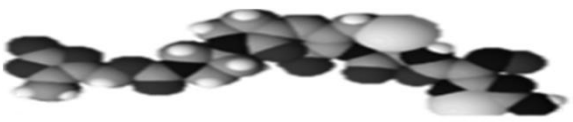
Awad SS[1], Rodriguez AH[2], Chuang YC[3], Marianek Z[4], Pareigis AJ[5], Reis G[6], Scheeren TW[7], Sánchez AS[8], Zhou X[9], Saulay M[10], Engelhardt M[11].

Antimicrob Agents Chemother. 2014 May;58(5):2512-9. doi: 10.1128/AAC.02611-13. Epub 2014 Feb 10.

Exposure to ceftobiprole is associated with microbiological eradication and clinical cure in patients with nosocomial pneumonia.

Muller AE[1], Punt N, Mouton JW.

- **Внебольничная пневмония**
- **Нозокомиальная пневмония** (кроме ВАП)
- **Осложненные инфекции кожи и мягких тканей**



Streptococcus spp.
Staphylococcus spp.
(MRSA, VISA, VRSA, DRSA)
H. influenzae
M. catarrhalis
Neisseria spp.
Enterobacteriaceae spp.
Aeromonas spp.
Pasteurella spp.
Peptostreptococcus spp.
P.aeruginosa (?)

Новые препараты…

- **Тейксобактин (Teixobactin):**

ARTICLE

doi:10.1038/nature14098

A new antibiotic kills pathogens without detectable resistance

Losee L. Ling[1]*, Tanja Schneider[2,3]*, Aaron J. Peoples[1], Amy L. Spoering[1], Ina Engels[2,3], Brian P. Conlon[4], Anna Mueller[2,3], Till F. Schäberle[2,3], Dallas E. Hughes[1], Slava Epstein[5], Michael Jones[1], Linos Lazarides[1], Victoria A. Steadman[1], Douglas R. Cohen[1], Cintia R. Felix[1], K. Ashley Fetterman[1], William P. Millett[1], Anthony G. Nitti[1], Ashley M. Zullo[1], Chao Chen[4] & Kim Lewis[4]

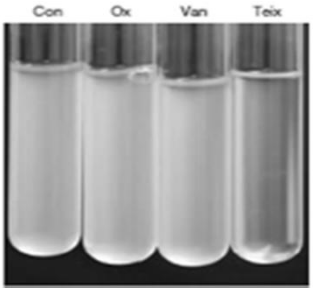
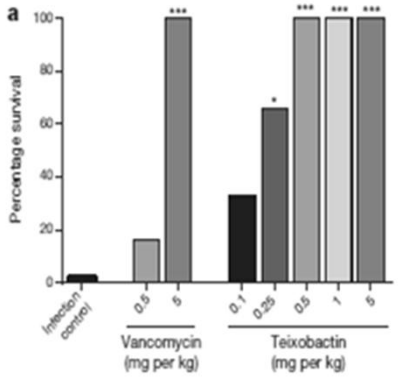


Table 1 | Activity of teixobactin against pathogenic microorganisms

Organism and genotype	Teixobactin MIC (μg ml^{-1})
S. aureus (MSSA)	0.25
S. aureus + 10% serum	0.25
S. aureus (MRSA)	0.25
Enterococcus faecalis (VRE)	0.5
Enterococcus faecium (VRE)	0.5
Streptococcus pneumoniae (penicillin^R)	≤ 0.03
Streptococcus pyogenes	0.06
Streptococcus agalactiae	0.12
Viridans group streptococci	0.12
B. anthracis	≤ 0.06
Clostridium difficile	0.005
Propionibacterium acnes	0.08
M. tuberculosis H37Rv	0.125
Haemophilus influenzae	4
Moraxella catarrhalis	2
Escherichia coli	25
Escherichia coli (*asmB1*)	2.5
Pseudomonas aeruginosa	>32
Klebsiella pneumoniae	>32

The MIC was determined by broth microdilution. MSSA, methicillin-sensitive *S. aureus*; VRE, vancomycin-resistant enterococci.



Спасибо за внимание!