MRSA的治疗方案:除了万古霉素和利奈唑胺，将何去何从?

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http://www.facm.ucl.ac.be

其中几张幻灯片是借鉴Françoise Van Bambeke, PharmD, PhD的

第三届上海国际临床微生物及抗微生物化疗学术会议

上海 中国

With approval of the Common Belgian Medical Ethical platform - visa no. 13/V1/5871/053304

葡萄球菌：前60年……

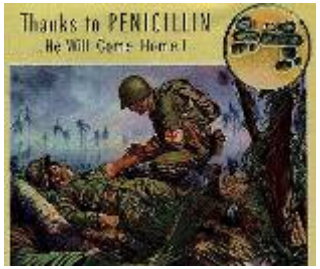
1881年:
Alexander Ogston
首次在脓液中观察到了葡萄球菌

"球菌被注射时毒性巨大，但是当它在伤口及溃疡表面时似乎是无害的."
Br Med J 1881;1:369e375

1884年：
Friedrich Rosenbach 首次对金黄色葡萄球菌和白葡萄球菌进行了鉴别

1914-1918年：
第一次世界大战，近半数伤亡是金黄色葡萄球菌感染所致

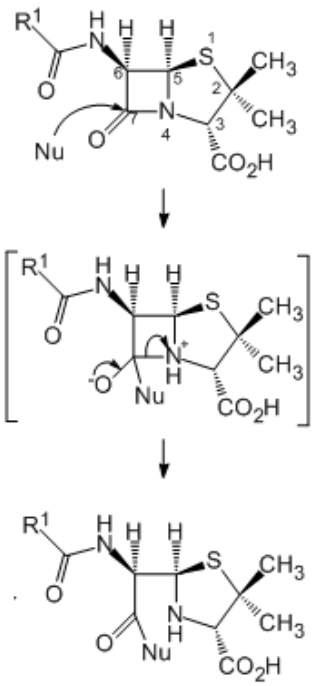
1940-45年：
青霉素（当时抗葡萄球菌*是普遍有效的）的生产方法仍然是个军事秘密



*弗莱明（1928）首次观察到金黄色葡萄球菌

葡萄球菌：接下来的17年……

1994年，首次描述了金葡菌*的β-内酰胺酶



Lee, S. (2008). State of C2/C3 substituents of ?-lactam antibiotics in the β-lactam ring cleavage by β-lactamases. *PHILICA.COM Article number 122*.

*1940年，在大肠埃希菌中首次发现β-内酰胺酶 (Nature 146, 837 (28 December 1940)

1950-70年，几乎所有的金葡菌产β-内酰胺酶

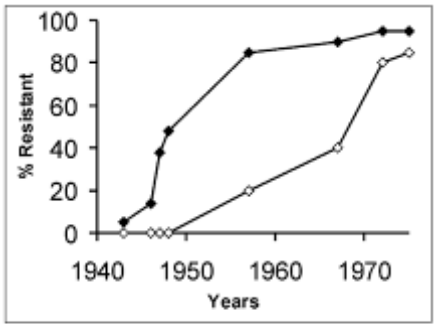


Figure. Secular trends of approximate prevalence rates for penicillinase-producing, methicillin-susceptible strains of *Staphylococcus aureus* in hospitals (closed symbols) and the community (open symbols).

1960年，引入甲氧西林……1961年，出现甲氧西林耐药

694 SEPT. 3, 1960 BRITISH MEDICAL JOURNAL BRL 1241

MICROBIOLOGICAL STUDIES ON SODIUM 6-(2,6 DIMETHOXYBENZAMIDO) PENICILLANATE MONOHYDRATE (BRL 1241) IN VITRO AND IN PATIENTS

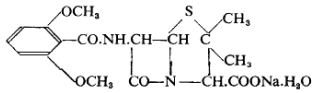
BY

G. T. STEWART, M.D., B.Sc.

With the Technical Assistance of PATRICIA M. HARRISON, B.Sc., and R. J. HOLT, F.I.M.L.T.

From Queen Mary's Hospital for Children and the Medical Research Council Laboratories, Carshalton, Surrey

A report in 1959 by Batchelor *et al.* on the isolation of 6-aminopenicillanic acid drew attention to the possibility of synthesizing new forms of penicillin by the introduction of side-chains. Derivatives prepared in this way may or may not possess antibacterial activity, but we were particularly impressed by the range and mode of action of one derivative, supplied to us in 1959 as BRL 1241 ("celbenin"). The compound—sodium 6-(2,6 dimethoxybenzamido)penicillanate monohydrate—may be represented by the following structural formula:



Methicillin-resistant staphylococci

MARY BARBER

From the Department of Bacteriology, Postgraduate Medical School of London

SYNOPSIS Eighteen strains of *Staph. pyogenes* (nine penicillin-sensitive and nine penicillin-destroying) were passaged 40 to 50 times on Celbenin[1] ditch plates.

All strains developed an increase in resistance to Celbenin and eight strains (four penicillin-sensitive and four penicillin-destroying) were able to grow in 100 μg/ml. or more Celbenin. Resistance was of the drug-tolerant type and none of the cultures inactivated Celbenin. There was an associated increase in tolerance to benzyl penicillin.

The highly Celbenin-resistant cultures isolated from penicillin-destroying staphylococci were in sharp contrast to those from penicillin-sensitive strains, as well as to penicillin G-tolerant staphylococci isolated *in vitro*, because they retained the cultural characteristics, coagulase and haemolytic activity, and mouse virulence of the parent strains, and the degree of resistance remained stable after repeated passage in the absence of Celbenin.

Three naturally occurring Celbenin-resistant strains of *Staph. pyogenes* isolated from infective processes were also studied. All three strains grew luxuriantly in concentrations of Celbenin up to 12·5 μg/ml. but very poorly in higher concentrations.

The possible significance of these findings is discussed.

金葡菌：1961年至今……

19世纪七十年代：
甲氧西林耐药菌
种在医院内传播

19世纪八十年代：
再次大规模使用
万古霉素*

1997年：出现对
万古霉素敏感菌
性减少的菌株

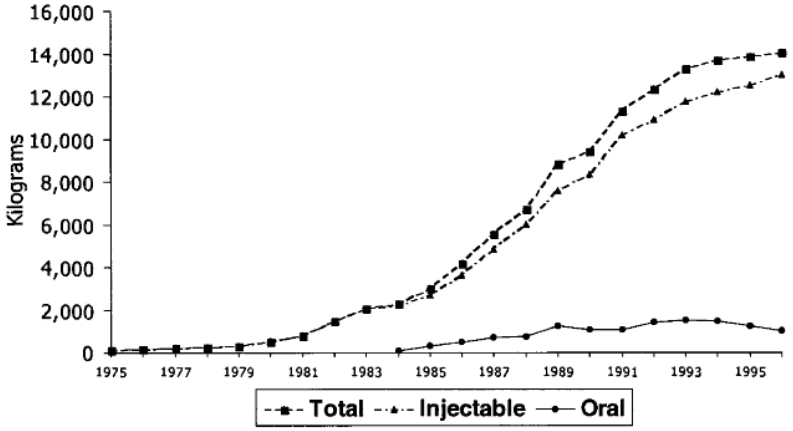


FIG. 1. Usage of vancomycin (in kilograms) in the United States, France, Italy, Germany, United Kingdom, and The Netherlands.

Kirst et al. Antimicrob Agents Chemother. 1998: 42:1303-4.

Journal of Antimicrobial Chemotherapy (1997) **40**, 135–146

Correspondence

Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility

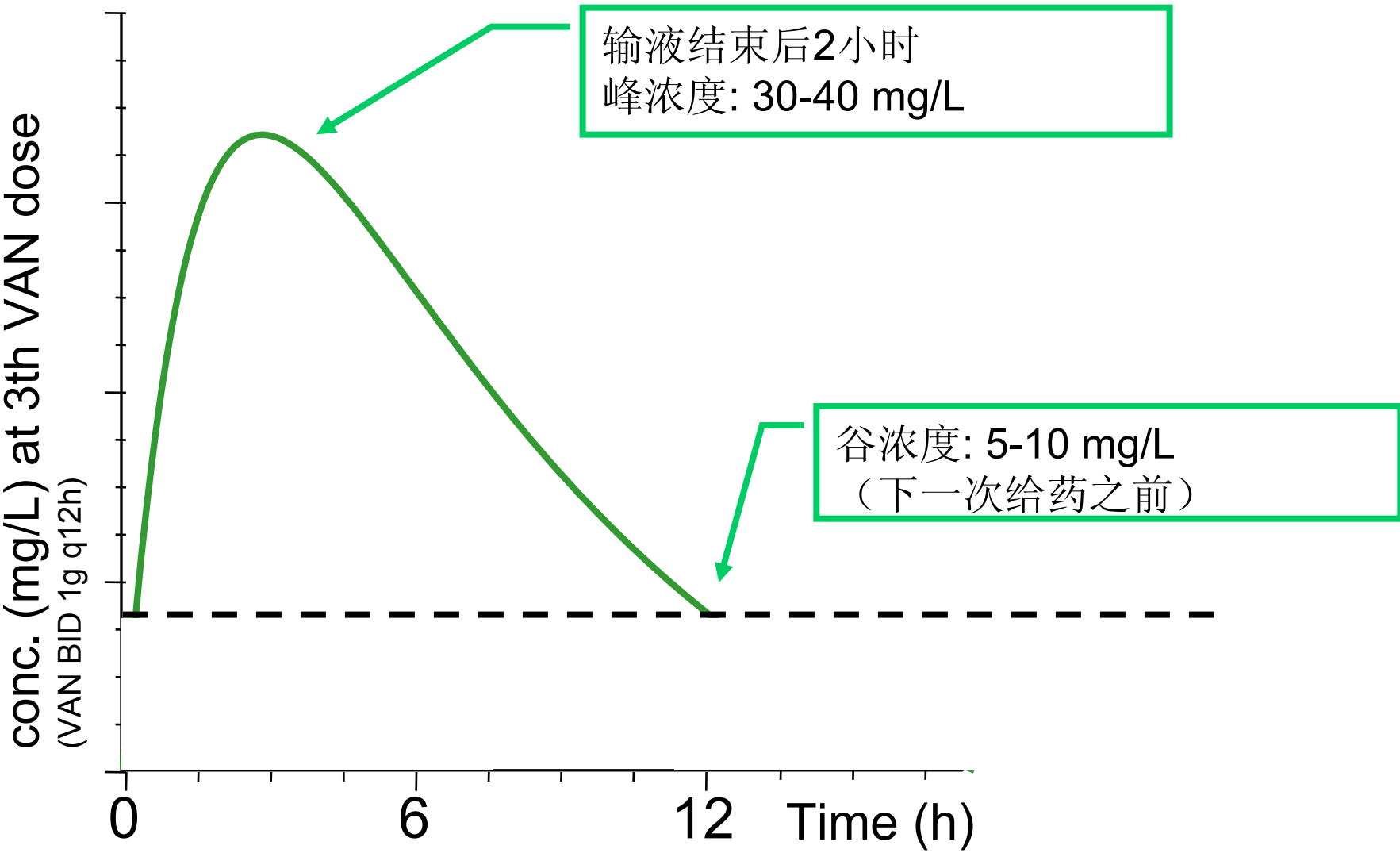
J Antimicrob Chemother 1997; **40:** 135–136

K. Hiramatsu[a]*, H. Hanaki[a], T. Ino[b], K. Yabuta[b], T. Oguri[c] and F. C. Tenover[d]

[a]*Department of Bacteriology;* [b]*Department of Pediatrics, Juntendo University, Tokyo;* [c]*Clinical Laboratory, Juntendo Hospital, Tokyo, Japan;* [d]*Nosocomial Pathogens Laboratory, Centers for Disease Control and Prevention, Atlanta, GA, USA*

* 1955-57年，引入万古霉素。
(Antibiot Annu. 1955-1956;3:606-322 and 1956-57;4:75-122)

万古霉素 (黄金时代)


输液结束后2小时
峰浓度: 30-40 mg/L
谷浓度: 5-10 mg/L
（下一次给药之前）
conc. (mg/L) at 3th VAN dose
(VAN BID 1g q12h)
0
6
12
Time (h)

2011年，万古霉素的相关报导

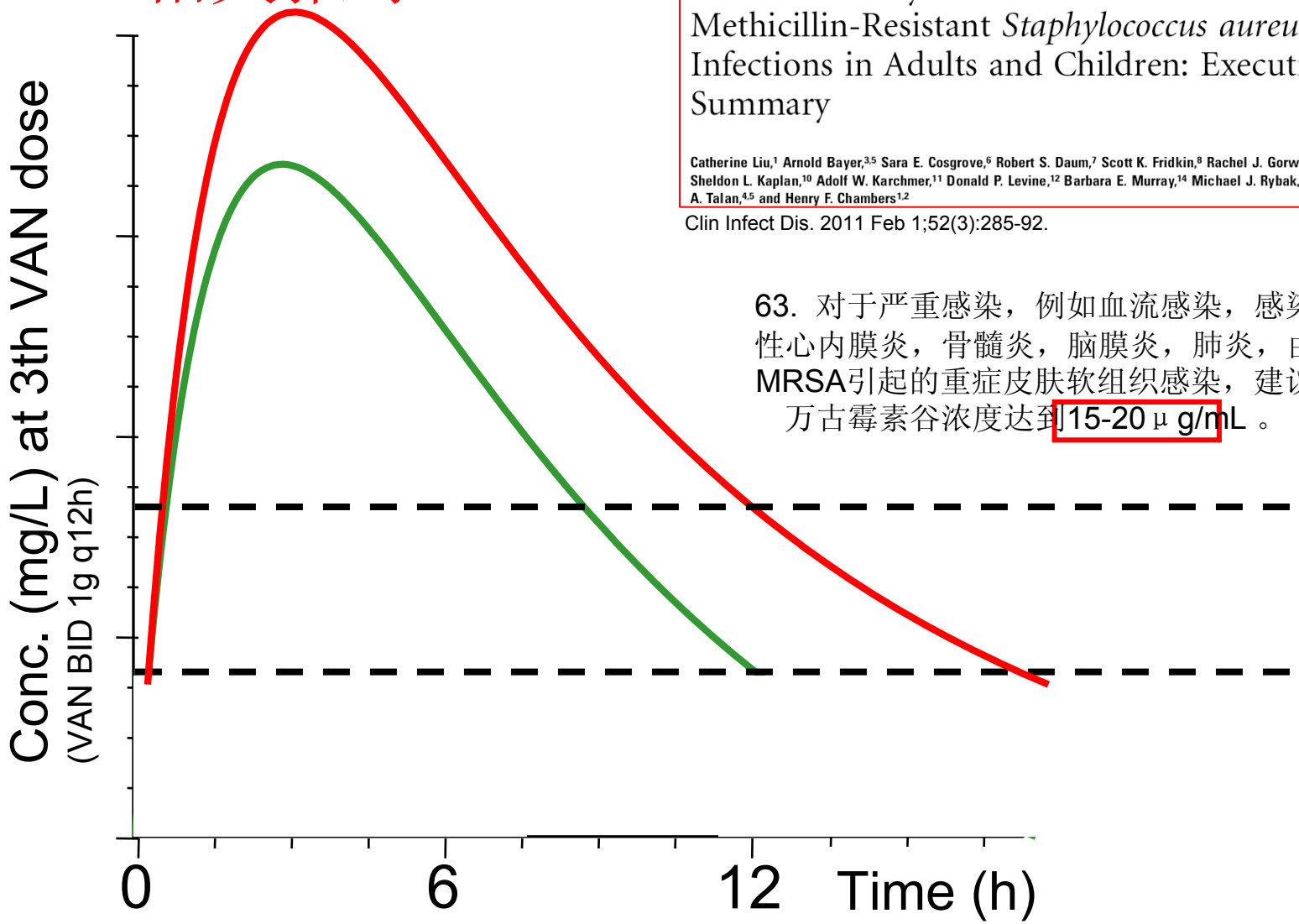
IDSA GUIDELINES

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

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[4,5] and Henry F. Chambers[1,2]

Clin Infect Dis. 2011 Feb 1;52(3):285-92.

63. 对于严重感染，例如血流感染，感染性心内膜炎，骨髓炎，脑膜炎，肺炎，由MRSA引起的重症皮肤软组织感染，建议万古霉素谷浓度达到15-20μg/mL。



2013年,万古霉素的相关报导

Hall *et al. BMC Pharmacology and Toxicology* 2013, **14**:12
http://www.biomedcentral.com/2050-6511/14/12

BMC Pharmacology & Toxicology

RESEARCH ARTICLE Open Access

Empiric guideline-recommended weight-based vancomycin dosing and nephrotoxicity rates in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: a retrospective cohort study

Ronald G Hall II[1,2*], Kathleen A Hazlewood[1,7], Sara D Brouse[1,8], Christopher A Giuliano[3,9], Krystal K Haase[3], Chistopher R Frei[4], Nicolas A Forcade[4,10], Todd Bell[5], Roger J Bedimo[6] and Carlos A Alvarez[1,2]

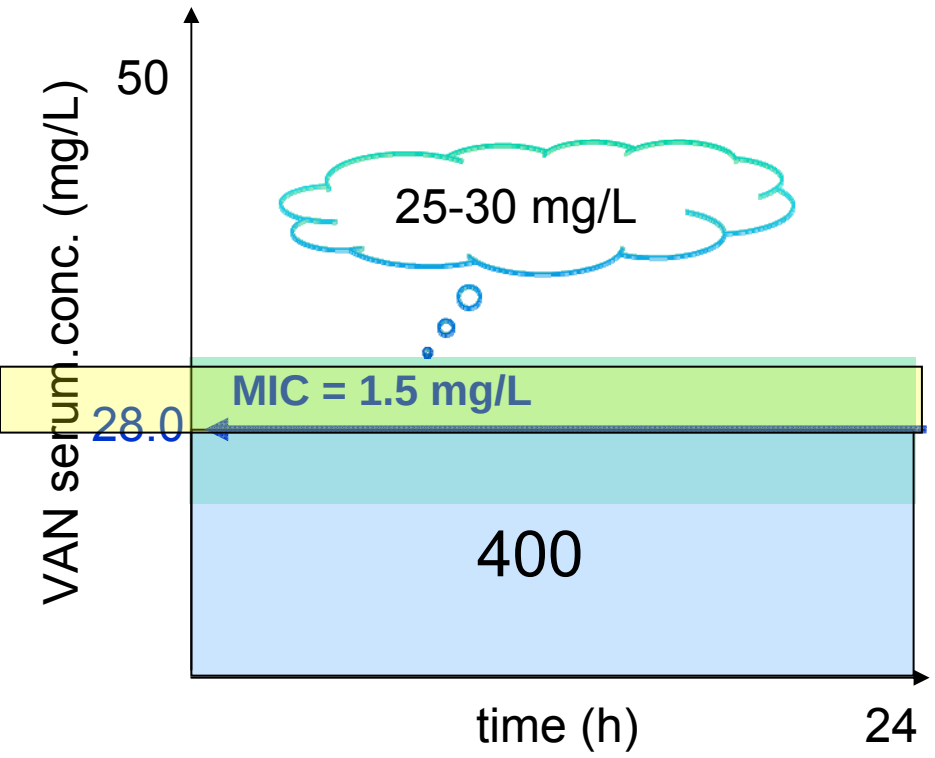
Nephrotoxicity occurred in 78 patients (23%), occurring in 56%, 11%, and 33% of patients at Hospitals A, B, and C, respectively. The median (interquartile range) increase from baseline to peak serum creatinine was 0.0 mg/dL (0.0, 0.2) for patients who did not develop nephrotoxicity versus 1.0 mg/dL (0.6, 2.1) for patients who developed nephrotoxicity. Fifteen percent of patients had a vancomycin trough concentration greater than 20 mcg/ml. Concurrent nephrotoxins included contrast dye (34%), aminoglycosides (19%), and vasopressors (12%). Concomitant antimicrobials active against MRSA were used in 23% of patients.

78例患者发生了肾毒性（23％）

15%的患者万古霉素谷浓度大于20ug/ml。

万古霉素: 持续输注是否有效?

疗效



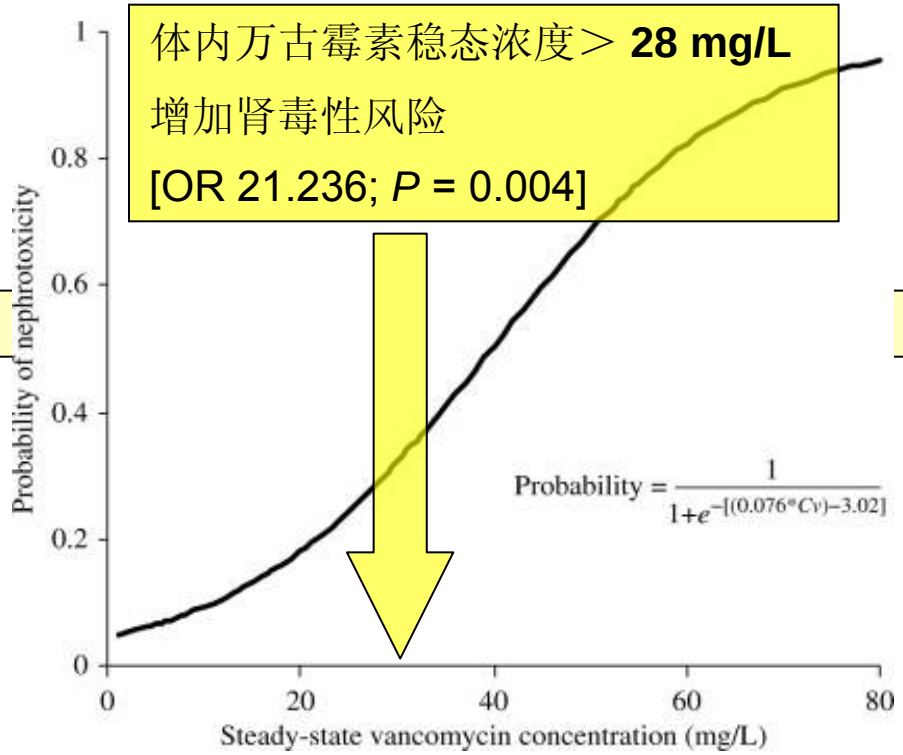
Moise-Broder et al. Clin Pharmacokinet. 2004;43:925-42

毒性

体内万古霉素稳态浓度＞ **28 mg/L**

增加肾毒性风险

[OR 21.236; *P* = 0.004]



Ingram, P. R. et al. J. Antimicrob. Chemother. 2008 Jul;62 (1): 168-71.

金黄色葡萄球菌与利奈唑胺

1996年：首次报导利奈唑胺

J. Med. Chem. 1996, 39, 673−679 673

Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potential Treatment of Multidrug-Resistant Gram-Positive Bacterial Infections

Steven J. Brickner,* Douglas K. Hutchinson, Michael R. Barbachyn, Peter R. Manninen, Debra A. Ulanowicz, Stuart A. Garmon, Kevin C. Grega, Susan K. Hendges, Dana S. Toops, Charles W. Ford, and Gary E. Zurenko
Upjohn Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

Received December 22, 1995[⊗]

Table 1. *In Vitro* Antibacterial Activity, Minimum Inhibitory Concentration (μg/mL)

organism	strain number	U-100592	U-100766	vancomycin
Staphylococcus aureus	UC[a] 9213	4	4	1
Staphylococcus aureus[c]	UC 12673	2	4	1
Staphylococcus aureus	ATCC[b] 29213	4	4	1
Staphylococcus epidermidis	UC 30031	1	1	1
Enterococcus faecalis	ATCC 29212	2	4	4
Enterococcus faecium	UC 12712	1	2	0.5
Streptococcus pneumoniae	UC 9912	0.5	1	0.5
Streptococcus pyogenes	UC 152	1	2	0.5
Bacteroides fragilis	ATCC 25285	1	1	>16[d]
Clostridium perfringens	ATCC 13124	1	1	1[e]
Mycobacterium tuberculosis	H37Rv	≤0.125	≤0.125	*f*

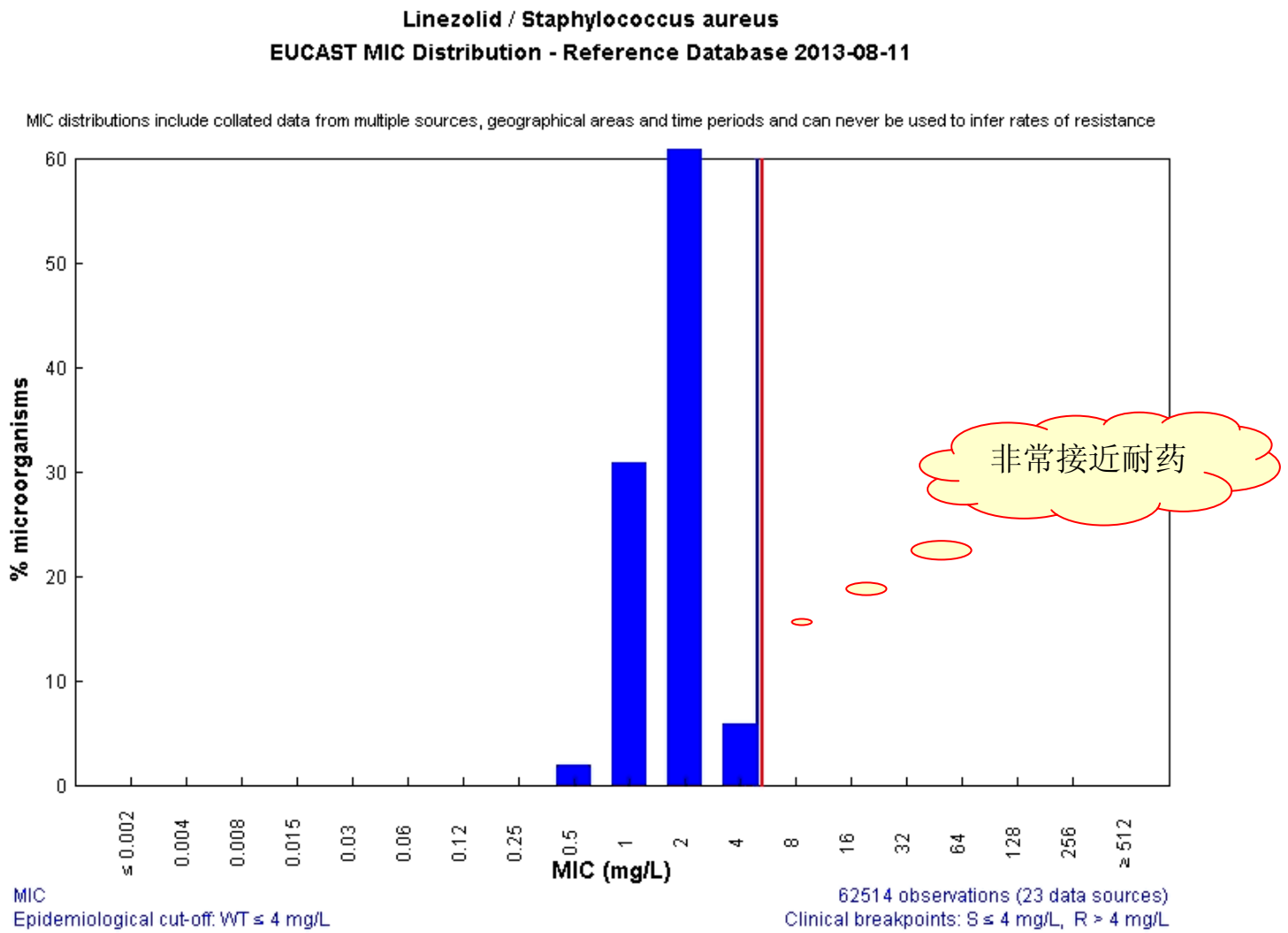
[a] Upjohn Culture (registered trademark of The Upjohn Co.).
[b] American Type Culture Collection.
[c] MRSA.
[d] Comparative control value for clindamycin was 0.5 μg/mL.
[e] Comparative control value for clindamycin was 0.06 μg/mL.
[f] Comparative control value for isoniazid was 0.20 μg/mL.

1998-2002年：靶点突变引起利奈唑胺耐药(保持比例)

2007年：对甲基化的利奈唑胺耐药 (*cfr*)

Toh et al. Mol Microbiol. 2007;64:1506-14.

利奈唑胺的折点


Linezolid / Staphylococcus aureus
EUCAST MIC Distribution - Reference Database 2013-08-11
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance
% microorganisms
0
10
20
30
40
50
60
≤ 0.002
0.004
0.008
0.015
0.03
0.06
0.12
0.25
0.5
1
2
4
8
16
32
64
128
256
≥ 512
MIC (mg/L)
MIC
Epidemiological cut-off: WT ≤ 4 mg/L
62514 observations (23 data sources)
Clinical breakpoints: S ≤ 4 mg/L, R > 4 mg/L
非常接近耐药

利奈唑胺的毒理学局限性

- **药物相互作用:**
  - 细胞色素P450： 无特殊作用
  - 抗生素:：利福平使利奈唑胺的血清水平降低21%
  - 单胺氧化酶抑制 (可逆的, 非选择性抑制剂):
    ↗ 肾上腺素和血清素制剂 (预防)
- **骨髓抑制** (包括贫血,白细胞减少症， 全血细胞减少症, 及血小板减少症)

(警惕)

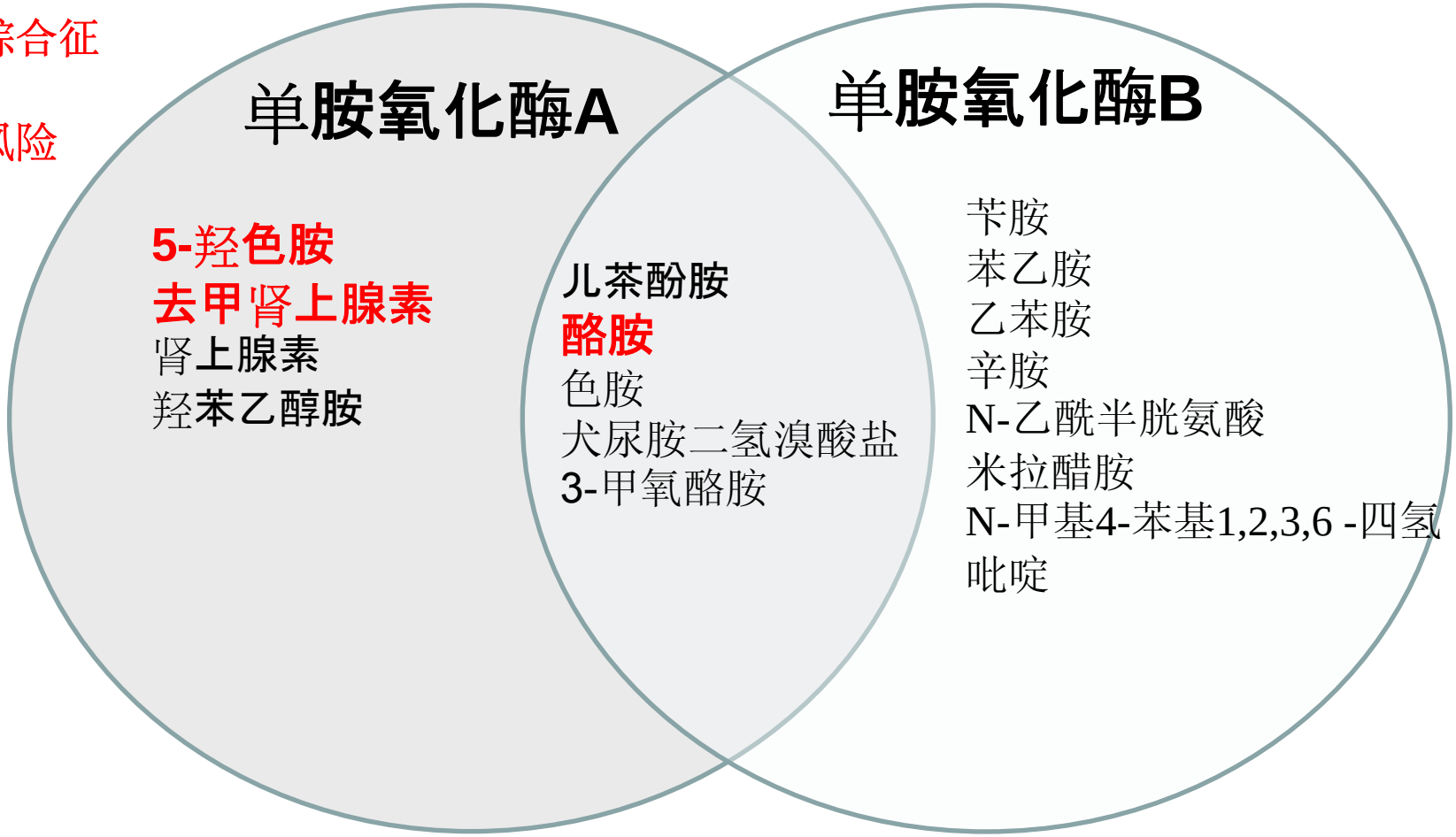
- 低血糖
- 乳酸性酸中毒 (预防措施 – 立即药物治疗)
- 周围和视神经病变 (> 28 天)
- 抽搐

利奈唑胺和单胺氧化酶 A

单胺氧化酶A受抑制的影响

血清素综合征

高血压风险



[a] MAO-A is the predominate form for oxidation of tyramine. Elmer and Bertoni. *Expert Opin Pharmacother*. 2008;9:2759-2772

以下是我们在比利时告诉药剂师的

Interactions linezolid - médicaments

Anti-migraineux
triptans
dihydroergotamine

Anti-dépresseurs
tricycliques
IMAO
ISRS

Anti-Parkinsoniens
L-Dopa
bromocryptine
selegiline

Anxiolytiques
buspirone

Sympathomimétiques
bronchodilatateurs
pseudoéphédrine

Vasopresseurs
(nor)adrénaline

Analgésiques
dextropropoxiphène
fentanyl
tramadol

Anti-émétiques
setrons
metoclopramide

Anti-psychotiques
clozapine
olanzapine
risperidone
lithium

Antitussifs
dextromethorphane
codéine

Lawrence et al., CID (2006) 42:1578-83

利奈唑胺与骨髓抑制: 中止治疗

Clinical Infectious Diseases 2006; 42:66–72

MAJOR ARTICLE

High Frequency of Linezolid-Associated Thrombocytopenia and Anemia among Patients with End-Stage Renal Disease

Vin-Cent Wu,[1,2] Yu-Ting Wang,[2] Cheng-Yi Wang,[2] I.-Jung Tsai,[3] Kwan-Dun Wu,[2] Juey-Jen Hwang,[1,2] and Po-Ren Hsueh[2,4]

[1]Department of Internal Medicine, Yun-Lin Branch, and Departments of [2]Internal Medicine, [3]Pediatrics, and [4]Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

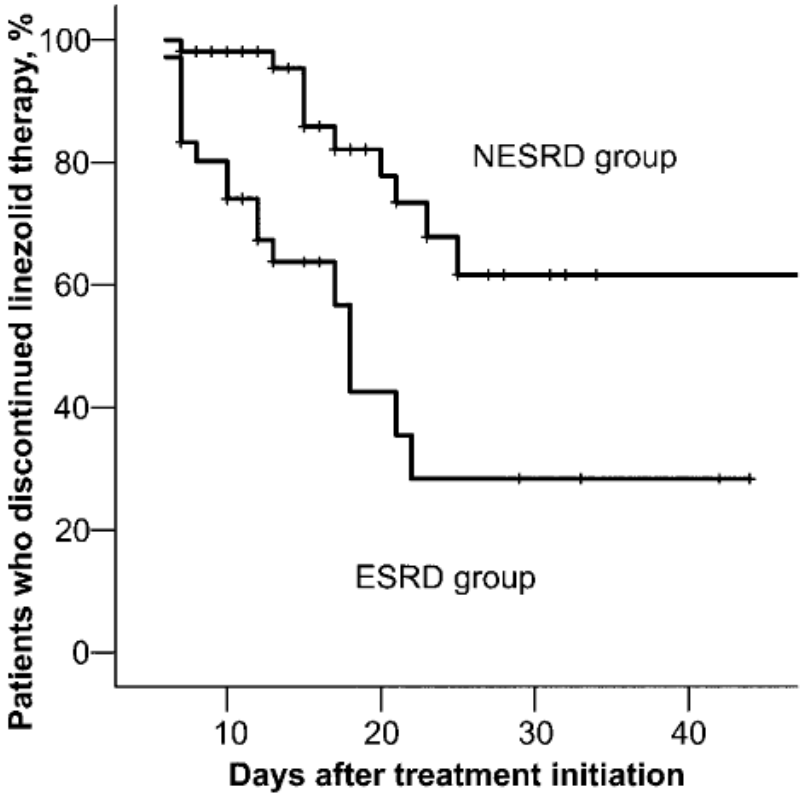
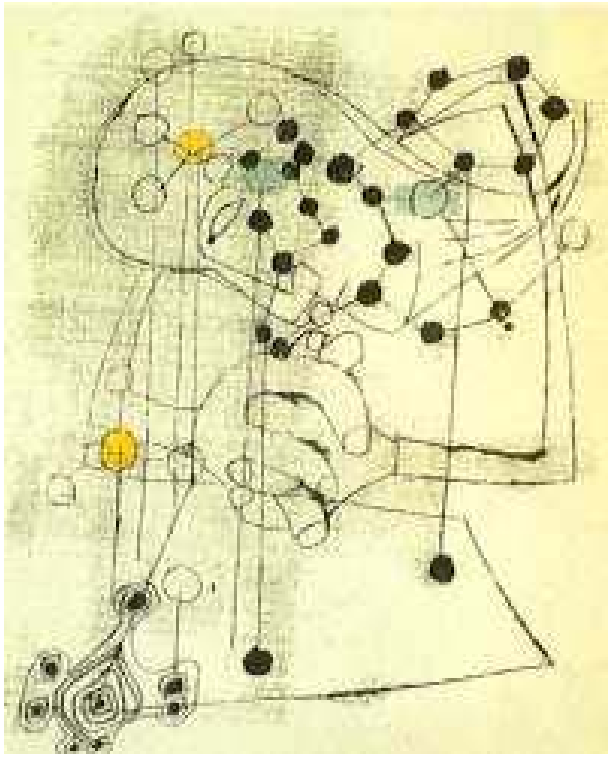


Figure 1. Kaplan-Meier survival estimates for patients receiving linezolid treatment who had end-stage renal disease (ESRD) or non–end-stage renal disease (NESRD) ($P < .001$, by the log-rank test).

所以，我们还有选择吗?



"Scientist" by Ben Shahn
New Jersey State Museum,
Trenton, N.J.

2008年前被批准上市的用于抗MRSA的药物

- 达托霉素 (2003年被批准)
- 替加环素 (2005年被批准)

- 磺胺甲基异恶唑，克林霉素，多西环素/米诺环素 (社区获得性耐甲氧西林金黄色葡萄球菌)
(也都是一些老药)

达托霉素: 具有历史意义的标志性事件....

1987 **1993** **1997**

发现一种新型的抗革兰氏阳性菌脂肽类药物：达托霉素

In vvitro and in ivo activity of LY 146032, a new cyclic lipopeptide antibiotic.
Eliopoulos *et al*, **1986** Antimicrob. Agents Chemother. 30, 532-5

中止研发
-抗菌活性差
- 毒性反应

*"Lilly was not satisfied with the overall clinical results observed with the **twice-daily** dosing regimen utilized in these studies"*

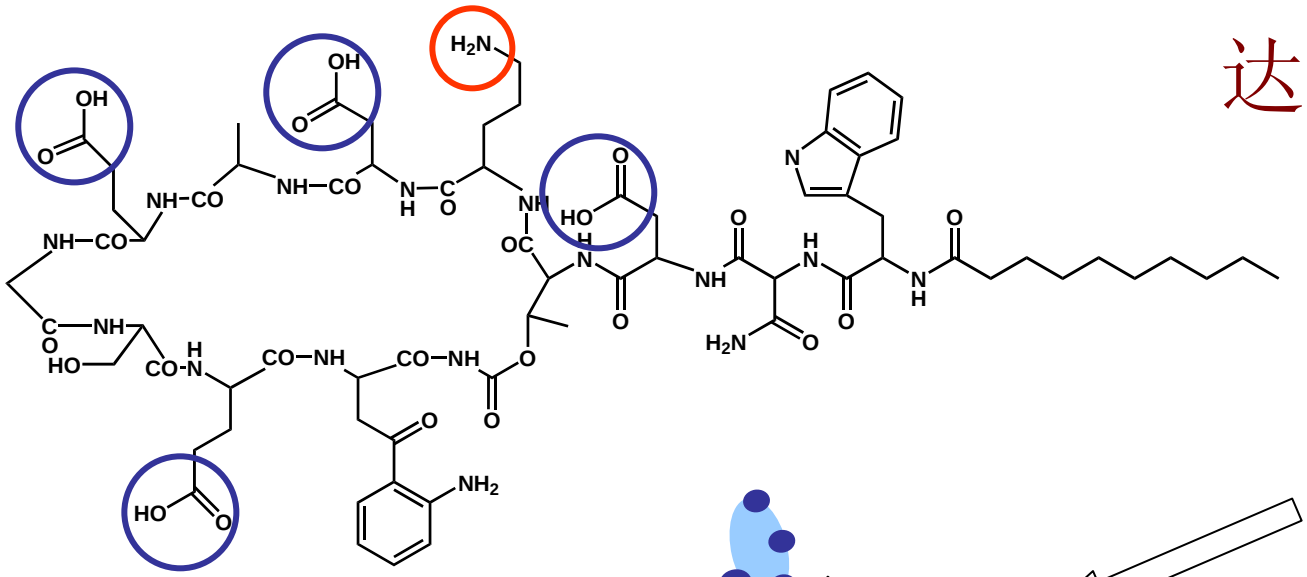
被CUBIST接管

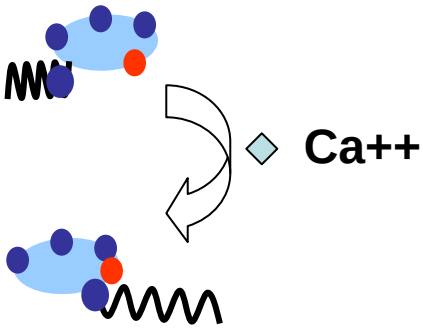
or *"pharmacodynamics in action ....."*

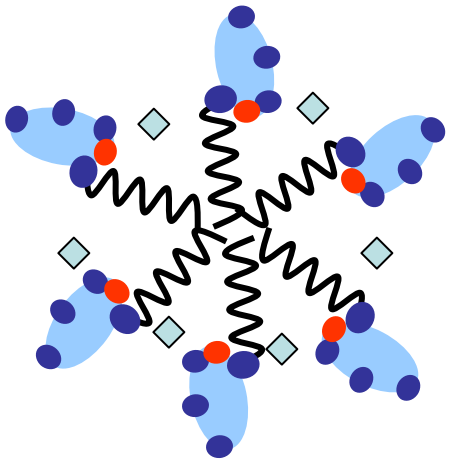
Once-daily dosing in dogs optimizes daptomycin safety.
Oleson *et al*, **2000**, AAC. 44:2948-53.

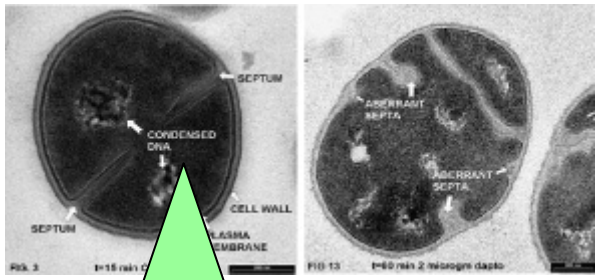
Daptomycin dose-effect relationship against resistant gram-positive organisms.
Cha *et al*, **2003,** AAC 47:1598-603

达托霉素…

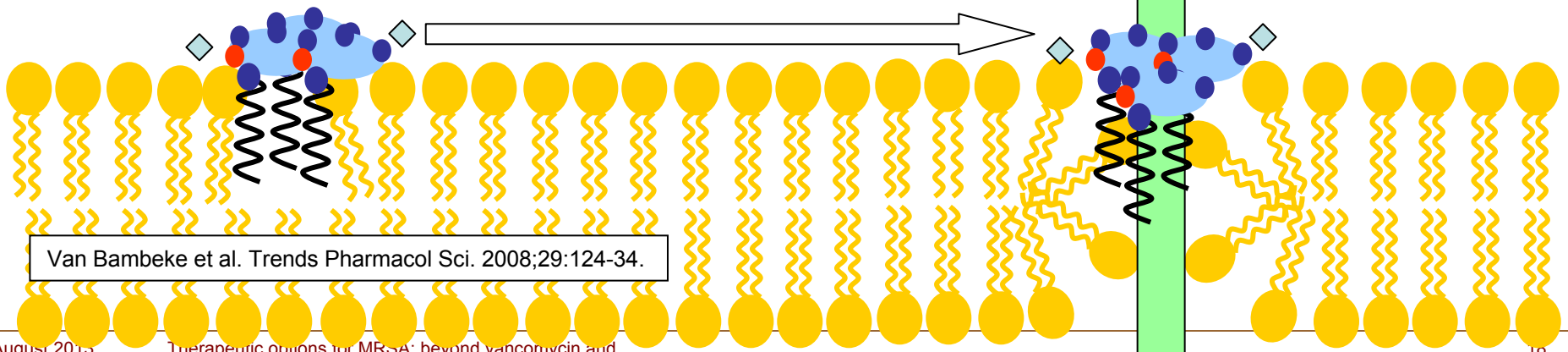








J. Silverman, 45thICAAC, 2005



Van Bambeke et al. Trends Pharmacol Sci. 2008;29:124-34.

达托霉素的PK/PD研究——应用于人体

剂量和给药途径	房室	AUC	AUC/MIC (1 mg/L)
4 mg/kg iv (用药剂量)	血清	417	417
	炎症渗出液	318	318
6 mg/kg iv	血清	747	747

当肌酐清除率< 30 ml/min，需调整剂量

EUCAST
折点*:*
1 mg/L

Wise *et al.*, AAC (2002) 46:31-3
Dvorchik *et al.*, AAC (2003) 47:1318-23

达托霉素的重新起飞...

1987 1993 1997 **2003-2006**

注册

美国: **2003**

欧洲: **2006**

在欧洲主治：

- 革兰氏阳性菌造成的复杂皮性肤及软组织感染

最低抑菌浓度达到**1 mg/L**才有效：

- 菌血症
- 心内膜炎
- 复杂性尿路感染

无效:

- 肺炎 (被表面活性物质中和)
- 万古霉素中介金葡菌(***VISA***)(无法到达靶点)

只能静脉给药！

Carpenter & Chambers CID (2004) 38: 994-1000

达托霉素: 在欧洲有哪些应用？

1987 1993 1997 **2003-2006**

European Medicines Agency
emea

4.1 Therapeutic indications

Cubicin is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1).

- Complicated skin and soft-tissue infections (cSSTI).
- Right-sided infective endocarditis (RIE) due to *Staphylococcus aureus*. It is recommended that the decision to use daptomycin should take into account the antibacterial susceptibility of the organism and should be based on expert advice. See sections 4.4 and 5.1.
- *Staphylococcus aureus* bacteraemia (SAB) when associated with RIE or with cSSTI.

Daptomycin is active against Gram positive bacteria only (see section 5.1). In mixed infections where Gram negative and/or certain types of anaerobic bacteria are suspected, Cubicin should be co-administered with appropriate antibacterial agent(s).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

达托霉素: 将何去何从?

1987 1993 1997 **2003-2006** 2009…

While emerging resistance is rare, the scatter of reports in settings with high bacterial loads is of concern.[32]

To minimize the risk, three steps are advised:

first to explore the potential for higher dosage, guaranteeing levels above a 'mutant prevention concentration';

secondly, to recognize patients where surgical debridement is warranted;

and thirdly, to prevent cross-infection with resistant organisms.

Limited registry and volunteer data suggest that it may be possible to use daptomycin at significantly higher doses than the present 4–6 mg/kg, but side effects remain to be evaluated in large-scale clinical trials.

Livermore DM. J Antimicrob Chemother. 2008;62 Suppl 3:iii41-iii49.

达托霉素

----------WARNINGS AND PRECAUTIONS----------

- Anaphylaxis/hypersensitivity reactions (including life-threatening): Discontinue CUBICIN and treat signs/symptoms. (5.1)
- Myopathy and rhabdomyolysis: Monitor CPK levels and follow muscle pain or weakness; if elevated CPK or myopathy occurs, consider discontinuation of CUBICIN. (5.2)
- Eosinophilic pneumonia: Discontinue CUBICIN and consider treatment with systemic steroids. (5.3)
- Peripheral neuropathy: Monitor for neuropathy and consider discontinuation. (5.4)
- *Clostridium difficile*–associated diarrhea: Evaluate patients if diarrhea occurs. (5.5)
- Persisting or relapsing *S. aureus* bacteremia/endocarditis: Perform susceptibility testing and rule out sequestered foci of infection. (5.6)
- Decreased efficacy was observed in patients with moderate baseline renal impairment. (5.7)

---------- 不良反应 ----------

达托霉素4mg/kg(复杂性皮肤和软组织感染)和6mg/kg（金葡菌血流感染/心内膜炎）的最严重副反应是肝功能异常、磷酸肌酸激酶升高及呼吸困难。(6.1)

达托霉素: 用药剂量合适吗?

Journal of Antimicrobial Chemotherapy (2008) **62**, *Suppl. 3*, iii41–iii49

JAC

Future directions with daptomycin

David M. Livermore*

Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK

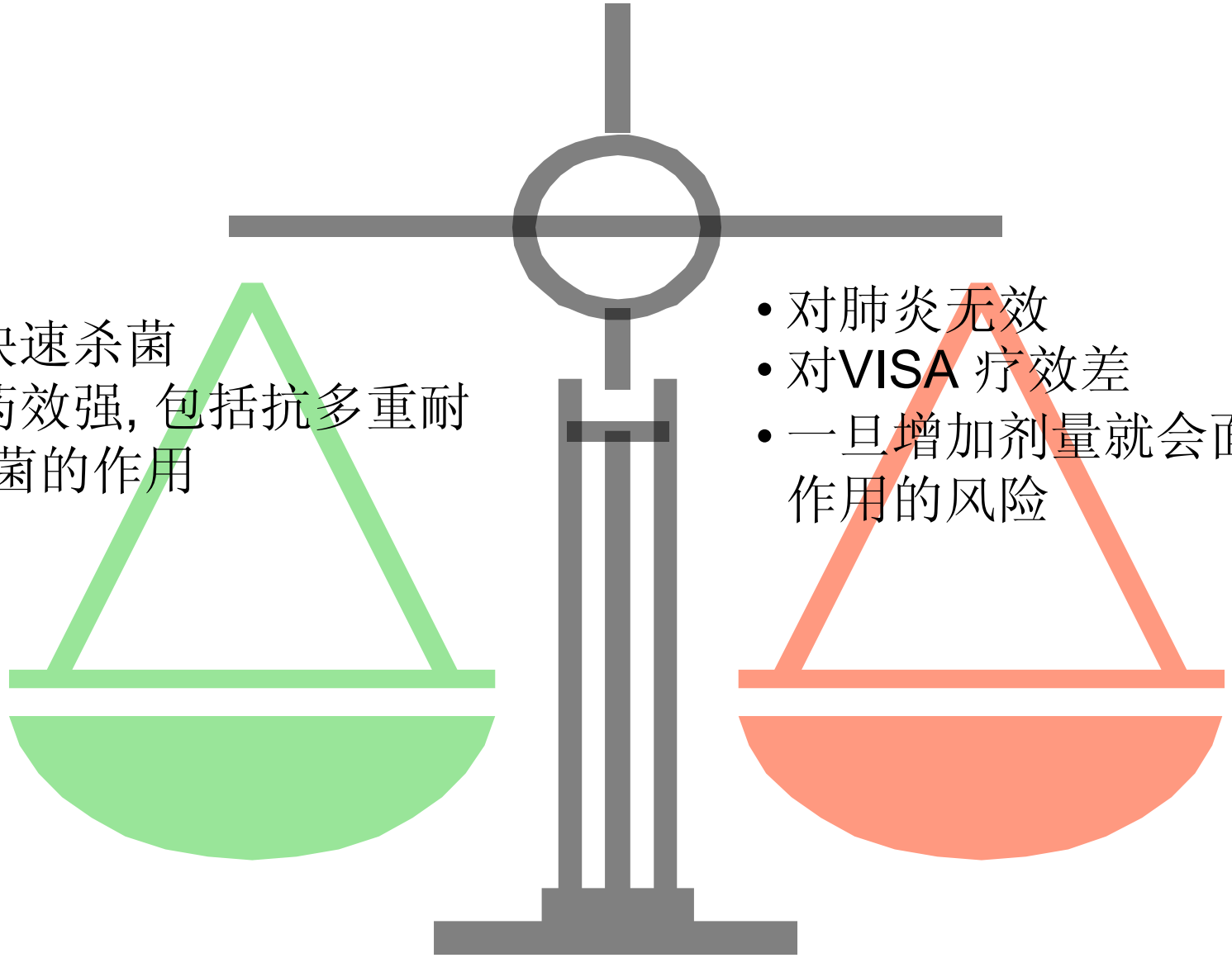
Daptomycin is the first new natural-product antibiotic launched in a generation. It was licensed first for skin and soft tissue infections (SSTIs) and, more recently, for staphylococcal bacteraemia and endocarditis. Further clinical trials are in progress, some investigating performance in subsets of SSTIs while others, more interestingly, are evaluating efficacy in enterococcal endocarditis and neutropenic fevers—settings where the compound's bactericidal activity is potentially advantageous. There is a need for further trials in bone and joint infections. On the negative side, there are several reports of mutational resistance emerging during the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections, mostly in settings with a heavy bacterial load, and there is a need to determine whether higher dosages or combination regimens will reduce this risk. A few patients have already been treated with doses of up to 12 mg/kg. Lastly, daptomycin is entering a market increasingly crowded with new anti-Gram-positive agents. More work is required to establish those settings where daptomycin and other new compounds offer real advantages over established glycopeptides and over each other. There is presently a paradox whereby vancomycin is agreed to be less than ideal, with outcomes impaired against MRSA with modestly raised MICs, but where new agents have yet to demonstrate unequivocal superiority.

Keywords: Gram-positive infections, MRSA, enterococci, *Staphylococcus aureus*

一些在治疗MRSA感染过程中发生了菌株耐药突变

一些病人的治疗剂量已高达12mg/kg。

达托霉素: 利与弊



- 快速杀菌
- 药效强, 包括抗多重耐药菌的作用

- 对肺炎无效
- 对VISA 疗效差
- 一旦增加剂量就会面临副作用的风险

替加环素: 有历史意义的标志性事件...

1993 **1999**

发现抗生素的一个新品种：甘氨环素类

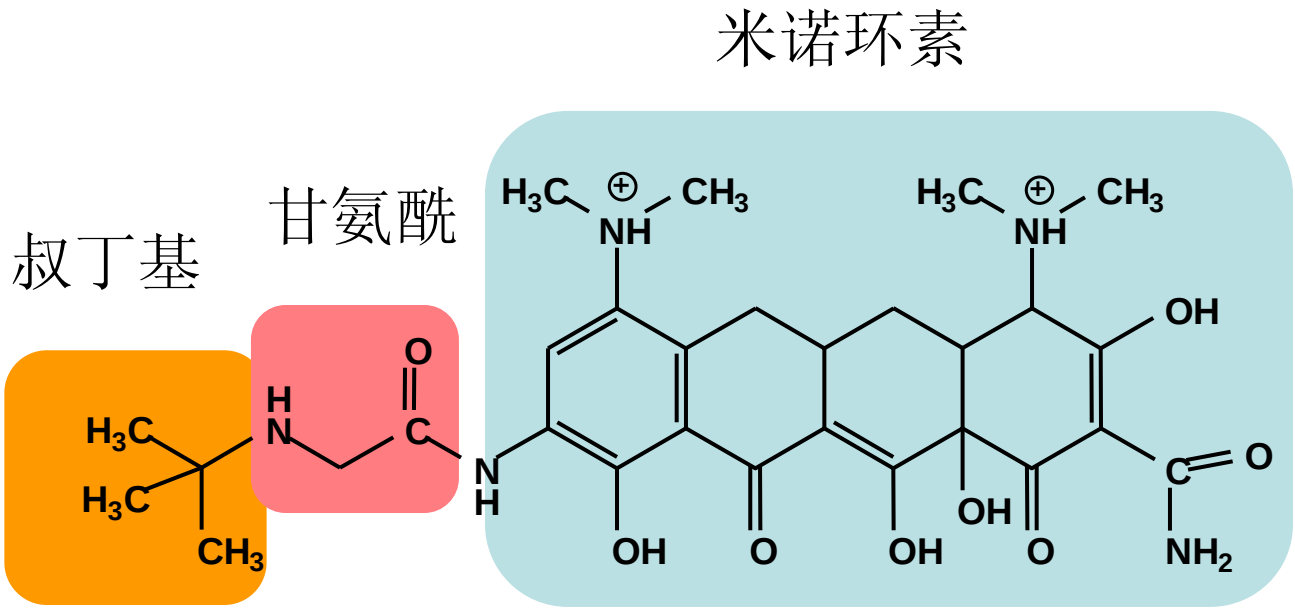
In vitro and in vivo antibacterial activities of the glycylcyclines, a new class of semisynthetic tetracyclines.
Testa *et al.* Antimicrob Agents Chemother. **1993** 37:2270-7

抗菌活性和备选药物

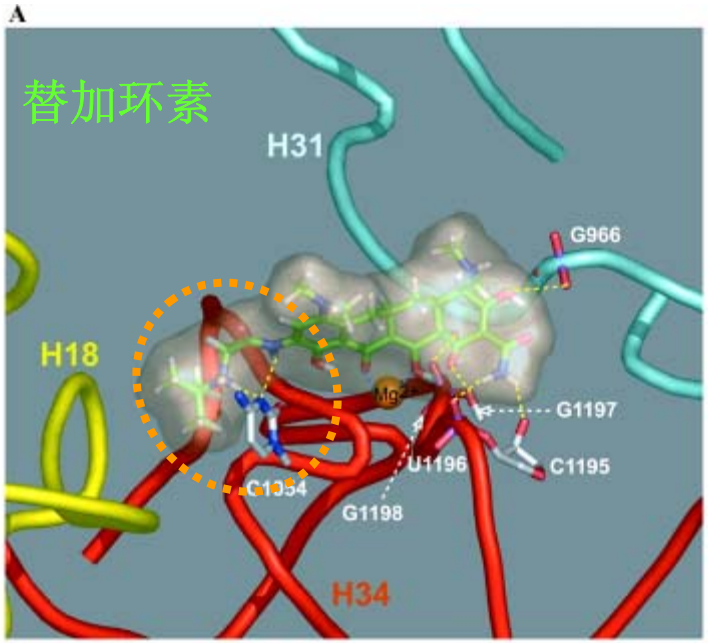
***In vitro* and *in vivo* antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936).**
Petersen *et al.* **(1999)** Antimicrob Agents Chemother. 43:738-44.

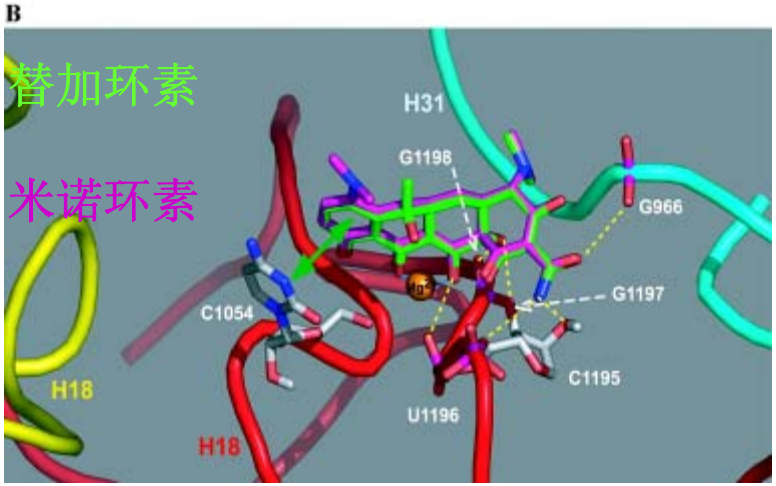
and then, Pfizer bought Wyeth…

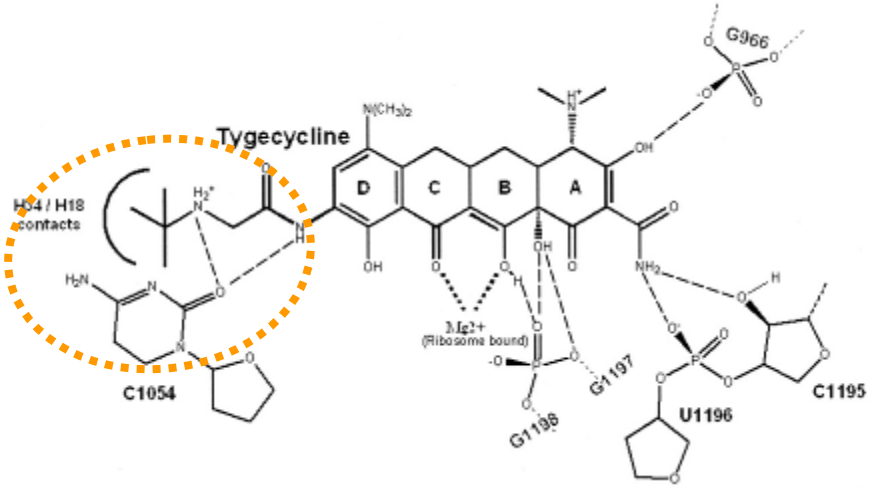
替加环素:化学结构


米诺环素
甘氨酰
叔丁基
H3C
H3C
CH3
H
N
O
C
N
H
H3C
CH3
NH
H3C
CH3
NH
OH
OH
O
OH
OH
O
C
O
NH2

替加环素的作用方式







- 与四环素一样能与16S核糖体的RNA结合；此外还有其他结合位点
- 不受耐药性的影响归功于
  - 核糖体保护
  - 四环素外排泵；
- 但是仍然对有广谱外排泵的革兰氏阴性菌敏感 (MexXY in *P. aeruginosa*)

Olson *et al.*, AAC (2006) 50:2156-66

四环素类和甘氨酰四环素类: 抗菌活性和耐药性

种类	表型	四环素	米诺环素	替加环素
大肠埃希菌	敏感	1	1	0.25
	外排 泵(四环素)	> 32	16	0.5
	核糖体保护	> 32	> 32	0.25
金黄色葡萄球菌	敏感	0.12	0.06	0.25
	外排泵 (四环素)	> 32	0.25	0.5
	核糖体保护	> 32	4	0.25

Petersen et al., AAC (1999) 43:738-44

替加环素:药物代谢动力学

	组织	AUC_{24h} (mg.h/L)	血清/组织AUC比值
Single dose: 100 mg	胆汁	2815	537
	膀胱	120	23
	结肠	17.3	2.6
	肺	9.19	2
	骨骼	2.05	0.4
	关节液	1.68	0.31
	脑脊液	0.46	0.11
100 mg + 6x50 mg q12h	支气管肺泡上皮表面液	4.54	1.31
	肺泡巨噬细胞	268	77.5

Rodvold, JAntimicrob Chemother (2006) 58:1221-9
Conte et al., Int J Antimicrob Agents (2005) 25:523-9

替加环素 EUCAST折点

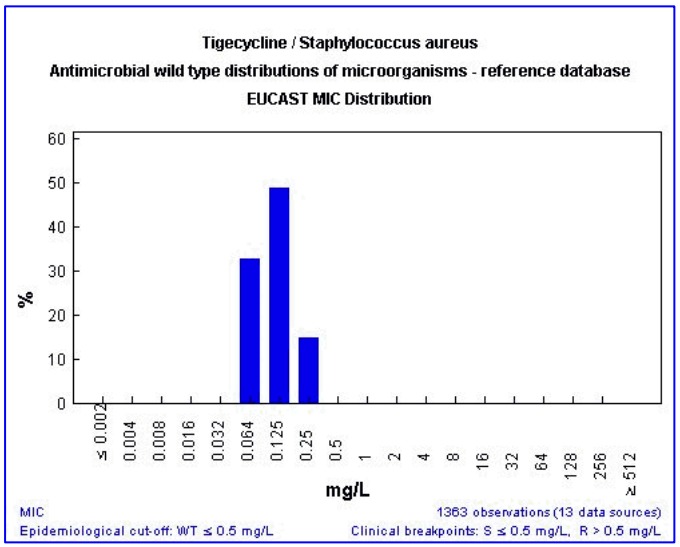
替加环素——EUCAST临床MIC折点
2008-06-19 (v 2.2)

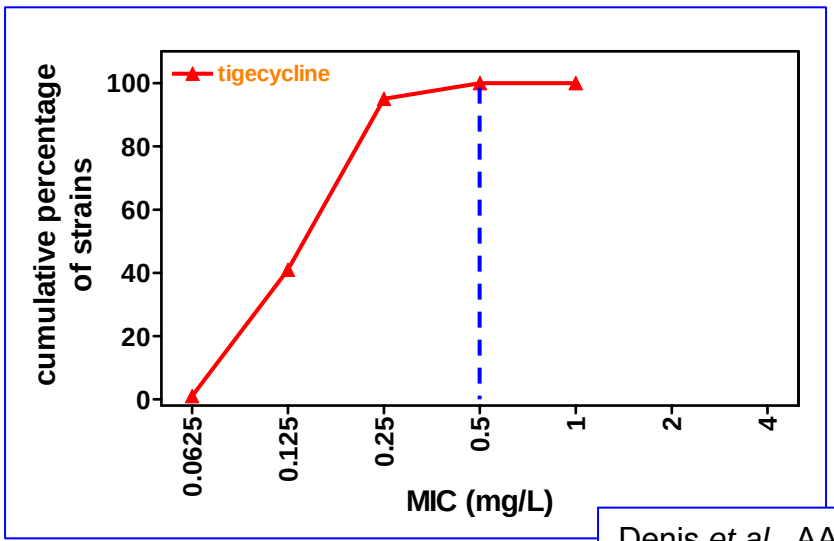
Tetracyclines Click on antibiotic name to see wild type MIC distributions and on RD to see ratinale document.		Species-related breakpoints (S≤/R>)				
		Enterobac-teriaceae	*Acineto-bacter*	*Staphylo-coccus*	*Entero-coccus*	*Strepto-coccus A,B,C,G*
Tigecycline	RD	1/2[E]	IE	0.5/0.5[F,G]	0.25/0.5[G]	0.25/0.5[G]

E. The S/I and I/R breakpoints were increased to avoid dividing wild type MIC distributions of relevant species.

F. The S/I breakpoint was increased to avoid dividing wild type MIC distributions of relevant species.

G. Strains with MIC values above the S/I breakpoint are very rare or not yet reported.





这种情况会持续吗?
(T.E.S.T. will tell but TK reports MIC_{90} at 0.75 In 2008)

Denis *et al.*, AAC (2006) 50:2680-5

替加环素的进程

1993 → 2005-6

European Medicines Agency

emea

4.1 Therapeutic indications

Tygacil is indicated for the treatment of the following infections (see sections 4.4 and 5.1):

- Complicated skin and soft tissue infections
- Complicated intra-abdominal infections

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Paediatric patients
Tygacil is not recommended for use in children and adolescents below 18 years due to the lack of data on safety and efficacy (see sections 5.2 and 4.4).

* pediatric studies are ongoing and/or proposed to Regulatory Authorities

替加环素: 副作用

Table 1. Incidence (%) of Adverse Reactions Through Test of Cure Reported in ≥ 2% of Patients Treated in Clinical Studies

Body System Adverse Reactions	TYGACIL (N=2514)	Comparators[a] (N=2307)
Body as a Whole		
Abdominal pain	6	4
Abscess	2	2
Asthenia	3	2
Headache	6	7
Infection	7	5
Cardiovascular System		
Phlebitis	3	4
Digestive System		
Diarrhea	12	11
Dyspepsia	2	2
Nausea	26	13
Vomiting	18	9
Hemic and Lymphatic System		
Anemia	5	6

替加环素: 治疗失败

Table 2. Patients with Outcome of Death by Infection Type

	TYGACIL		Comparator		Risk Difference*
Infection Type	n/N	%	n/N	%	% (95% CI)
cSSSI	12/834	1.4	6/813	0.7	0.7 (-0.3, 1.7)
cIAI	42/1382	3.0	31/1393	2.2	0.8 (-0.4, 2.0)
CAP	12/424	2.8	11/422	2.6	0.2 (-2.0, 2.4)
HAP	66/467	14.1	57/467	12.2	1.9 (-2.4, 6.3)
Non-VAP[a]	41/336	12.2	42/345	12.2	0.0 (-4.9, 4.9)
VAP[a]	25/131	19.1	15/122	12.3	6.8 (-2.1, 15.7)
RP	11/128	8.6	2/43	4.7	3.9 (-4.0, 11.9)
DFI	7/553	1.3	3/508	0.6	0.7 (-0.5, 1.8)
Overall Adjusted	150/3788	4.0	110/3646	3.0	0.6 (0.1, 1.2)**

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections; cSSSI = Complicated skin and skin structure infections; HAP = Hospital-acquired pneumonia; VAP = Ventilator-associated pneumonia; RP = Resistant pathogens; DFI = Diabetic foot infections.

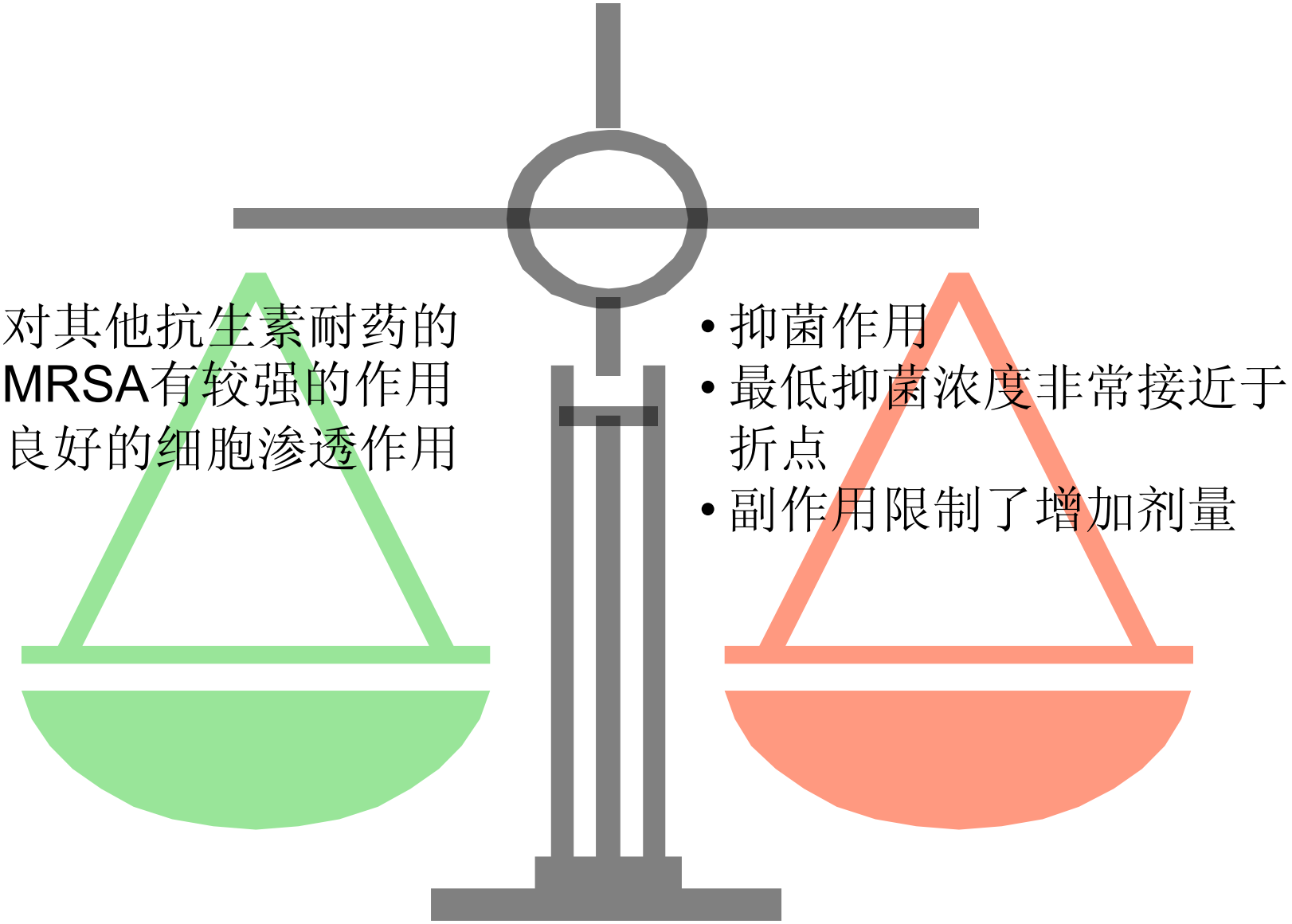
* The difference between the percentage of patients who died in TYGACIL and comparator treatment groups. The 95% CI for each infection type was calculated using the normal approximation method without continuity correction.

** Overall adjusted (random effects model by trial weight) risk difference estimate and 95% CI.

[a] These are subgroups of the HAP population.

Note: The studies include 300, 305, 900 (cSSSI), 301, 306, 315, 316, 400 (cIAI), 308 and 313 (CAP), 311 (HAP), 307 [Resistant gram-positive pathogen study in patients with MRSA or Vancomycin-Resistant Enterococcus (VRE)], and 319 (DFI with and without osteomyelitis).

替加环素: 利与弊



- 对其他抗生素耐药的MRSA有较强的作用
- 良好的细胞渗透作用

- 抑菌作用
- 最低抑菌浓度非常接近于折点
- 副作用限制了增加剂量

新药(2008年之后批准用于MRSA的治疗)

- 特拉万星 (2009年，批准用于复杂性皮肤软组织感染，后又批准用于呼吸机相关性肺炎的治疗)
- 头孢洛林 (2010年，批准用于急性细菌性皮肤软组织感染及非MRSA社区获得新肺炎的治疗)

- 尚未批准艾拉普林，奥利万星，头孢吡普，喹红霉素

新(脂)糖肽类: 构效关系

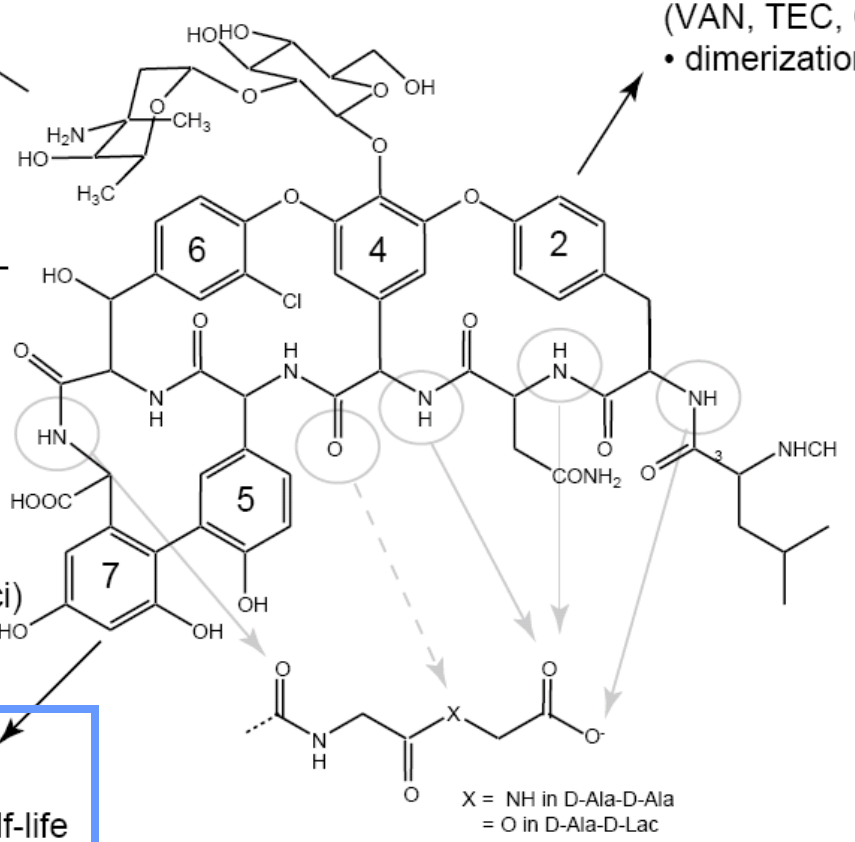
Lipophilic side chain
(TEC, ORI, TEL, DAL)
• membrane anchoring
• prolonged half-life
• increased activity (enterococci)

Sugar
(ORI)
• dimerization

Basic amide
(DAL)
• increased activity (staphylococci)

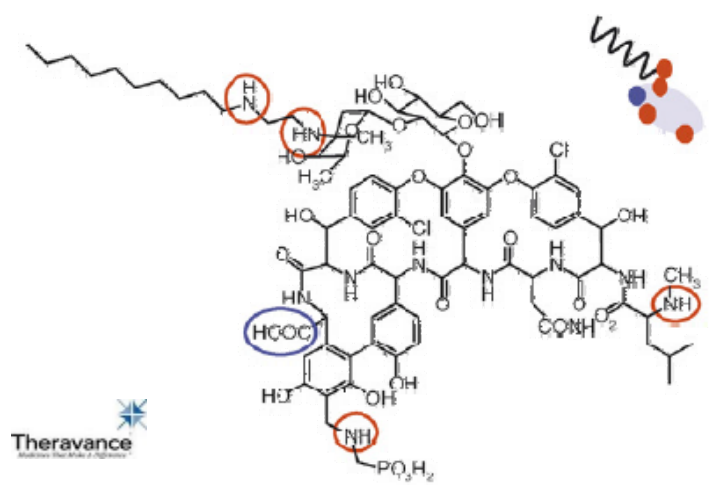
Polar group
(TEL)
• decreased half-life

Cl
(VAN, TEC, ORI, TEL)
• dimerization

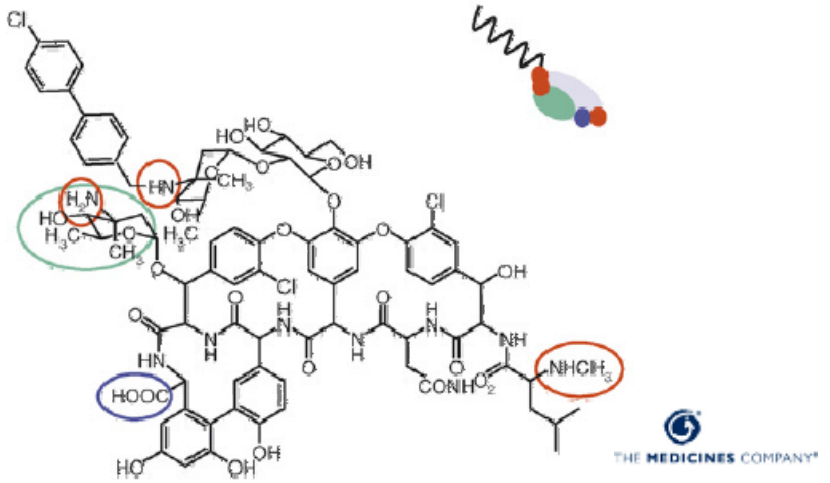


Van Bambeke, Cur. Opin. Pharmacol. (2004) 4:471-8

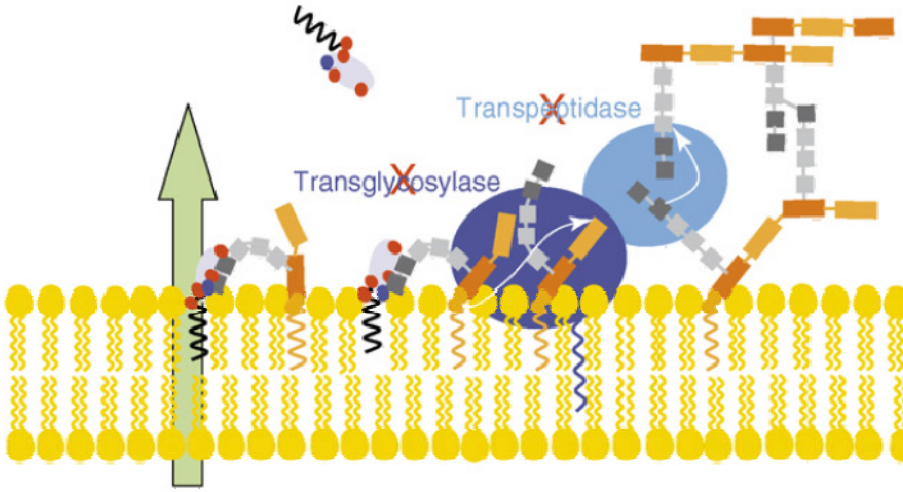
特拉万星和 Pritavancin

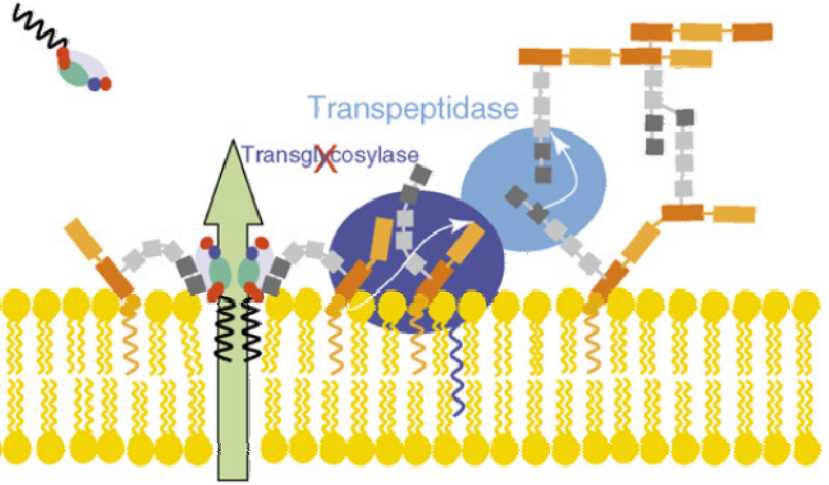


Telavancin (lipoglycopeptide)



Oritavancin (lipoglycopeptide)





Van Bambeke et al., TIPS (2008) 29:124-34

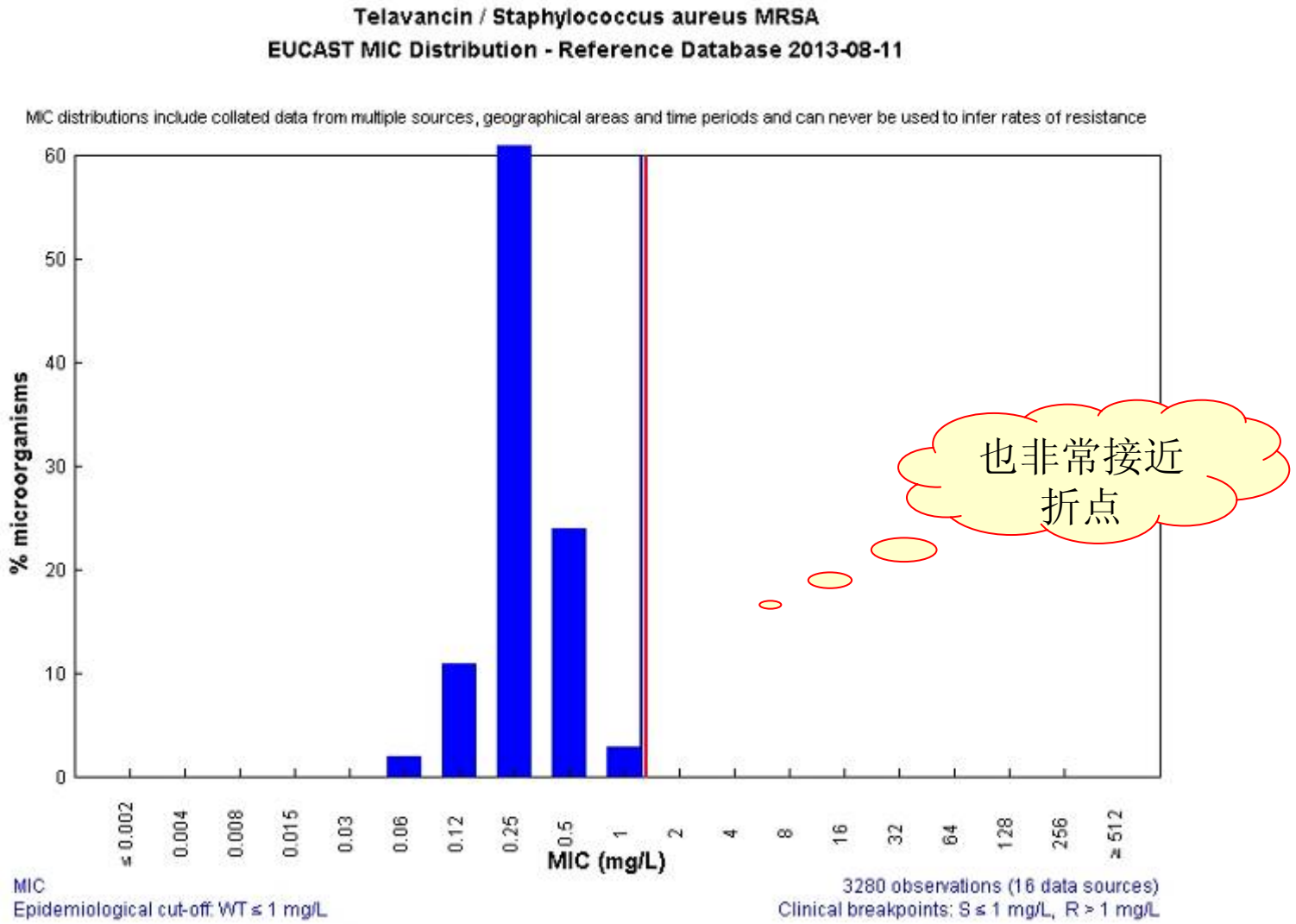
特拉万星: 体外抗菌活性

菌种	表型	ORI	TLV	VAN
S. aureus	MSSA	0.25/0.5	0.25/0.5	1/1
	MRSA	0.25/0.5	0.25/0.25	1/1
	VISA	1/1	0.5-1	4/4
	VRSA	0.5*	2-4	16*
S. pneumo	PenS	≤ 0.002/0.004	≤ 0.06/≤ 0.06	≤ 0.25/≤ 0.25
	Pen nonS	≤0.002/0.004	≤ 0.06/≤ 0.06	≤ 0.25/≤ 0.5
Enterococci	VanS	0.12/0.5	0.12/0.5	1/2
	VanR	0.03*	4-16	16*

* 中介值

Draghi et al., AAC (2008) 52:2383-2388
ICAAC (2008) C1-146,150,151

特拉万星: 体外抗菌活性和折点



特拉万星的临床研究: 安全性

不良反应和实验室检查指标异常促使了对复杂性皮肤软组织感染（cSSTIs）及院内肺炎（HAP）的联合研究

« metallic/soapy »

Overall AE	1454/1864 (78)	1393/1868 (74.6)	1.20 (0.97–1.49)
Serious AE	314/1864 (16.8)	251/1868 (13.4)	1.38 (0.90–2.13)
Withdrawals	144/1864 (7.7)	100/1868 (5.4)	1.48 (1.14–1.93)
Nausea	318/1864 (17.1)	190/1868 (10.2)	1.88 (1.54–2.29)
Vomiting	143/1113 (12.8)	78/1116 (7)	1.97 (1.47–2.63)
Taste disturbance	325/1029 (31.6)	62/1033 (6)	7.37 (5.52–9.85)
Diarrhoea	73/1029 (7.1)	81/1033 (7.8)	0.90 (0.65–1.25)
Constipation	174/1864 (9.3)	144/1868 (7.7)	1.12 (0.72–1.74)
Insomnia	137/1780 (7.7)	136/1785 (7.6)	1.14 (0.62–2.11)
Pruritus	34/1029 (3.3)	68/1033 (6.6)	0.48 (0.32–0.74)
Headache	147/1113 (13.2)	132/1116 (11.8)	1.14 (0.89–1.47)
Chills	47/1029 (4.6)	23/1033 (2.2)	2.10 (1.27–3.48)
Cr elevation	166/1638 (10.1)	88/1674 (5.3)	2.22 (1.38–3.57)
Hypokalemia	73/1528 (4.8)	44/1521 (2.9)	1.91 (0.91–4.00)
AST increase	36/1045 (3.4)	39/1084 (3.6)	0.93 (0.43–2.04)
ALT increase	38/1101 (3.5)	61/1165 (5.2)	0.64 (0.42–0.97)
QTcF increase[b]	59/1560 (3.8)	49/1578 (3.1)	1.24 (0.84–1.83)
Anemia	66/1052 (6.3)	65/1058 (6.1)	1.01 (0.71–1.46)
Leukopenia	12/1006 (1.2)	19/989 (1.9)	0.62 (0.30–1.28)
Platelet decrease[c]	8/1064 (0.8)	10/1110 (0.9)	0.87 (0.35–2.17)

[a]The FAST 1 study is included in the analysis.
[b]>60 ms.
[c]<75×109/L.
doi:10.1371/journal.pone.0041870.t003

Polysos et al., PLoSone (2012) 7: e41870

特拉万星: 目前的适应症

经EMA批准的适应症(2011):

治疗成人院内肺炎，包括呼吸机相关性肺炎

- 已知或者怀疑是由MRSA引起的感染；
- 仅在已知或怀疑其他治疗方法不适用时。

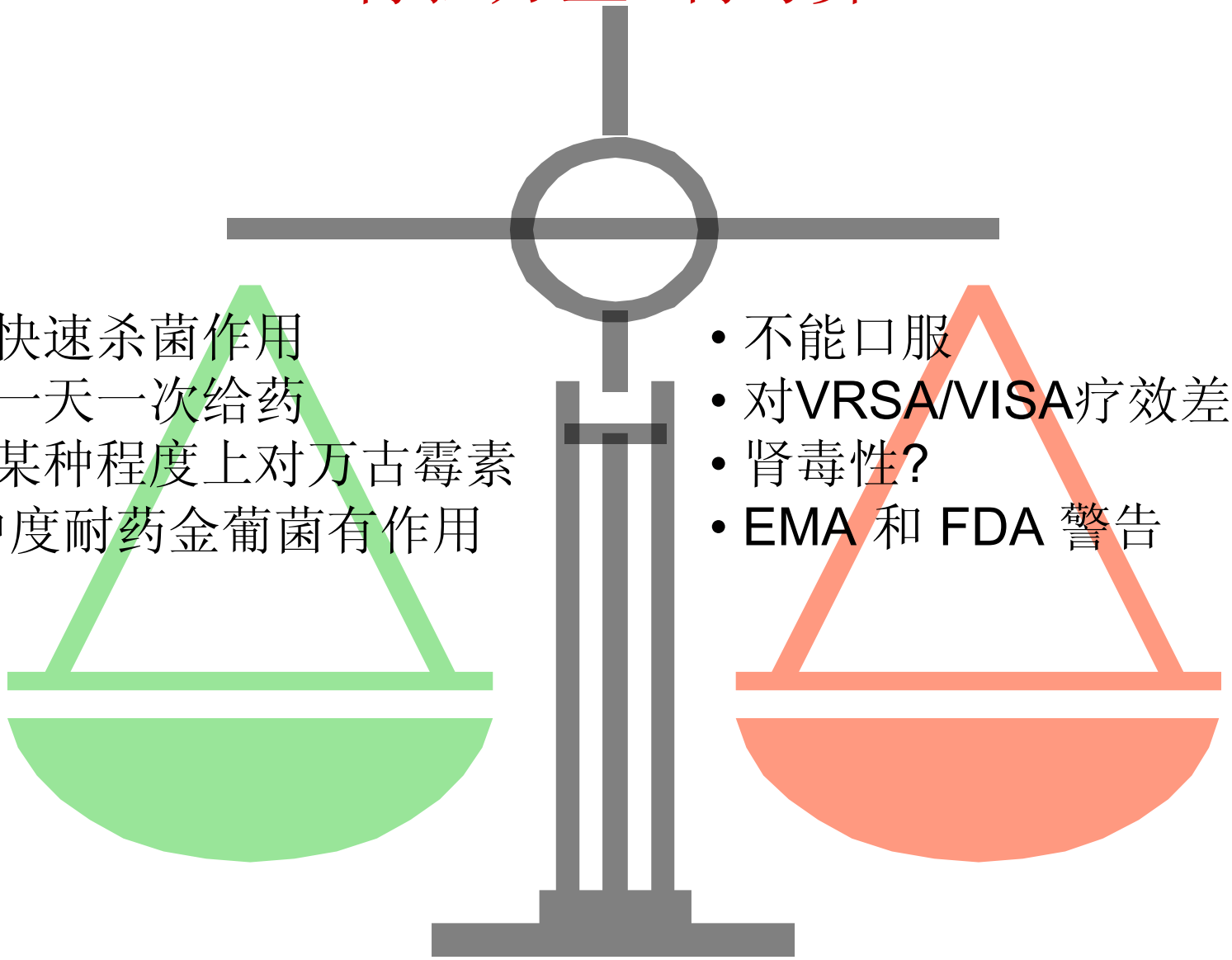
经FDA 批准的适应症(2009):

治疗成人复杂性皮肤和皮肤结构组织感染

- 由敏感的革兰氏阳性菌引起的
- 包括金黄色葡萄球菌，MRSA和MSSA

当其他药物不适用于由敏感金葡菌引起的院内获得性和呼吸机相关性肺炎时，可考虑特拉万星。

特拉万星: 利与弊



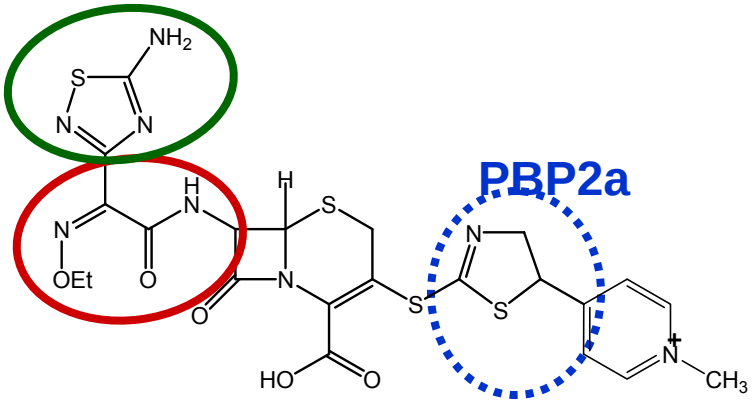
- 快速杀菌作用
- 一天一次给药
- 某种程度上对万古霉素中度耐药金葡菌有作用

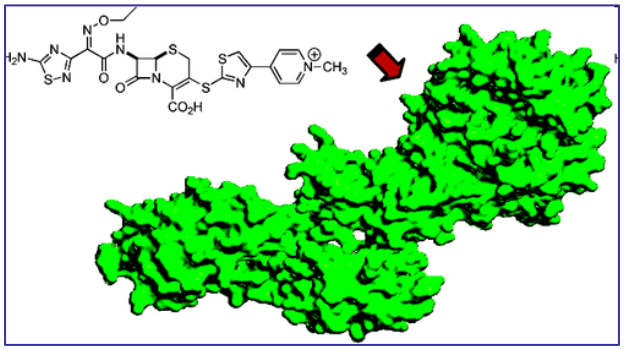
- 不能口服
- 对VRSA/VISA疗效差
- 肾毒性?
- EMA 和 FDA 警告

头孢洛林

革兰氏阴性

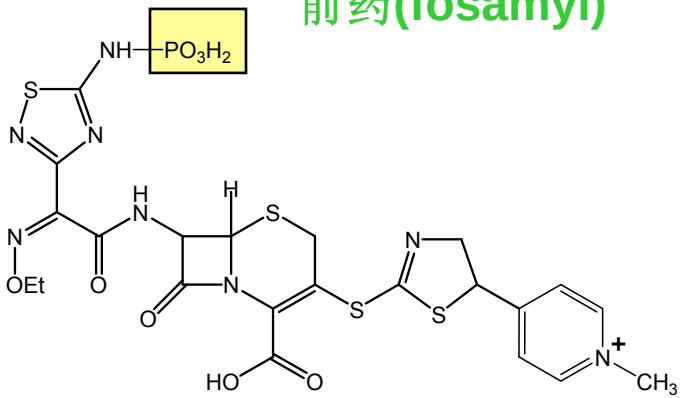
β-内酰胺酶





前药(fosamyl)

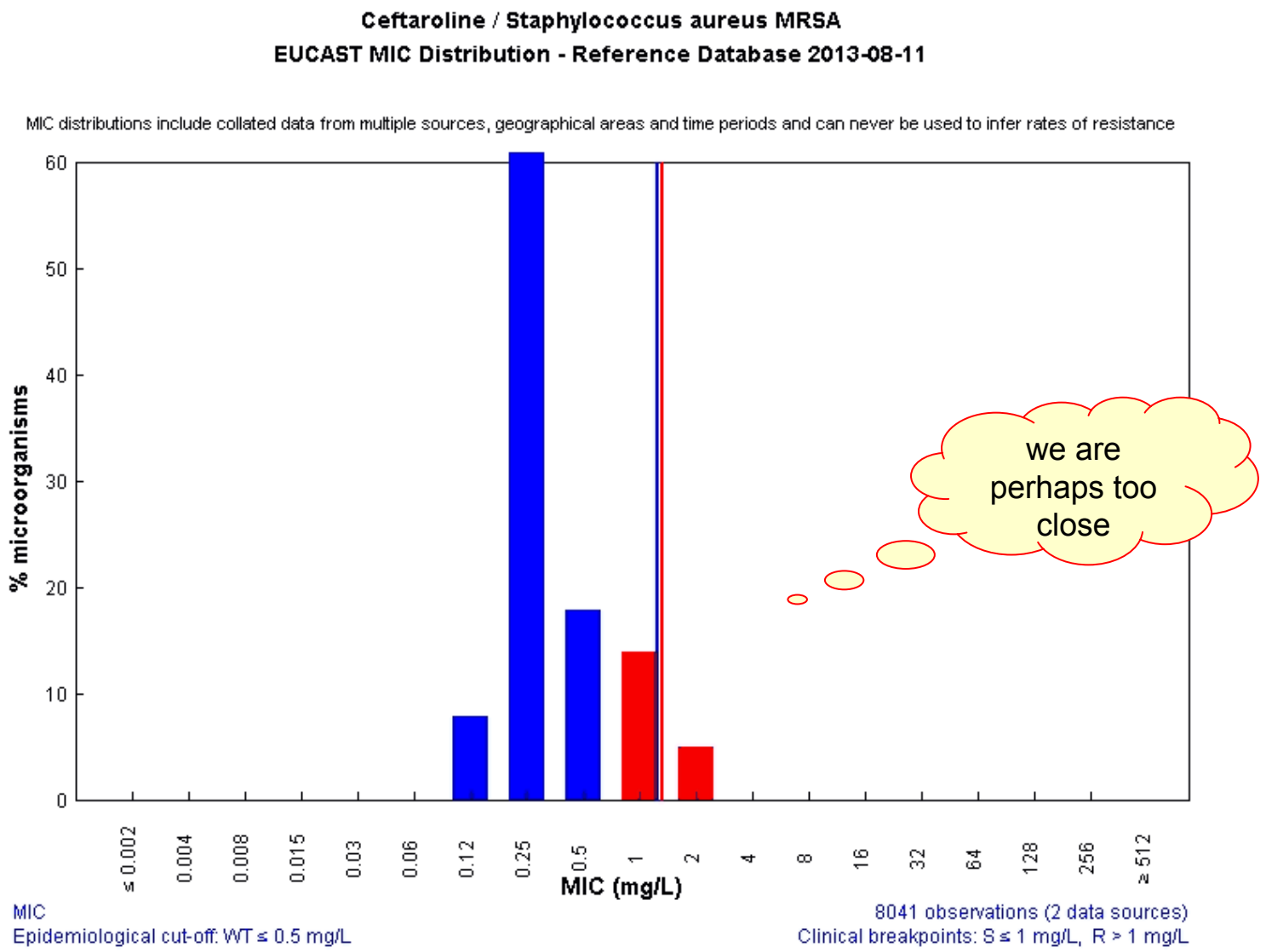
TAK-599



TAK-91825

Ishikawa et al., Bioorg Med Chem. (2003) 11:2427-37

头孢洛林和MRSA


Ceftaroline / Staphylococcus aureus MRSA
EUCAST MIC Distribution - Reference Database 2013-08-11
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance
% microorganisms
0
10
20
30
40
50
60
≤ 0.002
0.004
0.008
0.015
0.03
0.06
0.12
0.25
0.5
1
2
4
8
16
32
64
128
256
≥ 512
MIC (mg/L)
we are perhaps too close
MIC
Epidemiological cut-off: WT ≤ 0.5 mg/L
8041 observations (2 data sources)
Clinical breakpoints: S ≤ 1 mg/L, R > 1 mg/L

头孢洛林: 目前的适应症

经EMA 批准的适应症(2012):

用于成人治疗
- 社区获得性肺炎
- 复杂性皮肤软组织感染

经FDA 批准的适应症(2010):

- 以下引起社区获得性细菌性肺炎的革兰氏阳性和阴性菌：肺炎链球菌(包括并发菌血症的特例)， 金葡菌(仅针对甲氧西林敏感菌株)，流感嗜血杆菌，肺炎克雷伯菌，产酸克雷伯菌， 以及大肠埃希菌。

- 以下引起急性细菌性皮肤软组织感染的革兰氏阳性及阴性敏感菌株：
金葡菌(包括甲氧西林敏感菌株和耐药菌株)，化脓性链球菌，链球菌，大肠埃希菌，肺炎克雷伯菌， 以及产酸克雷伯菌属。

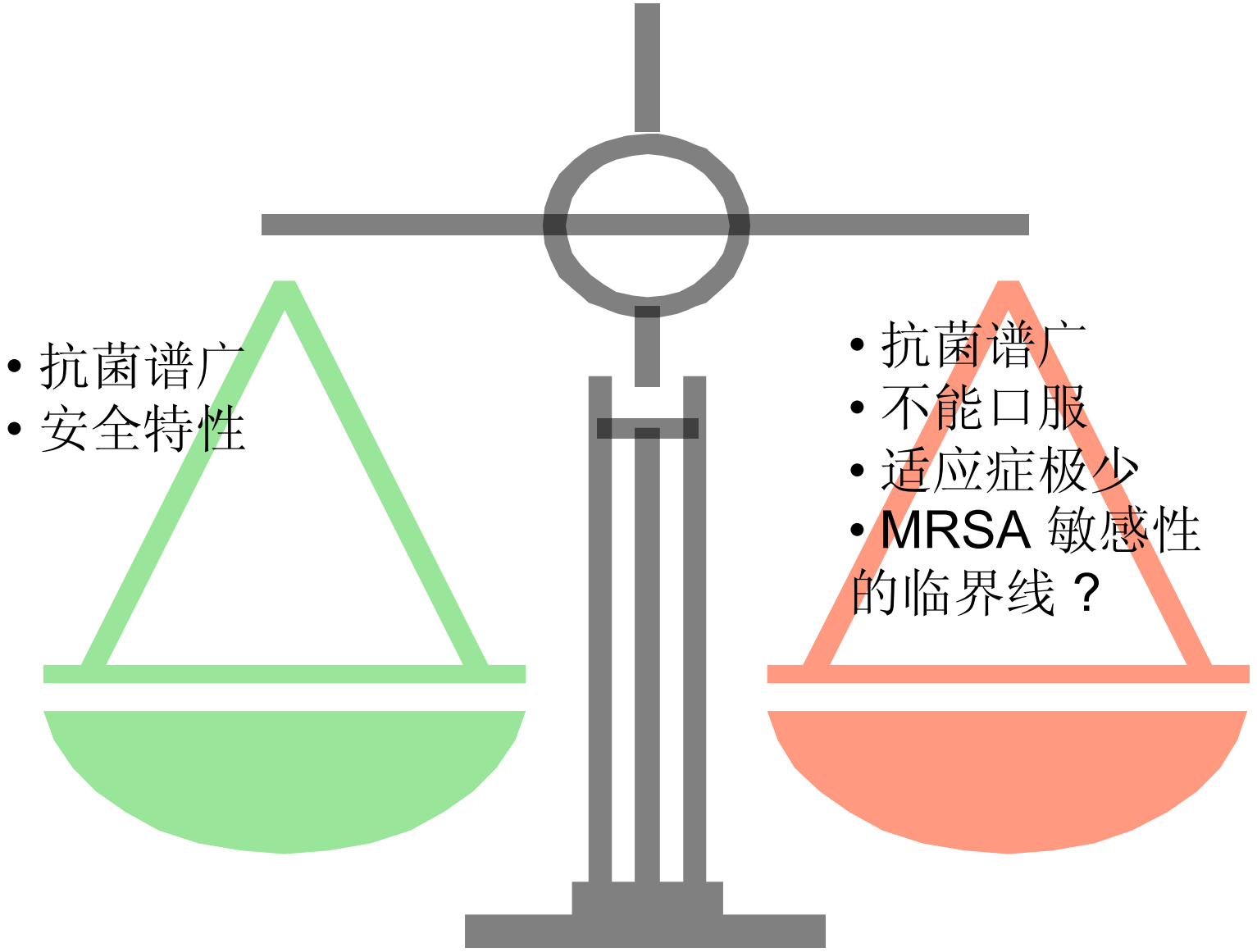
头孢洛林
安全性
(III期临床试验)

Table 4: Adverse Reactions Occurring in ≥ 2% of Patients Receiving Teflaro in the Pooled Phase 3 Clinical Trials

System Organ Class/ Preferred Term	Pooled Phase 3 Clinical Trials (four trials, two in ABSSSI and two in CABP)	
	Teflaro (N=1300)	Pooled Comparators[a] (N=1297)
Gastrointestinal disorders		
Diarrhea	5 %	3 %
Nausea	4 %	4 %
Constipation	2 %	2 %
Vomiting	2 %	2 %
Investigations		
Increased transaminases	2%	3 %
Metabolism and nutrition disorders		
Hypokalemia	2 %	3 %
Skin and subcutaneous tissue disorders		
Rash	3%	2%
Vascular disorders		
Phlebitis	2%	1%

[a] Comparators included vancomycin 1 gram IV every 12h plus aztreonam 1 gram IV every 12h in the Phase 3 ABSSSI trials, and ceftriaxone 1 gram IV every 24h in the Phase 3 CABP trials.

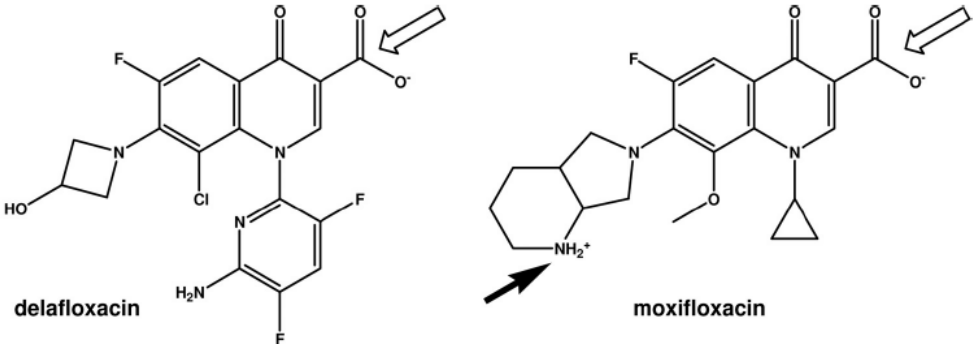
头孢洛林：利与弊



即将注册的药物

- 氟喹诺酮类
  - 德拉沙星
  - JNJ-Q2
- 恶唑烷酮类
  - Tedizolid
- 酮内酯类抗菌药
  - Solithromycin
- 脂糖肽类
  - 达巴万星
  - 奥利万星
- 抗MRSA β内酰胺类
  - 头孢吡普

德拉沙星



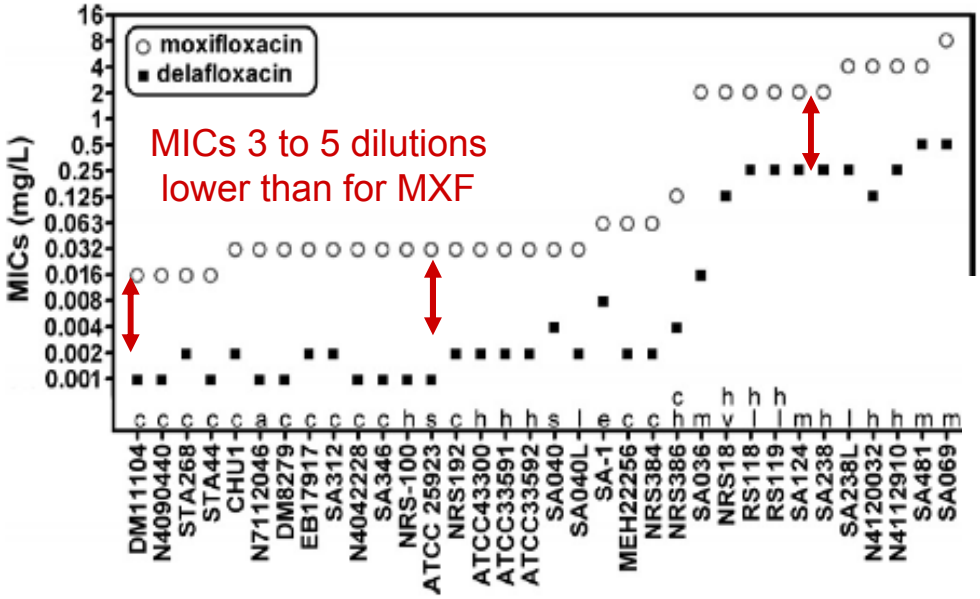
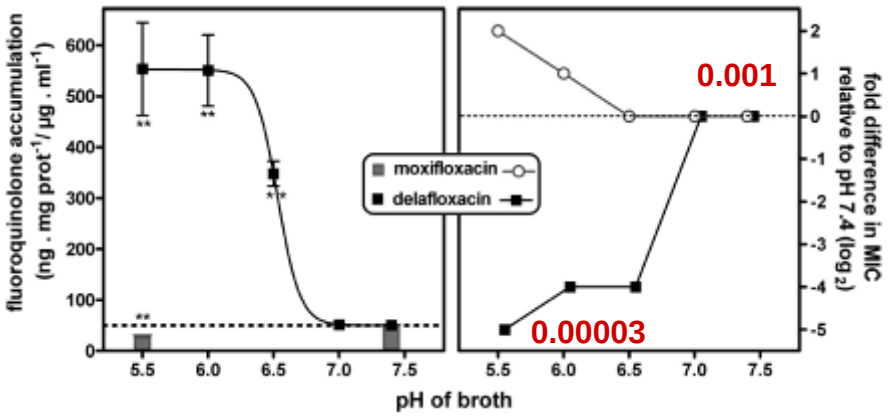


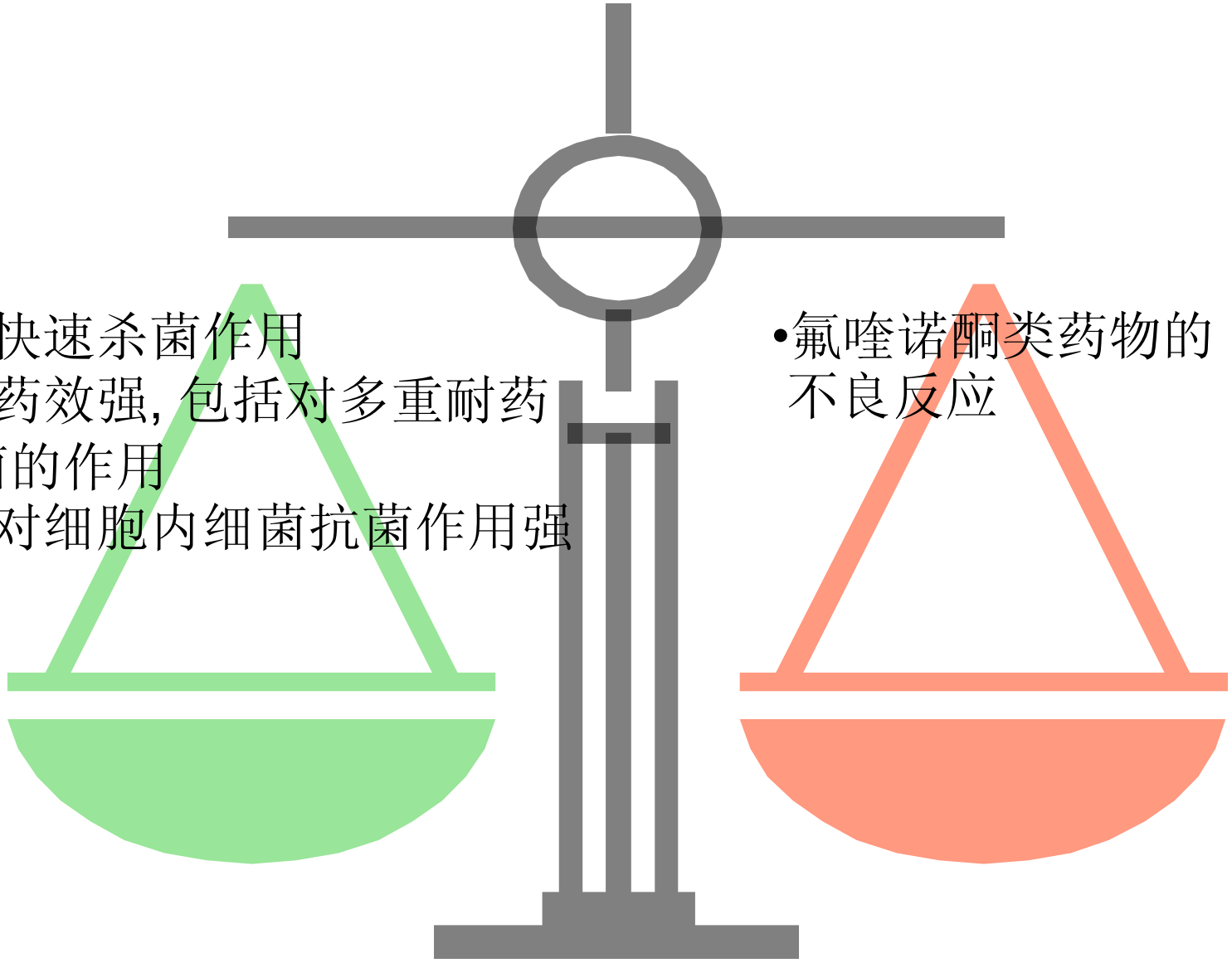
FIG. 2. Comparative susceptibilities of various *S. aureus* isolates t moxifloxacin (circles) or delafloxacin (squares). MICs were measure at pH 7.4, and strains are ranked based on their susceptibility to moxifloxacin. Resistance phenotypes and/or strain source are designated by lowercase letters along the *x* axis: a, animal MRSA; c, CA-MRSA; e, efflux (NorA); h, HA-MRSA; l, linezolid-resistant; m, characterized mutations in fluoroquinolone targets; s, MSSA.

该药物在酸性环境中对细菌渗透性增加，抗菌活性也提高



Lemaire et al, AAC (2011) 55:649-58

德拉沙星: 利与弊



- 快速杀菌作用
- 药效强, 包括对多重耐药菌的作用
- 对细胞内细菌抗菌作用强

- 氟喹诺酮类药物的不良反应

JNJ-Q2

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2011, p. 5790–5797 Vol. 55, No. 12
0066-4804/11/$12.00 doi:10.1128/AAC.05044-11

Randomized, Double-Blind, Phase II, Multicenter Study Evaluating the Safety/Tolerability and Efficacy of JNJ-Q2, a Novel Fluoroquinolone, Compared with Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infection[▽]†

Paul Covington,[1]* J. Michael Davenport,[1] David Andrae,[1] William O'Riordan,[2] Lisa Liverman,[1] Gail McIntyre,[1] and June Almenoff[1]

Furiex Pharmaceuticals, Morrisville, North Carolina,[1] and eStudySite, San Diego, California[2]

Received 8 June 2011/Returned for modification 15 August 2011/Accepted 15 September 2011

JNJ-Q2

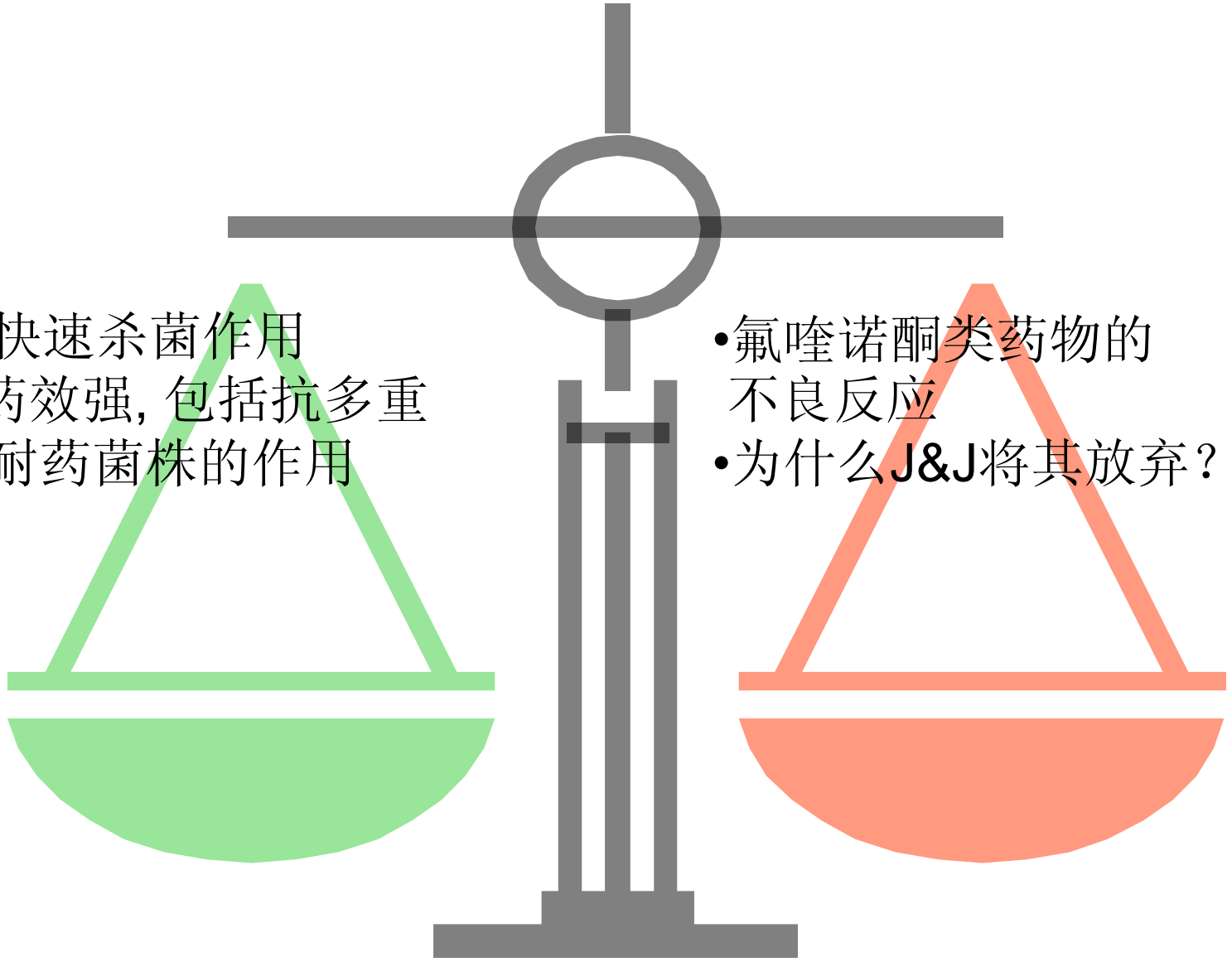
TABLE 10. Summary of adverse events

Adverse event category	No. (%) patients with indicated no. and type of adverse event[a]	
	JNJ-Q2 (n = 83)	Linezolid (n = 79)
Total no. of adverse events	111	110
No. of unique patients with at least 1 adverse event	50 (60.2)	51 (64.6)
Adverse events that occurred in >5% of either group		
Nausea	19 (22.9)	9 (11.4)
Diarrhea	12 (14.5)	13 (16.5)
Vomiting	10 (12.0)	5 (6.3)
Headache	6 (7.2)	4 (5.1)
Dizziness	3 (3.6)	4 (5.1)
Elevated ALT[b]	7 (8.4)	7 (8.9)

[a] Percentages are based on the total number of patients in each treatment group.

[b] Although not recorded by investigators as adverse events, patients with elevated ALT levels were included in the chart if they demonstrated the combination of at least 1.5× the ULN and at least a 1.5-fold increase above baseline for ALT. No subject had a simultaneous elevation of ALT and bilirubin. One subject included in the JNJ-Q2 group experienced an asymptomatic ALT elevation to 875, but without concomitant elevation of bilirubin, and the ALT elevation resolved by day 30.

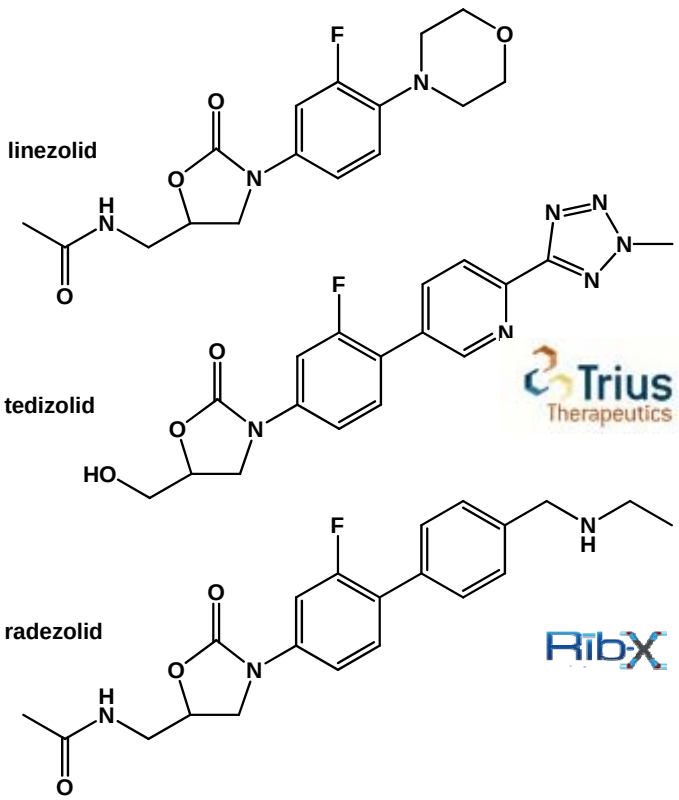
JNJ-Q2



- 快速杀菌作用
- 药效强, 包括抗多重耐药菌株的作用

- 氟喹诺酮类药物的不良反应
- 为什么J&J将其放弃？

Tedizolid - Radezolid

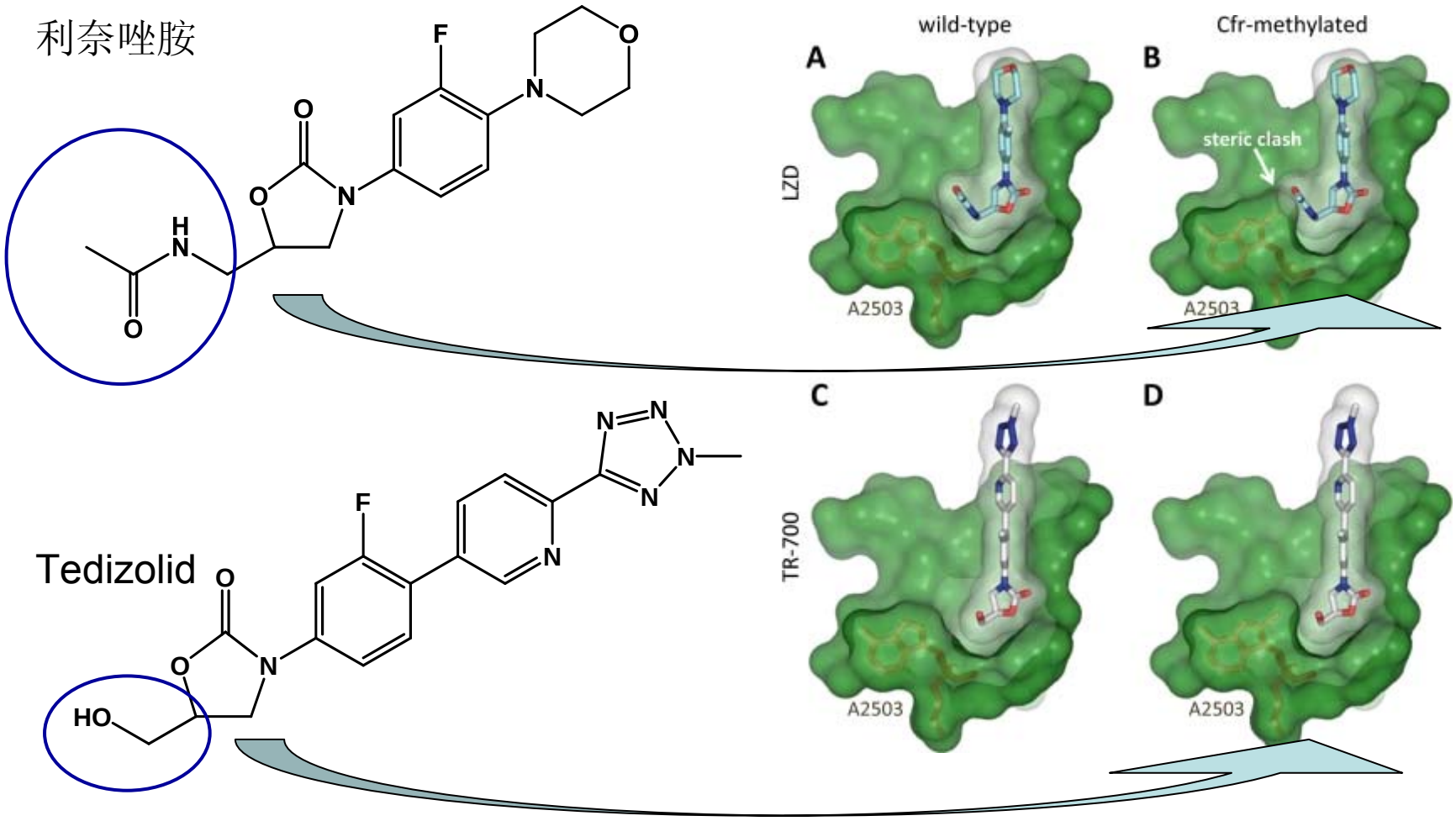


strain	Phenotype	Linezolid	Tedizolid	Radezolid
Staphylococcus aureus				
ATCC 25923	MSSA	2	0.25	0.25-0.5
ATCC 33591	HA-MRSA	1	0.125-0.25	0.5-1
SA 238	HA-MRSA	2	0.25-0.5	0.5-1
SA 238L	HA-MRSA, LZD^R	16	1	2
NRS 192	CA-MRSA	2	0.125-0.25	0.5
NRS 384	CA-MRSA	2	0.25	0.5
NRS 52	VISA	2	0.125	2
VRS 1	VRSA	1-2	0.125-0.25	0.5
VRS 2	VRSA	1-2	0.25	2
Listeria monocytogenes				
EGD		1-2	0.125	0.03-0.06
Legionella pneumophila				
ATCC 33153		4-8	0.25-0.5	0.5-1

Lemaire et al, JAC (2009) 64:1035-43 ; AAC (2010) 54:2549-59

Tedizolid 对cfr+菌株的抗菌活性

将Tedizolid 结合到甲基化的核糖体上



Locke et al, AAC (2010) 54: 5337–43

Tedizolid 和单胺氧化酶抑制作用

AAC Journals.ASM.org
Antimicrobial Agents and Chemotherapy 2013 57 p. 3060–3066

In Vitro, *In Vivo*, and Clinical Studies of Tedizolid To Assess the Potential for Peripheral or Central Monoamine Oxidase Interactions

S. Flanagan,[a] K. Bartizal,[a] S. L. Minassian,[b] E. Fang,[a] P. Prokocimer[a]
Trius Therapeutics, Inc., San Diego, California, USA[a]; Minassian Biostatistics, Inc., San Diego, California, USA[b]

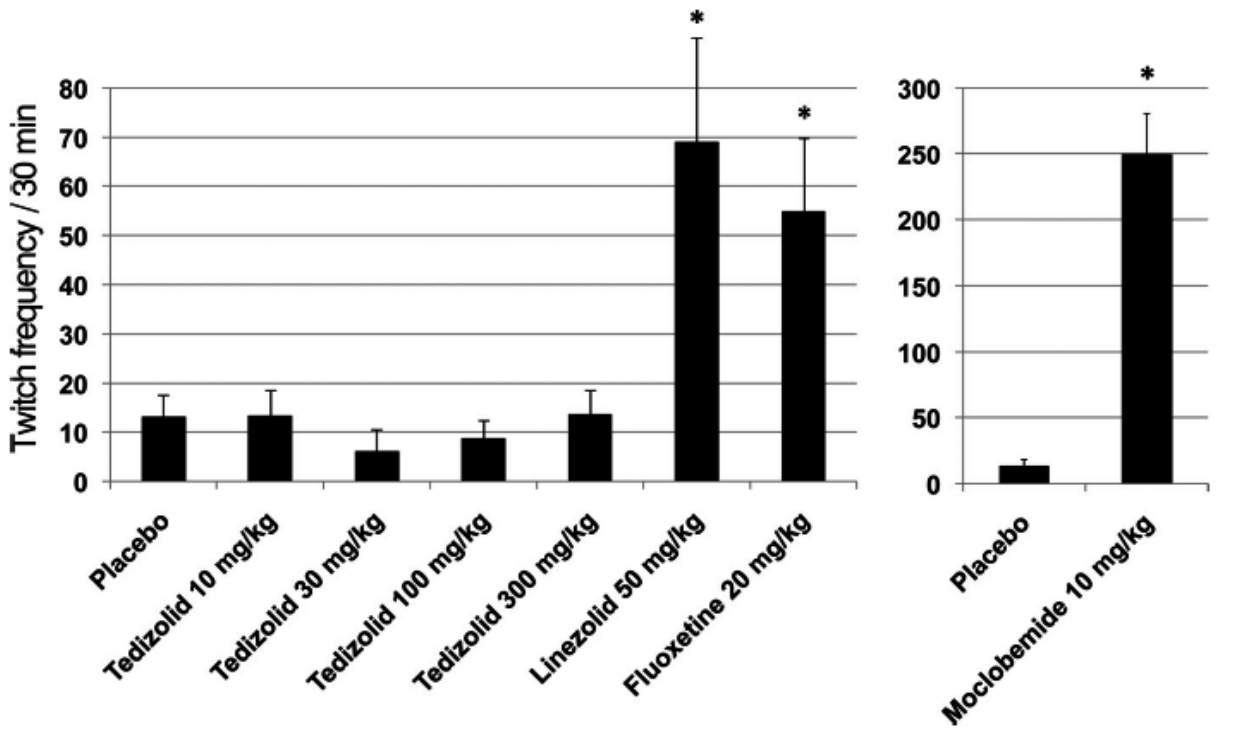


FIG 3 Mouse head twitch rate following tedizolid phosphate, linezolid, fluoxetine, or moclobemide treatment. Twitch frequency is shown as means ± SD ($n = 8$ mice/group). Tedizolid refers to tedizolid phosphate. *, $P < 0.05$ versus the control group.

Tedizolid III期临床试验

ORIGINAL CONTRIBUTION

Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections

The ESTABLISH-1 Randomized Trial

Philippe Prokocimer, MD
Carisa De Anda, PharmD
Edward Fang, MD
Purvi Mehra, MD
Anita Das, PhD

Trial Registration clinicaltrials.gov Identifier: NCT01170221

JAMA. 2013;309(6):559-569

Official Title: A Phase 3 Randomized, Double-Blind, Multicenter Study Comparing the Efficacy and Safety of 6-Day Oral TR-701 Free Acid and 10-Day Oral Linezolid for the Treatment of Acute Bacterial Skin and Skin Structure Infections

TEDIZOLID III期临床试验

Table 6. Patients With Treatment-Emergent Adverse Events (TEAEs) in the Safety Analysis Set[a]

Preferred Term	No. (%) of Patients[b]	
	Tedizolid Phosphate (n = 331)	Linezolid (n = 335)
≥1 TEAE	135 (40.8)	145 (43.3)
≥1 Serious TEAE	5 (1.5)	4 (1.2)
Death	1 (0.3)	0
Discontinuation due to TEAE	2 (0.6)	2 (0.6)
Most commonly reported TEAE[c]		
Nausea	28 (8.5)	45 (13.4)
Headache	21 (6.3)	17 (5.1)
Diarrhea	15 (4.5)	18 (5.4)
Abscess	14 (4.2)	8 (2.4)
Abscess limb	12 (3.6)	10 (3.0)
Vomiting	9 (2.7)	20 (6.0)
Cellulitis	8 (2.4)	8 (2.4)
Dizziness	8 (2.4)	7 (2.1)
Pruritus	3 (0.9)	8 (2.4)
Dyspepsia	2 (0.6)	7 (2.1)

[a] Patients reporting a particular adverse event more than once are counted only once by preferred term.
[b] Percentages were calculated as 100 × (number of patients/total number).
[c] In either treatment group, 2% or more reported 1 of these adverse events.

TEDIZOLID III期临床试验

Table 6. Patients With Treatment-Emergent Adverse Events (TEAEs) in the Safety Analysis Set[a]

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Death	1 (0.3)	0
Headache	21 (6.3)	17 (5.1)
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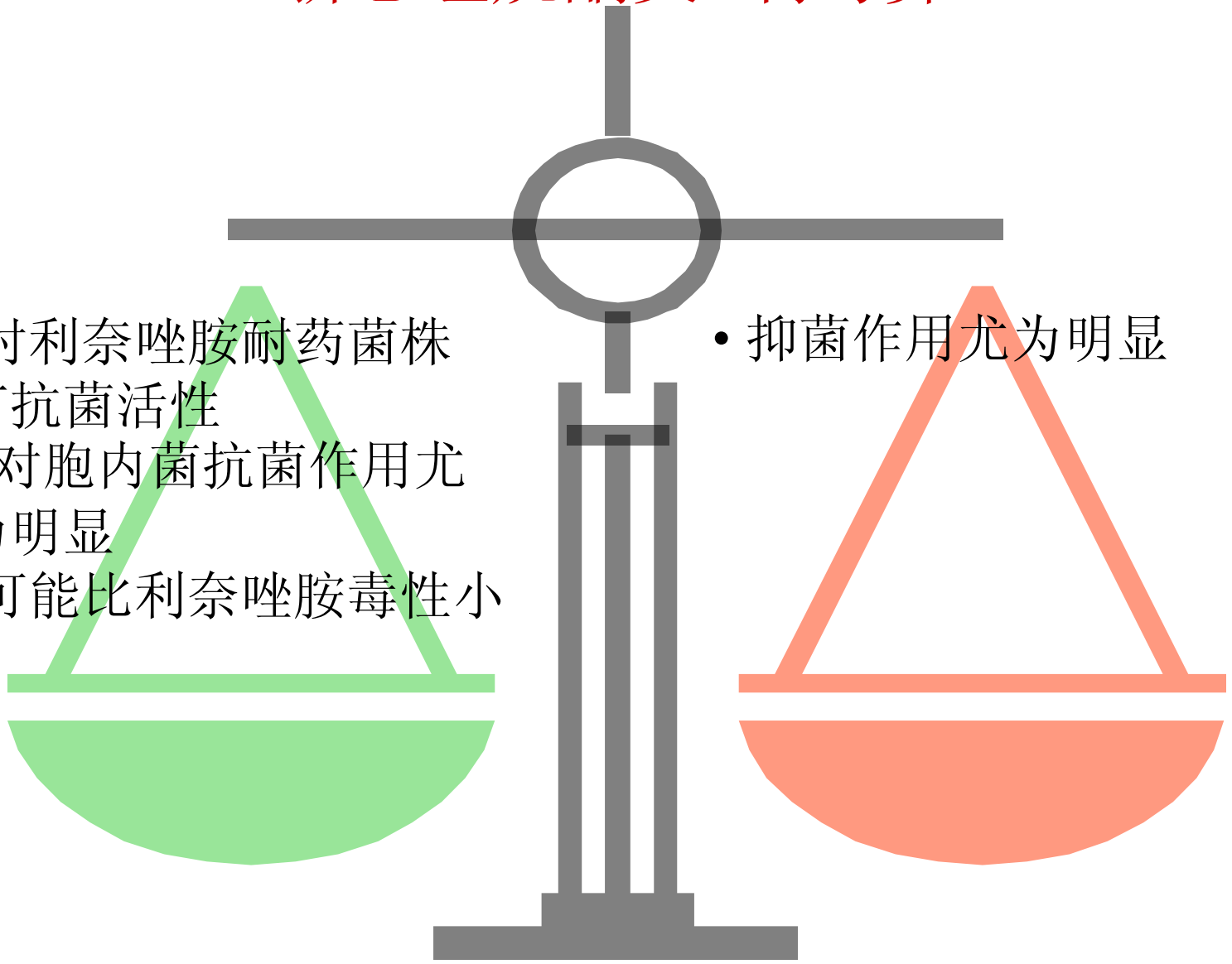
[a] Patients reporting a particular adverse event more than once are counted only once by preferred term.
[b] Percentages were calculated as 100 × (number of patients/total number).
[c] In either treatment group, 2% or more reported 1 of these adverse events.

利奈唑胺组的血小板计数下降发生率较 Tedizolid组降低了接近一半，但是这项研究还不足以得出使用Tedizolid引起骨髓抑制风险的结论。

新恶唑烷酮类: 利与弊



- 对利奈唑胺耐药菌株有抗菌活性
- 对胞内菌抗菌作用尤为明显
- 可能比利奈唑胺毒性小

- 抑菌作用尤为明显

喹红霉素-SOLITHROMYCIN

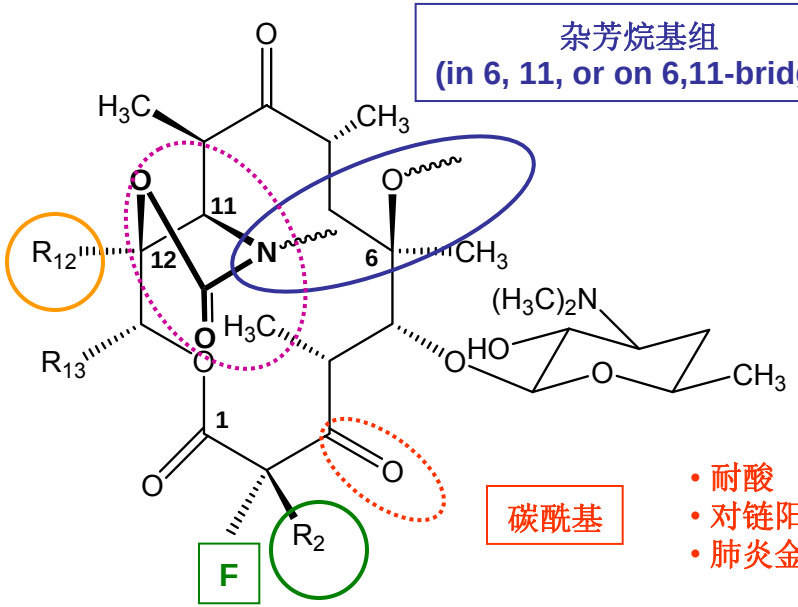
氨基甲酸酯 抗菌活性增强

乙烯基

药代动力学:
- 半衰期延长,
- 组织穿透力增强

杂芳烷基组
(in 6, 11, or on 6,11-bridge)

- 结合到核糖体II号位点;
  作用于甲基化的核糖体
- 肺炎金葡菌外排泵对其识别力差
- 药代动力学:
  细胞内累积率, 半衰期
- 耐受性

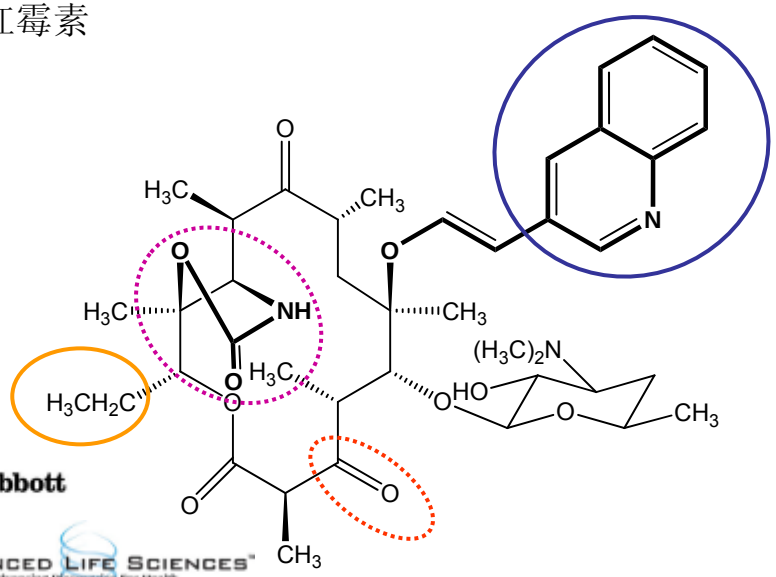


碳酰基

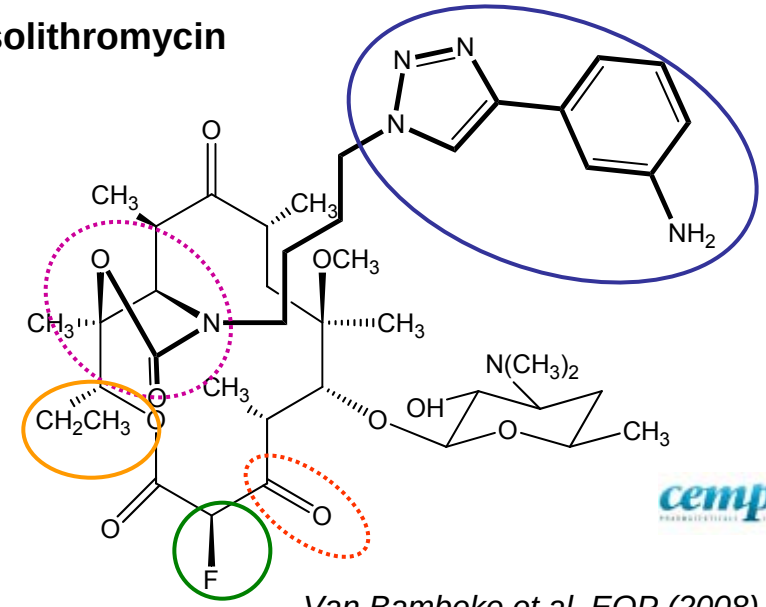
- 耐酸
- 对链阳霉素B耐药无诱导性
- 肺炎金葡菌外排泵对其识别能力差

- 增强抗菌活性
- 提高药代动力学

喹红霉素



solithromycin



Abbott

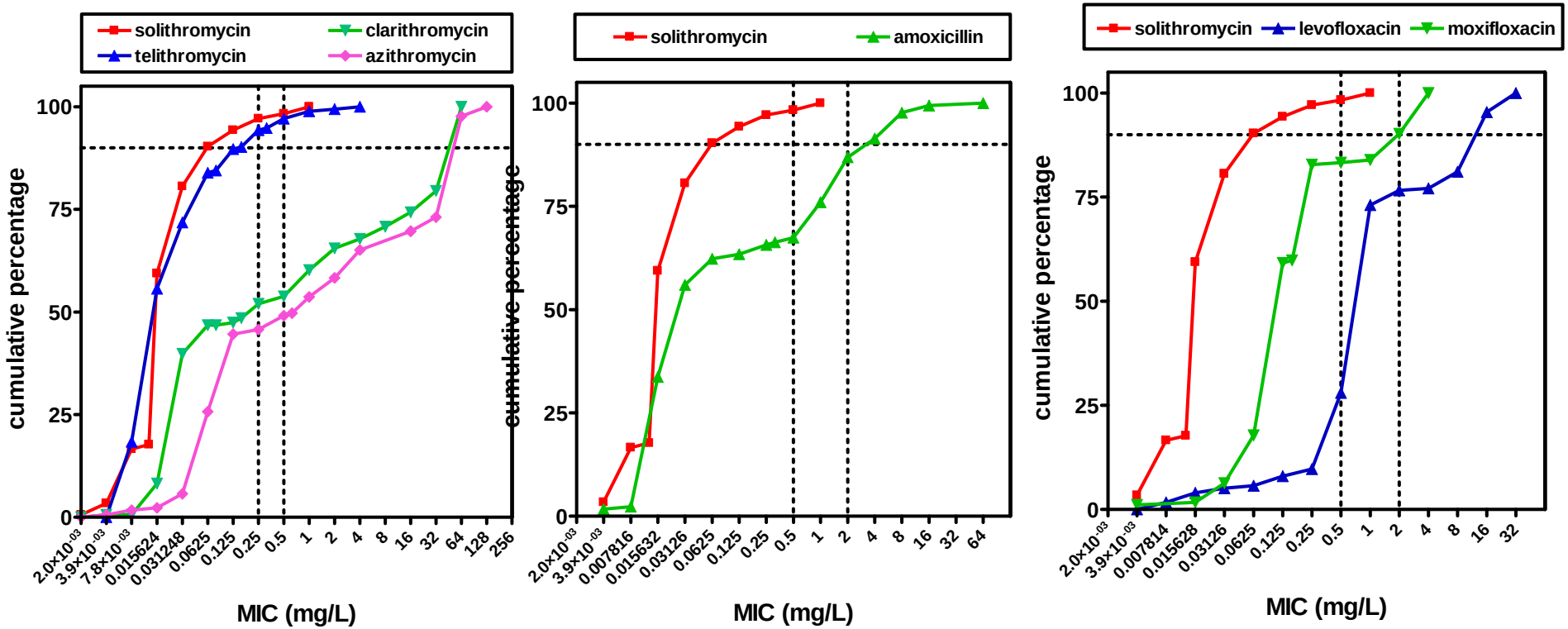
ADVANCED LIFE SCIENCES

cempra

Van Bambeke et al, EOP (2008) 9:267-283

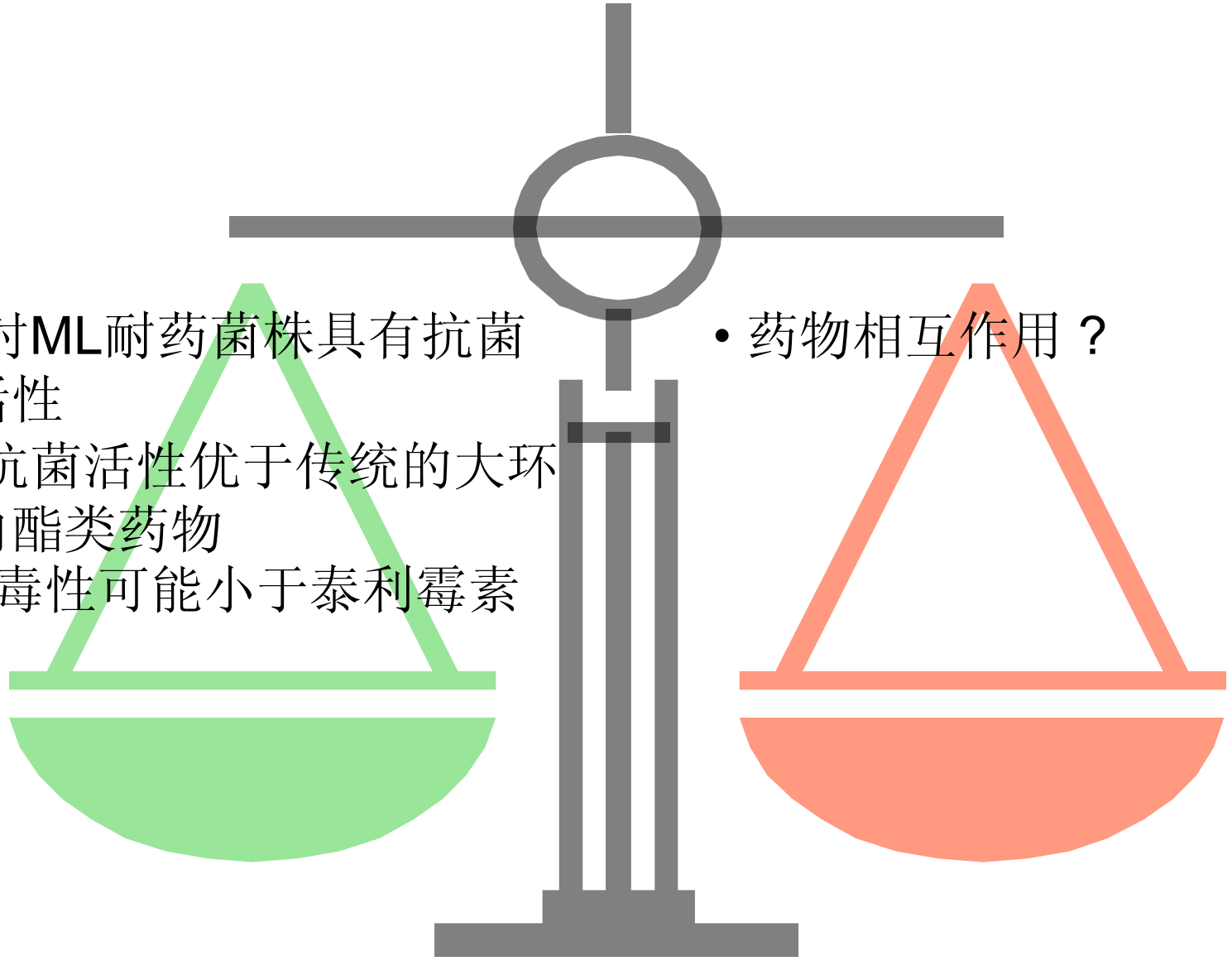
Solithromycin: 体外抗菌活性

对肺炎球菌的抗菌活性 (比利时-德国菌株，包含多重耐药菌)



Lemaire et al, ICC (2013) P105

新酮内酯类抗生素：利与弊



- 对ML耐药菌株具有抗菌活性
- 抗菌活性优于传统的大环内酯类药物
- 毒性可能小于泰利霉素

- 药物相互作用？

达巴万星

- 非常长的半衰期(首剂1 g，一周后再500g)
- 皮肤软组织感染
- 导管相关性血液感染(II度)
- ➔ 在治疗MRSA导致的复杂性皮肤软组织感染，FDA给予了其极高的评价

辉瑞公司在2008年9月撤回

- 自2009年开始再次被DURATA研发
- 从那时起没有任何临床数据被发表，但是网上宣称

“达巴万星在过去将近10年总共完成了15个III期，II期，I期临床试验，约1000个病人使用了达巴万星。"

奥利万星

- 半衰期也很长 (5-10 mg/kg 1 天 ~ 10 天)
- 皮肤和软组织感染
- 血流感染(II度)

2008年
FDA禁用，EMA要求退市

- 2009年，医药公司再次研发奥利万星，单剂量、非 常规剂量应用，静脉注射治疗革兰氏阳性菌导致的复杂性皮肤软组织感染。

奥利万星

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3476–3484 Vol. 55, No. 7
0066-4804/11/$12.00 doi:10.1128/AAC.00029-11

Comparison of the Efficacy and Safety of Oritavancin Front-Loaded Dosing Regimens to Daily Dosing: an Analysis of the SIMPLIFI Trial[▽]

Lala M. Dunbar,[1]* Joe Milata,[2] Ty McClure,[3] Margaret M. Wasilewski,[4] and the SIMPLIFI Study Team

LSU Health Sciences Center, School of Medicine at New Orleans, New Orleans, Louisiana[1]; Eli Lilly and Company, Indianapolis, Indiana[2]; Infinity Pharmaceuticals, Inc., Cambridge, Massachusetts[3]; and ID Remedies, LLC, Arlington, Massachusetts[4]

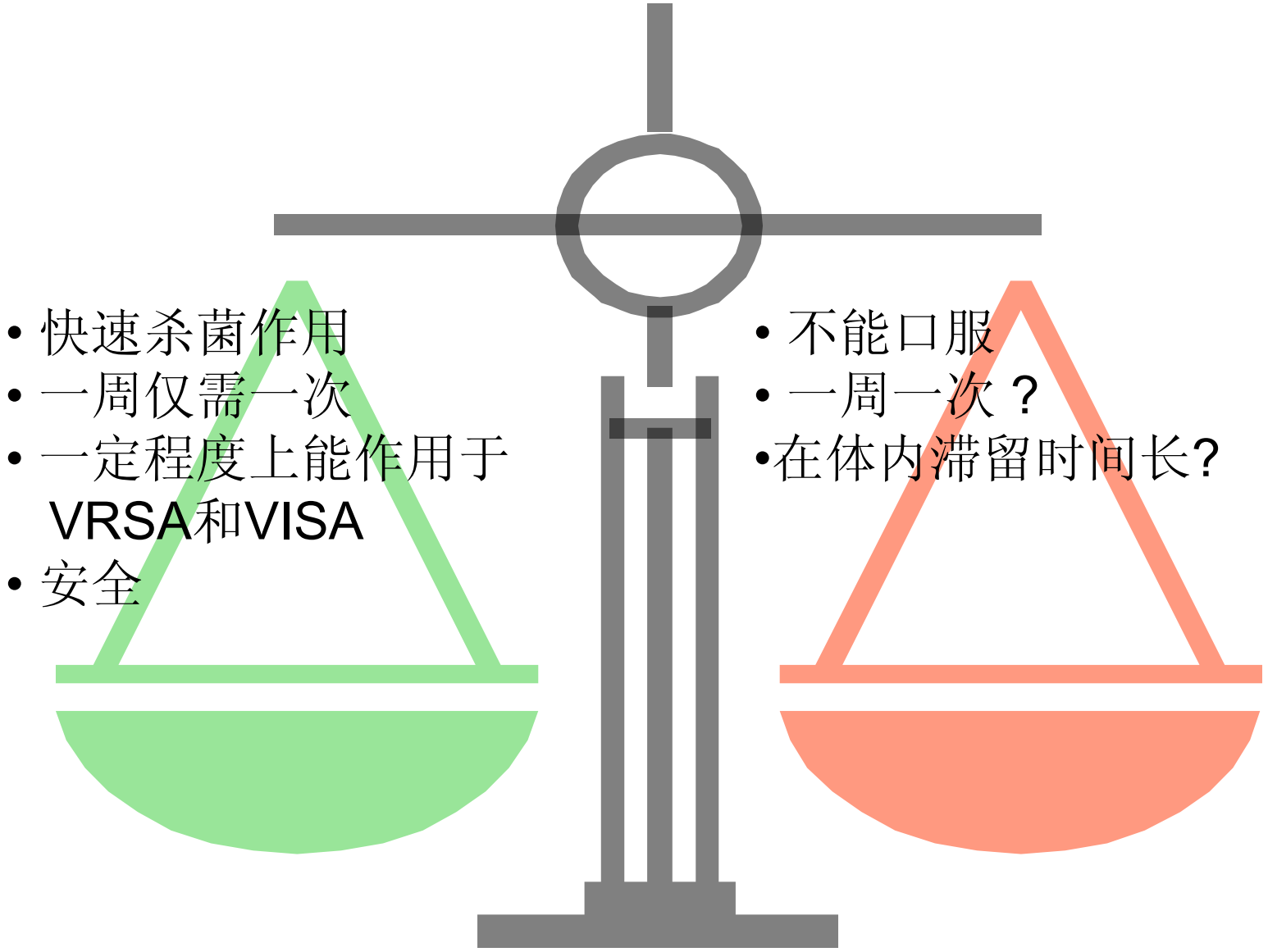
Received 9 January 2011/Returned for modification 10 February 2011/Accepted 18 April 2011

Oritavancin is a novel lipoglycopeptide with demonstrated effectiveness against complicated skin and skin structure infections (cSSSI) caused by Gram-positive pathogens, including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA). The pharmacokinetic and pharmacodynamic profile of oritavancin is favorable for single or infrequent dosing. A phase 2, multicenter, randomized, double-blind, parallel, active-comparator study (ClinicalTrials.gov identifier, NCT00514527) of single and infrequent dosing of intravenous (i.v.) oritavancin for the treatment of cSSSI caused by Gram-positive pathogens (wound infections, major abscess, and cellulitis) was undertaken to evaluate the noninferiority of front-loaded dosing regimens compared to a daily-dosing regimen. A total of 302 patients ≥18 years of age were randomized equally to one of three oritavancin treatment groups, receiving either a daily dose (200 mg) administered for 3 to 7 days, a single dose (1,200 mg), or an infrequent dose (800-mg dose, with the option for an additional 400 mg on day 5). The primary efficacy was defined as a clinical response in clinically evaluable (CE) patients assessed at days 21 to 29 (test of cure [TOC]). The cure rates in the CE population were 72.4% (55/76) in the daily-dose group, 81.5% (66/81) in the 1,200-mg-single-dose group, and 77.5% (55/71) in the infrequent-dose group. In patients with MRSA at baseline, the cure rates were 78.3% (18/23), 73.0% (27/37), and 87.0% (20/23) in the daily-, 1,200-mg-single-, and infrequent-dose groups, respectively; however, the study was not powered to assess outcomes in the MRSA subpopulation, and given the heterogeneity of the types of infection and the small sample size these do not suggest any true differences in efficacy rates for these pathogens. The frequencies of adverse events were similar among treatment groups. The results of this study show that single- and infrequent-dosing schedules of oritavancin were as efficacious as daily administration and had a similar safety profile in treating cSSSI caused by Gram-positive pathogens, including MRSA.

日剂量（200mg）治疗3—7天，单剂量（1200mg），或者使用非常规剂量（800mg）在第5天剂量增加400mg

单剂量、非常规剂量及日剂量这三种治疗方式疗效相同，且安全性相近。

达巴万星/奥利万星 ：利与弊

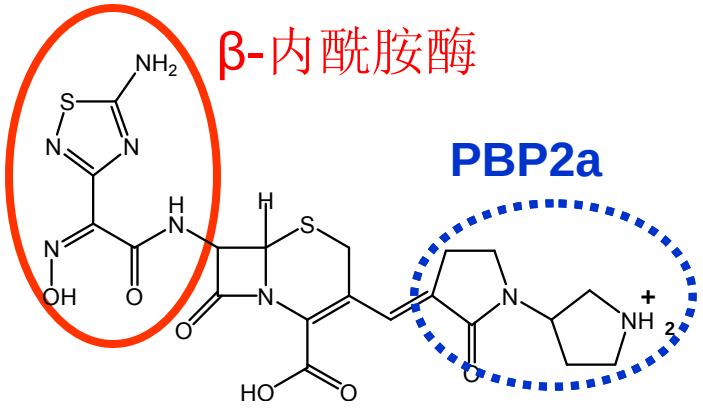


- 快速杀菌作用
- 一周仅需一次
- 一定程度上能作用于VRSA和VISA
- 安全

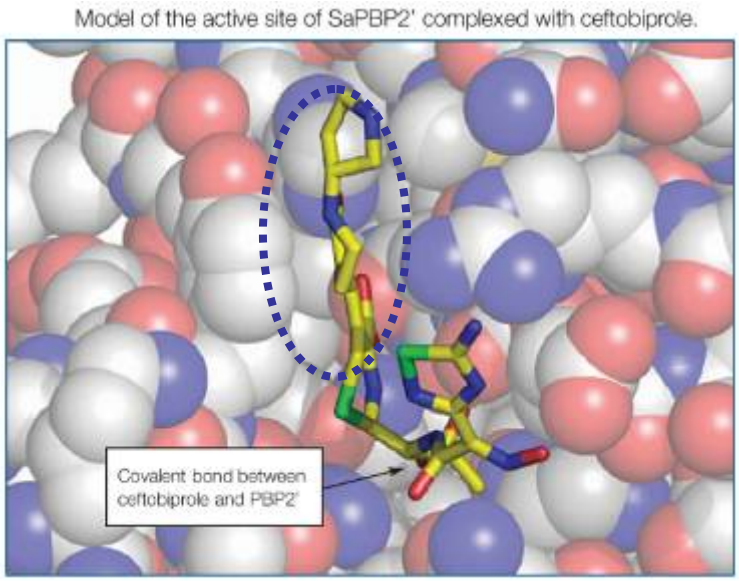
- 不能口服
- 一周一次？
- 在体内滞留时间长?

头孢吡普

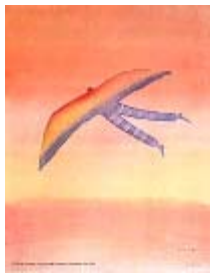
Compound	Rates of hydrolysis by purified β-lactamases: Class A — *Staphylococcus aureus* PC 1
Ro 63-9141	0.93
Ceftriaxone	19
Cephalothin	200
Penicillin G	10,000



Compound	Affinity for PBPs: IC_{50} for competition with fluorescein-labeled ampicillin (μM) — *Staphylococcus epidermidis* PBP 2′
Ro 63-9141	0.87
Ceftriaxone	115
Imipenem	>500
Methicillin	>500



开环



Lovering et al., ECCMID (2006) P1586
Hebeisen et al., AAC (2001) 45:825-31

头孢吡普

- 抗菌谱广？
  (治疗多种微生物感染)
- 杀菌作用
- 与AG具有协同作用
- 组织渗透力
- 强效作用于复杂性皮肤软组织感染、社区获得性肺炎

- 抗菌谱广？
- 可能会增加MIC值
- 仅能静脉注射
- 2-3 x/天
- 味觉障碍，恶心
- 对呼吸机相关性肺炎疗效差

小结

- 与我们常说的相悖，抗革兰氏阳性菌（包括金黄色葡萄球菌）药物还远没有到无药可用的地步。
- 考虑到对万古霉素和利奈唑胺的进一步研发势在必行，强调的是对其他药物来说应当将开发和注册结合起来，从以下几个方面考虑：
  - 提高抗微生物活性
  - 对万古霉素敏感菌具有同等效力，抗万古霉素不敏感菌和利奈唑胺耐药菌的疗效更好
  - 提高安全系数
  - 给药方法更简单
- 还要有有优势的价格，否则研发将受到限制

备选药物

万古霉素

----------**WARNINGS / PRECAUTIONS**----------

- **Vancomycin must be given orally for treatment of staphylococcal enterocolitis and *C. difficile*-associated diarrhea. Orally administered Vancomycin capsules are not effective for other types of infections.** (5.1)
- Clinically significant serum concentrations have been reported in some patients who have taken multiple oral doses of vancomycin for active *C. difficile*-associated diarrhea. Monitoring of serum concentrations may be appropriate in some instances. (5.2)
- Nephrotoxicity has occurred following oral vancomycin therapy and can occur either during or after completion of therapy. The risk is increased in geriatric patients (5.3) Monitor renal function.
- Ototoxicity has occurred in patients receiving vancomycin (5.4) Assessment of auditory function may be appropriate in some instances.
- Prescribing vancomycin in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria. (5.6)

----------**ADVERSE REACTIONS**----------

The most common adverse reactions (≥ 10%) were nausea (17%), abdominal pain (15%), and hypokalemia (13%). (6.1)

口服万古霉素的患者，治疗期间或结束治疗后都可发生肾毒性。老年人发生肾毒性的风险更大（5.3）需要监测肾功能。

万古霉素

Nephrotoxicity (e.g., reports of renal failure, renal impairment, blood creatinine increased) occurred in 5% of subjects treated with vancomycin hydrochloride. Nephrotoxicity following Vancomycin typically first occurred within one week after completion of treatment (median day of onset was Day 16). Nephrotoxicity following vancomycin hydrochloride occurred in 6% of subjects >65 years of age and 3% of subjects ≤65 years of age (*see WARNINGS AND PRECAUTIONS, Nephrotoxicity [5.3]*).

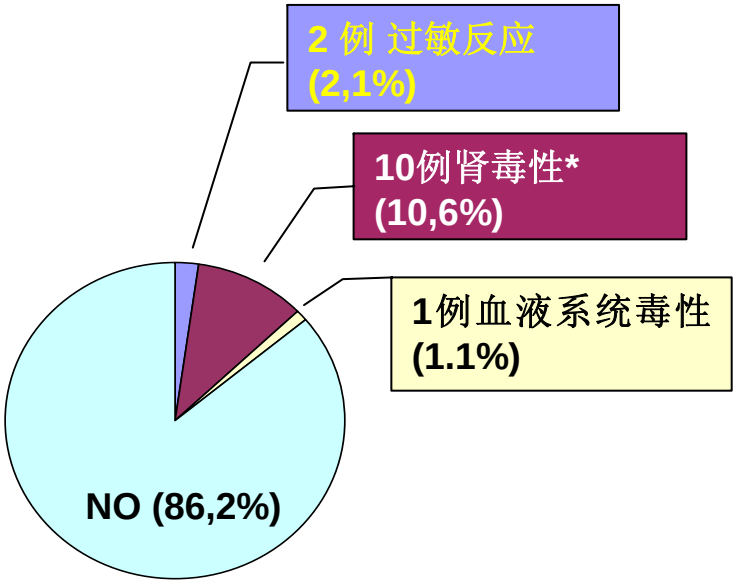
在使用过万古霉素盐酸盐的患者中，肾毒性（如已报导的肾衰竭，肾损害，血肌酐升高）发生率为5%。

万古霉素: 实际毒性

所有登记的病人出现多项不良反应(n = 94)。

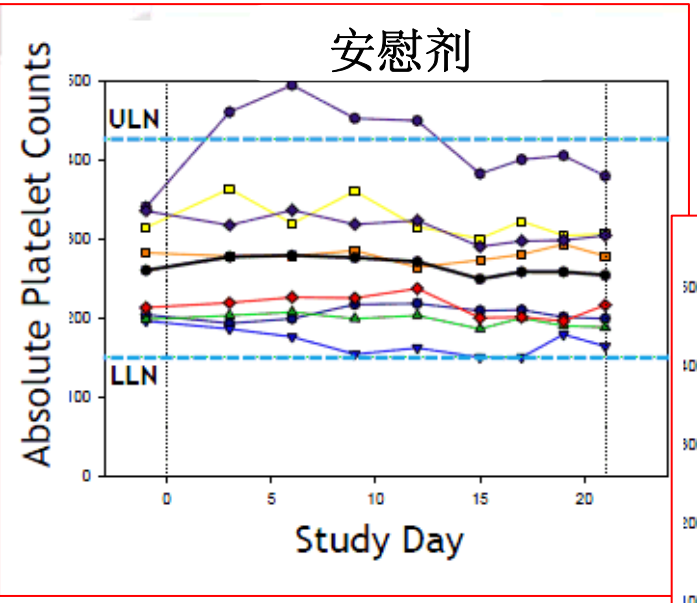
Ampe *et al.* Int J Antimicrob Agents. 2013 May;41(5):439-46

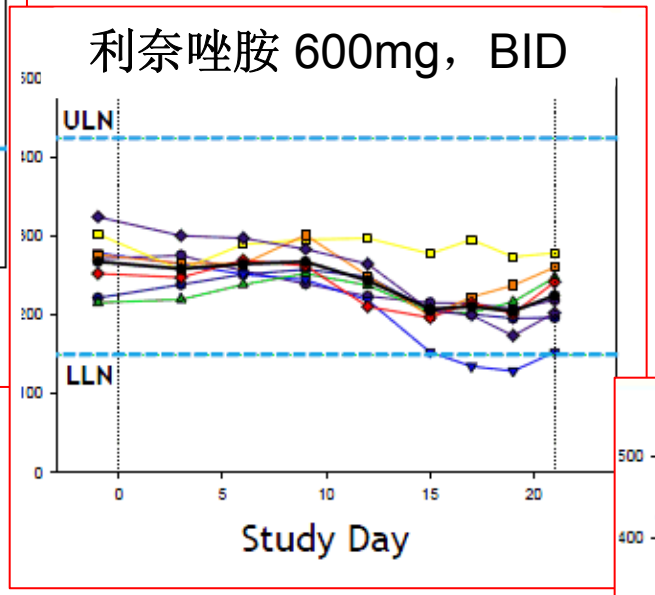
- 至少有一例不良反应: 13.8%
- 肾毒性可能导致肾衰竭不良事件
- 仅2例被迫中止治疗

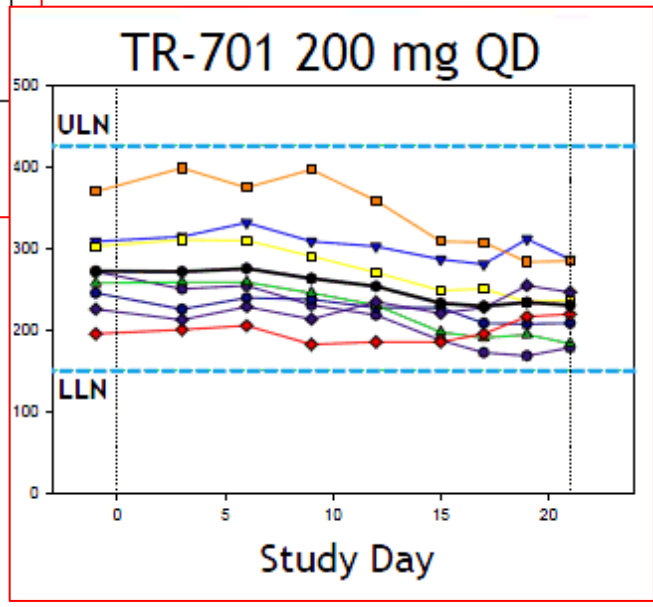


*IDSA consensus statement def. of vancomycin nephrotoxicity (Rybak et al. Am J Health-Syst Pharm 2009):
2 or 3 documented increases in serum creatinine level; increase of 0.5 mg/dL OR ⩾ 50% increase from baseline after several days of vancomycin therapy.

TEDIZOLID I期实验: 血小板 (21 days)



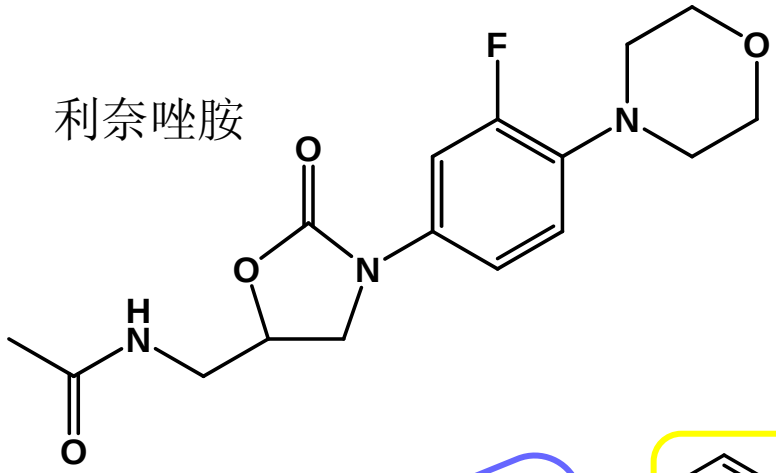


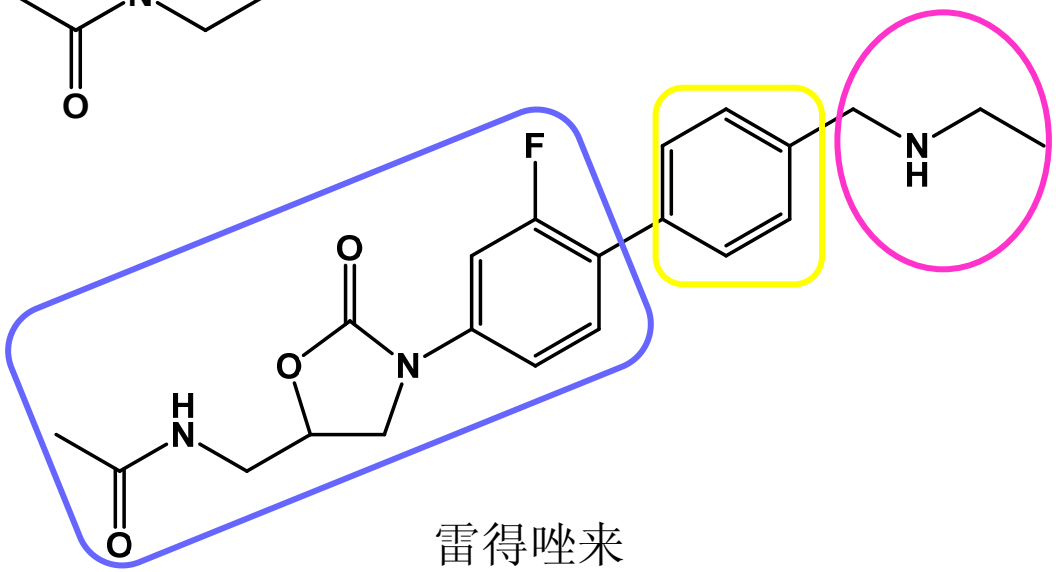


雷得唑来

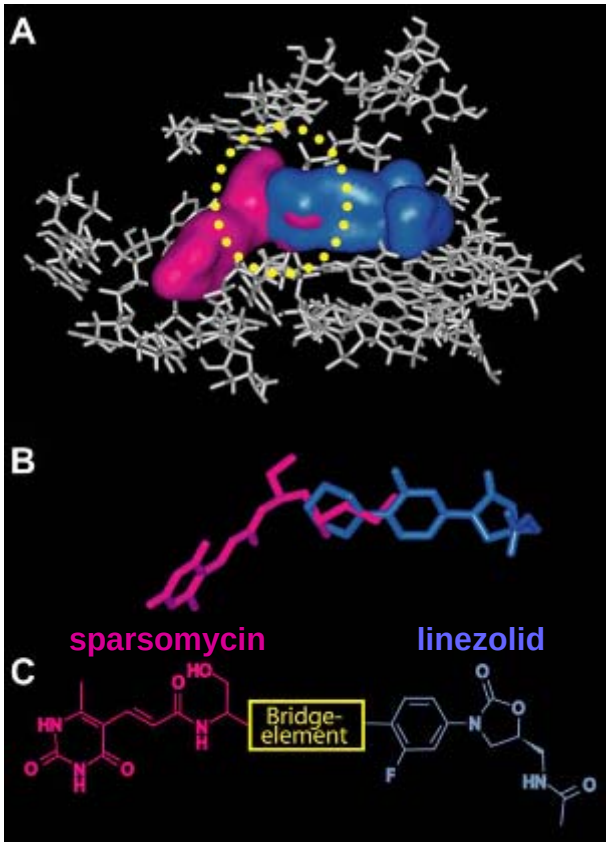
设计将司帕霉素和利奈唑胺最重要的作用部分合成一个单分子物质。

利奈唑胺





雷得唑来



Zhou et al., J. Bioorg. Med. Chem. Lett. (2008) 18:6179-83
Skripkin et al. AAC (2008) 52:3350-57

研发中的抗革兰氏阳性菌药物

公司	类别	药物	分级 (临床)
Rib-X	喹诺酮类	德拉沙星	III (ABSSSI) II (CAP)
TaiGen		奈诺沙星	II (CAP/diabetic foot)
Furiex		JNJ-Q2	III CAP/ABSSSI
Trius	恶唑烷酮类	tedizolid	III (ABSSSI)
Rib-X		雷得咗来	II ABSSSI/CAP)
Adv. Life Sci.	酮内酯类抗生素	喹红霉素	III (CAP) / anthrax
Cempra		solithromycin	III (CAP)
Durata	脂糖肽类(*)	dalbavancin	III ABSSSI
The MedCo		oritavancin	III (ABSSSI)
Nabriva	泰妙菌素 (*)	BC-3781	II (ABSSSI)
Polymedics	拟肽类 (**)	PMX-30063	II (ABSSSI)
Affinium	Fab 抑制剂 (**)	AFN-1252	II (ABSSSI)
GSK	去甲酰酶抑制剂 (**)	GSK1322322	II (ABSSSI/CAP)

* new target (not yet exploited) – dual site of action for oritavancin
** old target but not exploited in human systemic medicine

酮内酯类和神经毒性

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2010, p. 5399–5402 Vol. 54, No. 12
0066-4804/10/$12.00 doi:10.1128/AAC.00840-10

Molecular Characterization of Off-Target Activities of Telithromycin: a Potential Role for Nicotinic Acetylcholine Receptors▽†

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Adverse effects have limited the clinical use of telithromycin. Preferential inhibition of the nicotinic acetylcholine receptors (nAChR) at the neuromuscular junction (α3β2 and NMJ), the ciliary ganglion of the eye (α3β4 and α7), and the vagus nerve innervating the liver (α7) could account for the exacerbation of myasthenia gravis, the visual disturbance, and the liver failure seen with telithromycin use. The studies presented here enable the prediction of expected side effects of macrolides in development, such as solithromycin (CEM-101).

酮内酯类和神经毒性

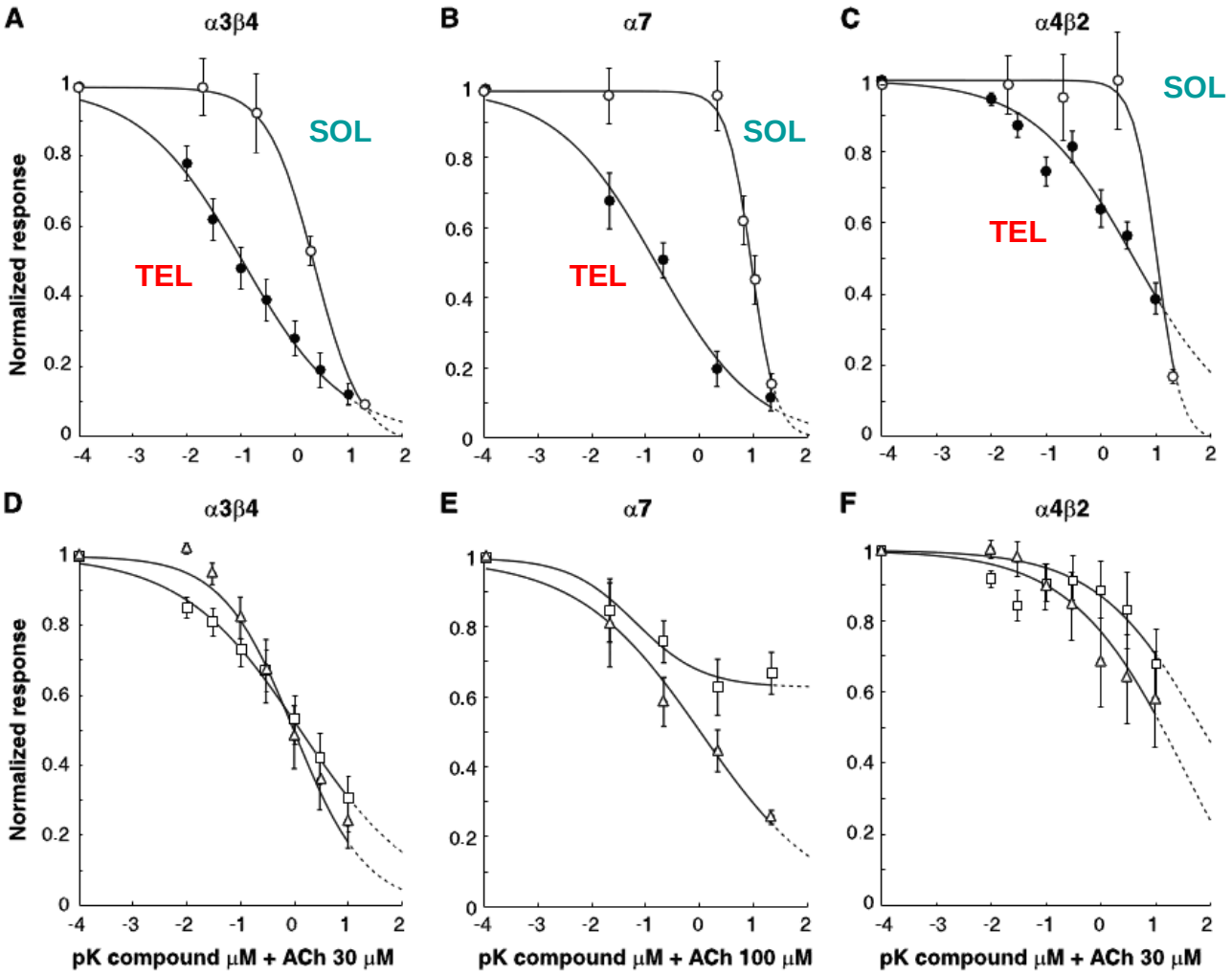

FIG. 5. Inhibition of ganglionic and central nAChRs by four macrolides. (A to C) Concentration-inhibition curves for α3β4, α7, and α4β2 with telithromycin (closed circles) and the novel ketolide CEM-101 (open circles). (D to F) Concentration-inhibition curves for α3β4, α7, and α4β2 with azithromycin (open triangles) and clarithromycin (open squares). Responses obtained from three to seven cells were normalized versus the ACh-evoked current measured as a control and plotted as a function of the logarithm of the macrolide concentration. Bars indicate the standard errors of means. Continuous curves through the data points are the best fits obtained with the empirical Hill equation.