SEICAV congreso

Madrid, del 6 al 8 de octubre de 2016

Características y usos de Tedizolid

16:25- 16:50

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MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

Instituto de Salud Carlos III

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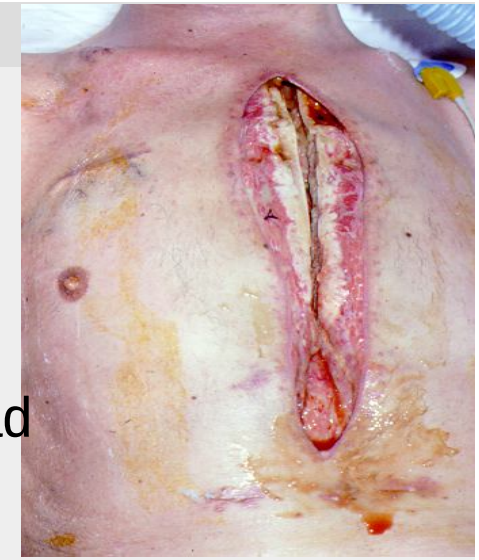
- Caso clínico
- El fármaco
- Espectro
- PK/PD
- Indicaciones
- Seguridad
- Futuro

Caso clínico

- Varón de 83 años, HTA, DL, Cardiopatía isquémica
- Leucopenia por síndrome mielodisplásico y polimialgia reumática.

- **Ingresa por** síndrome coronario agudo que requirió triple by-pass
- Reintervenido en las primeras 24h por sangrado a nivel del by-pass, realizándose lavado mediastínico y desbridamiento.
- Cierre esternal diferido al día siguiente.

Caso clínico



- Dia +18: fiebre, enrojecimiento de hx qx e inestabilidad esternal.
- HC: *S. epidermidis* meti-R y *Morganella morganii*.
- Mediastinitis postquirúrgica
- **Intervención qx:** abundante material purulento preesternal y destrucción ósea, realizándose limpieza y desbridamiento.
- Cultivo esternal: lo mismo que en HC.

- Tto. Empírico: piperacilina/tazobactam 4/0,5 g c/6h + Linezolid 600 mg c/ 12h.
- Tras antibiograma se cambió a ciprofloxacino + linezolid.

Caso clínico

- Ocho días después: **trombopenia (18mil),** se cambió de linezolid a **vancomicina** ajustada a fx renal.
- A las 48 h y ante empeoramiento de la fx renal, se sustituyó vancomicina x **daptomicina** (350 mg c/ 48h).
- Una semana después: **rabdomiólisis sec. a daptomicina (CK 2491).**
- Se sustituyó por Tedizolid 200 mg c/ 24 h durante **4 sem**.
- No trombopenia, recuperación de la fx renal. CPK se normalizó.
- Ciprofloxacino se mantuvo hasta el final del tto.
- Buena evolución clínica. No recidiva.

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¿Novedades para cocos gram positivos resistentes?

Ceftarolina fosamil ***Zinforo*** *(600 mg/12h IV)* • *SARM, VISA, VRSA* • *Neumococo peniR, CF·R* • *E. faecalis vancoR* • *Enterobacterias (NO BLEE/AmpC/CBP)* • **NAC, IPPBc.**	**Ceftobiprole medocaril** ***Zevtera*** *(500 mg/8h IV)* • *SARM, E. faecalis ampiR, BGN (NO BLEE/AmpC/CBP)* • **NAC, NN, IPPBc**	**Fosfato de Tedizolid** ***Sivextro*** *(200 mg/24 x 6 d)* • *SARM, VISA* • **IPPBc**
Dalbavancina ***Xydalba*** *(1g d0, 0,5g d8)* • *SARM, VISA* • **IPPBc**	**Telavancina** ***Vivatib*** *(10 mg/K/d)* • *SARM, VISA* • *Warnings FDA: Nefrotoxicidad, QT, C difficile* • **NN, NAV**	***Oritavancina*** ***Orbactiv*** *(1500 mg/d)* • *SARM, VISA* • **IPPBc**

Table 1. Antibiotic Drug Details, Development Milestones, and ESKAPE Status

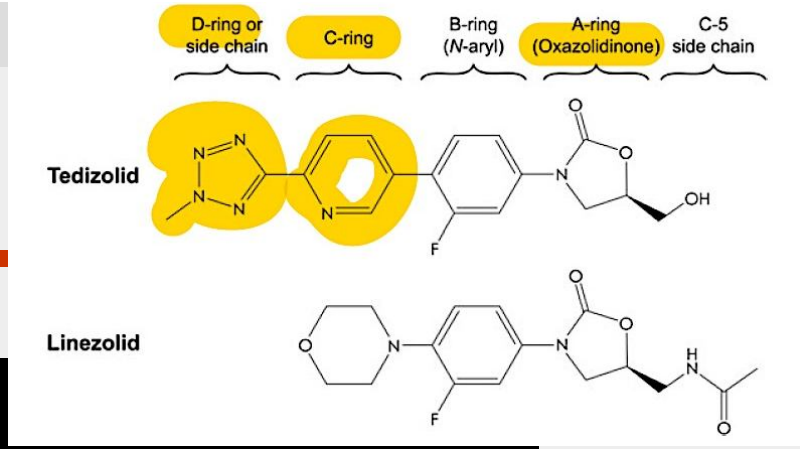
Drug	IND Filed	NDA Filed	Approval Date	Current Manufacturer	Drug Class (Year of Discovery)	Method of Administration	Novel Mechanism of Action	Indications	In Vitro Activity Against ESKAPE Pathogens?
Ceftaroline	December 2004	December 2009	29 October 2010	Actavis	Cephalosporin (1928)	Intravenous	No	ABSSSI; CABP	Yes
Fidaxomicin	August 2003	November 2010	27 May 2011	Cubist Pharmaceuticals (subsidiary of Merck)	Macrolide (1948)	Oral	No	CDAD and prevention of recurrences	No*
Bedaquiline	November 2006	June 2012	28 December 2012	Janssen Research and Development (Johnson & Johnson)	Diarylquinoline (1997)	Oral	Yes	Pulmonary tuberculosis caused by multidrug-resistant tuberculosis	No†
Dalbavancin	July 2000	September 2013	23 May 2014	Actavis	Lipoglycopeptide (1953)	Intravenous	No	ABSSSI	No
Tedizolid	November 2007; August 2009	October 2013	20 June 2014	Cubist Pharmaceuticals (subsidiary of Merck)	Oxazolidinone (1955)	Oral; intravenous	No	ABSSSI	No
Oritavancin	August 1996	December 2013	6 August 2014	The Medicines Company	Glycopeptide (1953)	Intravenous	No	ABSSSI	No
Ceftolozane-tazobactam	July 2009	April 2014	19 December 2014	Cubist Pharmaceuticals (subsidiary of Merck)	Cephalosporin (1928) + β-lactamase inhibitor	Intravenous	No	CIAI; CUTI	Yes
Ceftazidime-avibactam	January 2008	June 2014	25 February 2015	AstraZeneca/ Actavis	Cephalosporin (1928) + β-lactamase inhibitor	Intravenous	No	CIAI; CUTI	Yes

ABSSSI = acute bacterial skin and skin-structure infection; CABP = community-acquired bacterial pneumonia; CDAD = *Clostridium difficile*-associated diarrhea; CIAI = complicated intra-abdominal infection; CUTI = complicated urinary tract infection; ESKAPE = *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species; IND = investigational new drug; NDA = new drug application.

* *Clostridium difficile* is a Centers for Disease Control and Prevention urgent-threat pathogen.

† Multidrug-resistant tuberculosis is a global health priority.

¿Que es tedizolid?

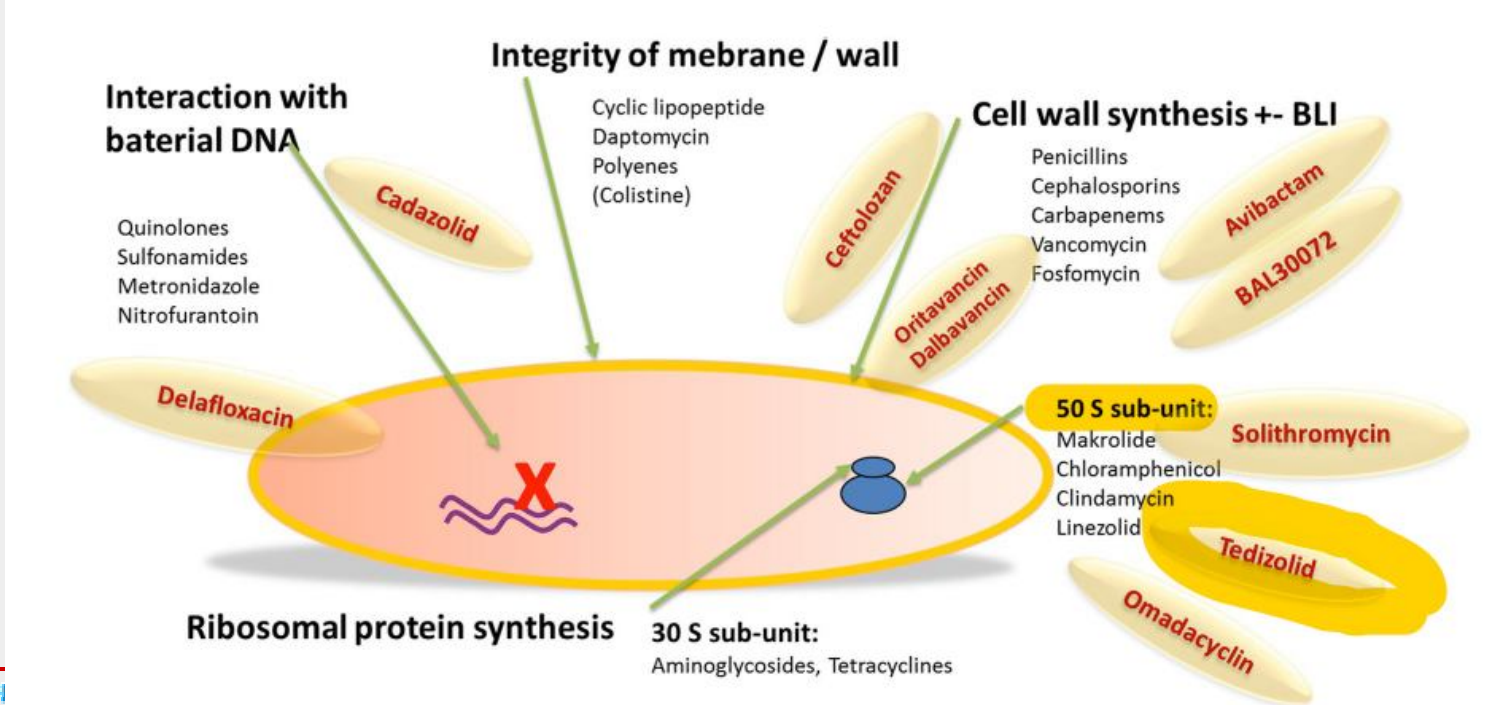


- OXADOZILIDINONA (~ linezolid)
  - modified side chain at the C-5 position of the oxazolidinone nucleus which confers activity against certain linezolid-resistant pathogens
  - Optimized C- and D-ring system that improves potency through additional binding site interactions

- Anti-grampositivo, incluido SARM y R a linezolid
- Infecciones de piel y p. blandas
- Una vez al día (IV / Oral)
- Buena tolerancia

Mecanismo de acción

- Tedizolid fosfato (TR-701) se transforma en tedizolid (TR-700) mediante las fosfatasas plasmáticas o intestinales tras la administración PO O IV
- Una vez activado, inhibe síntesis proteica uniendose al **23S rRNA** de la subunidad **50S del ribosoma** bacteriano. **Bacteriostático** in vitro a las 24 h y bactericida a las 72 h frente *S. aureus*. **BACTERICIDA** EN MODELO ANIMAL*



*Louie A. AAC 2011; 55:3453–3460

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Tedizolid: Actividad in vitro

Actividad	Resistencia
>Linezolid (R-vanco, R-linezolid)	
Gram positivos	Gram negativos
S. aureus: SAMS-SAMR	Enterobacterias
SCN	*Pseudomonas*
S. pyogenes	*Acinetobacter*
S. agalactiae	
S. anginosus	
E. faecalis, E. faecium (VRE)	

Algunas micobacterias no tuberculosas, algunos anaerobios

Parámetro PD q predice actividad en modelo animal: AUC/MIC

Med Lett Drugs Ther 2014; 56: 73

Breakpoints

***Staphylococcus* spp.** — **EUCAST Clinical Breakpoint Tables v. 6.0, valid from 2016-01-01**

Oxazolidinones	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
	S ≤	R >		S ≥	R <	
Linezolid	4	4	10	19[A]	19[A]	1. Isolates susceptible to linezolid can be reported susceptible to tedizolid.
Tedizolid	0.5[1]	0.5		Note[B]	Note[B]	A. Examine zone edges with transmitted light (plate held up to light). B. Isolates susceptible to linezolid can be reported susceptible to tedizolid. For isolates resistant to linezolid, perform an MIC test.

***Enterococcus* spp.** — **EUCAST Clinical Breakpoint Tables v. 6.0, valid from 2016-01-01**

Oxazolidinones	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
	S ≤	R >		S ≥	R <	
Linezolid	4	4	10	19	19	
Tedizolid	IE	IE		IE	IE	

Oxazolidinones **Streptococcus groups A, B, C and G**	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
	S ≤	R >		S ≥	R <	
Linezolid[1]	2	4	10	19	16	1. Non-susceptible isolates are rare or not yet reported. The identification and antimicrobial susceptibility test result on any such isolate must be confirmed and the isolate sent to a reference laboratory. 2. Isolates susceptible to linezolid can be reported susceptible to tedizolid.
Tedizolid[1]	0.5[2]	0.5		Note[A]	Note[A]	A. Isolates susceptible to linezolid can be reported susceptible to tedizolid. For isolates resistant to linezolid, perform an MIC test.

Oxazolidinones ***Streptococcus pneumoniae***	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
	S ≤	R >		S ≥	R <	
Linezolid	2	4	10	22	19	
Tedizolid	IE	IE		IE	IE	

Oxazolidinones **Viridans group streptococci**	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
	S ≤	R >		S ≥	R <	
Linezolid	-	-		-	-	A. Perform an MIC test.
Tedizolid, *S. anginosus* group	0.25	0.25		Note[A]	Note[A]	

Any trailing of growth after the first major reduction in bacterial growth in the microbroth dilution panel should be ignored.

In Vitro Activities of Tedizolid Compared with Other Antibiotics against Gram-positive Pathogens Associated with Hospital Acquired Pneumonia (HAP), Skin and Soft Tissue Infection (SSTI) and Bloodstream Infection (BSI) collected from Hospitals in China.

- **2140 isolates** (23.7% HAP, 46.8% SSTI and 29.5% BSI)
- 26 hospitals in 17 cities across China during 2014.
- 632 MRSA, 867 MSSA, 299 CoNS, 104 *E. faecalis*, 99 *E. faecium*, 13 *S. pneumoniae*, 23 -hemolytic *Streptococcus* and 103 -hemolytic *Streptococcus*.

- **98% S.** Tedizolid exhibited **4-8-fold > activity** than linezolid
  - MRSA, *Streptococcus* (0.25 g/ml vs. 2 g/ml)
  - MSSA, *E. faecalis* and *E. faecium* (0.5 g/ml vs. 2 g/ml)
  - MRCoNS and MSCoNS (0.25 g/ml vs. 1 g/ml)
  - *S. pneumoniae* (0.125 g/ml vs. 0.5 g/ml)

Li S. et al. J Med Microb 2016

In vitro activity of tedizolid against *Staphylococcus aureus* and *Streptococcus pneumoniae* collected in 2013 and 2014 from sites in Latin American countries, Australia, New Zealand, and China

D. J. Biedenbach[1] · S. K. Bouchillon[1] · B. Johnson[1] · J. Alder[2] · D. F. Sahm[1]

- *S. aureus:* ***x 4-8 fold more active than linezolid***
  - Latin America (MIC90, 0.5 mg/L) n=1500
  - Australia and New Zealand (MIC90, 0.25 mg/L) n=593
  - China (MIC90, 0.5 mg/L) n=1326
- *S. pneumoniae:* ***x 4 fold more active than linezolid***
  - MIC90, 0.25 mg/L vs 1 mg/L line

- Only two tedizolid non-susceptible strains were observed
  - Both intermediate MICs (1 mg/L)

Eur J Clin Microbiol Infect Dis 2016

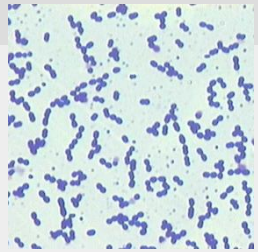
In Vitro Activities of Tedizolid and Linezolid against Gram-Positive Cocci Associated with Acute Bacterial Skin and Skin Structure Infections and Pneumonia.

- **425 isolates** of Gram-positive bacteria: 100 MSSA, 100 MRSA, 50 *Streptococcus pyogenes*, 50 *S. agalactiae*, 75 *S. anginosus* group, 50 *E. faecalis*, and 50 vancomycin-resistant enterococci (VRE)

- Tedizolid exhibited 2-4-fold > activity than linezolid
  - MRSA, *Streptococcus* (0.5 g/ml vs. 2 g/ml)
  - MSSA, *E. faecalis, E. faecium, VRE* (0.5 g/ml vs. 2 g/ml)
  - MRCoNS and MSCoNS (0.25 g/ml vs. 1 g/ml)
  - *S. pneumoniae* (0.125 g/ml vs. 0.5 g/ml)
  - *S. pyogenes* (0.5 g/ml vs. 2 g/ml)
  - *S. agalactiae* (0.5 g/ml vs. 2 g/ml)
  - *S. anginosus* group (0.5 g/ml vs. 2 g/ml)
  - Line intermediate *E. faecalis* and *E. faecium* (n=5) (1 µg/ml and 0.5 µg/ml)

Chen KH. Antimicrob Agents Chemother 2015.

Tedizolid susceptibility in linezolid- and vancomycin-resistant *Enterococcus faecium* isolates



- Tedizolid: Remains active against a subset of LR-VRE, (isolates expressing the plasmid-encoded chloramphenicol-florfenicol resistance **(cfr) gene**
- 30 LR *E. faecium* VRE (MIC range 32-256 mg/l) isolated between 2012 and 2015 from clinical and screening specimens.
- All isolates, carried mutations within the 23S rDNA
- Compared to linezolid, tedizolid lower MICs (MIC range 2-32 mg/l), but above the FDA tedizolid breakpoint for *E. faecalis* at 0.5 mg/l.
- **Thus, related to the predominant resistance mechanism, tedizolid is of limited value for treatment of most LR-VRE and represents a therapeutic option only for a limited subset of isolates.**

Klupp EM. Eur J Microbiol Infect Dis 2016.

In Vitro Activities of Tedizolid and Linezolid against Gram-Positive Cocci Associated with Acute Bacterial Skin and Skin Structure Infections and Pneumonia

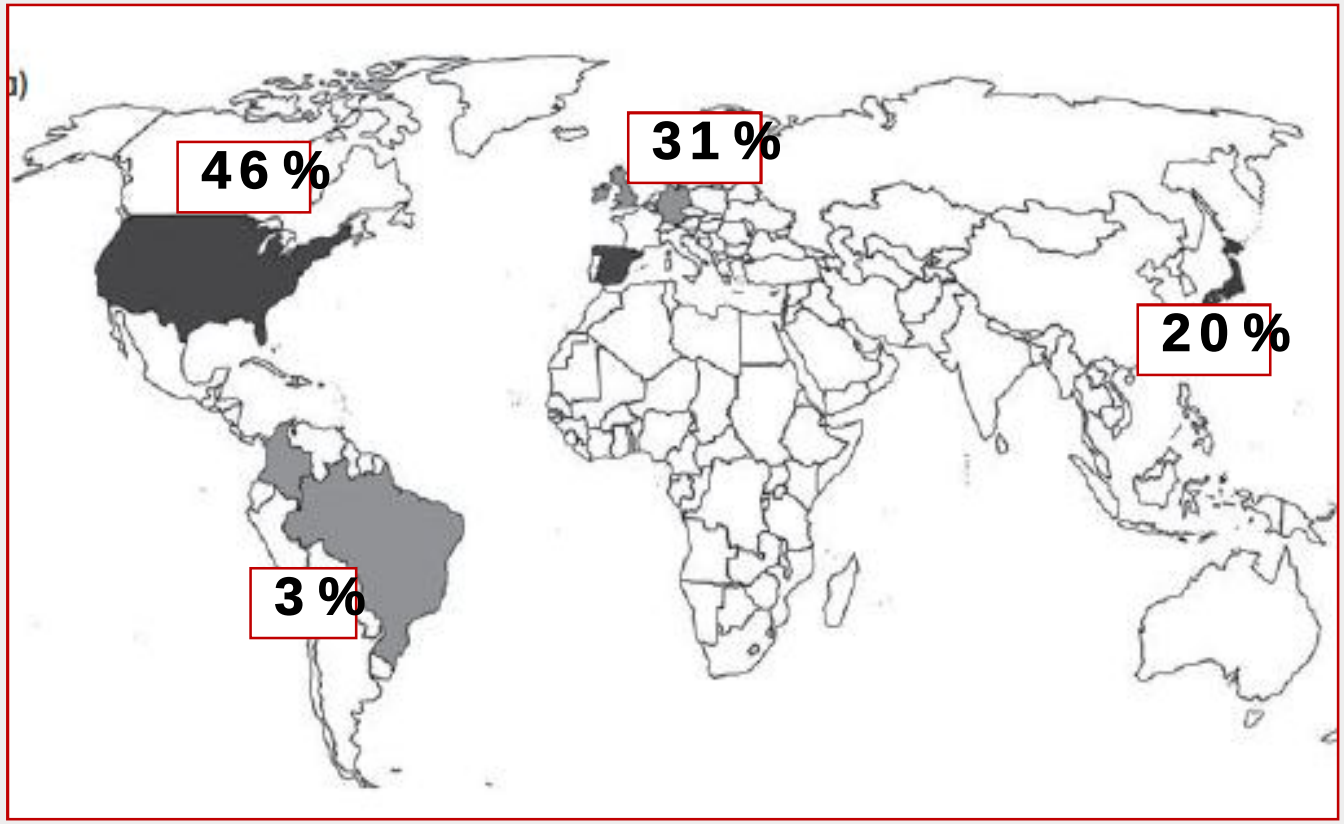
- Rates of susceptibility (U.S. FDA MIC)
  - ***S. anginosus* (0.5 µg/ml) : 16%**
  - ***S. constellatus* (1 µg/ml) : 28%**
  - *S. intermedius* (0.5 µg/ml) : 72%
  - and 0.5 µg/ml, respectively, and the rates of

- Lower susceptibilities of tedizolid against isolates of *S. anginosus* and *S. constellatus* than against those of *S. intermedius* in Taiwan

Chen KH. Antimicrob Agents Chemother 2015.

S. aureus resistente a linezolid

Distribución mundial de casos de SARM-LR



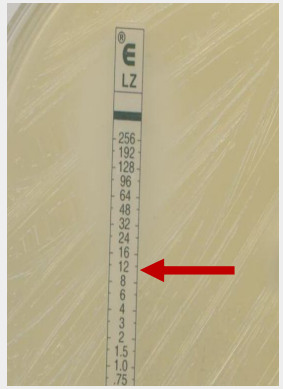
SARM-LR brote o nosocomial

Cepas descritas de SARM-LR

Gu B, et al. JAC 2013; 68:4-11

Resistencia a linezolid en grampositivos

- **Mecanismos de R (R cruzada con tedizolid excepto *cfr*):**
  - Diversas mutaciones 23S ARNr (1 o más copias; *rrn*)
  - R mediada por el gen *cfr* (metilasa, transferible)
  - Mutaciones proteínas ribosómicas L3, L4, L22 (genes *rplC, rplD, rplV)*
  - genes transferibles *cfr-B*, *optrA*
  - Coexistencia de varios mecanismos
- **Adquisición:**
  - Tratamiento tiempo prolongado con linezolid
  - Diseminación clones resistentes (pacientes-sanitarios)
  - Diseminación transposones o plásmidos (*cfr*)
  - Aumento de nivel de R según nº alelos mutados del gen 23S ARNr



Cortesía de Dra. Cercenado

Marina Peñuelas[1]
Francisco Javier Candel[1]
Clara Lejarraga[1]
Laura López-González[1]
Jose Manuel Viñuela-Prieto[1]
Diego López de Mendoza[2]

Activity of linezolid and tedizolid against clinical isolates of methicillin-resistant and methicillin and linezolid resistant *Staphylococcus aureus*: an *in vitro* comparison

[1]Clinical Microbiology Department, Hospital Clínico San Carlos, Universidad Complutense, Madrid, Spain
[2]Medical Department, Antimicrobial Drugs, Antibiotics Division, Merck Sharp & Dohme, Spain

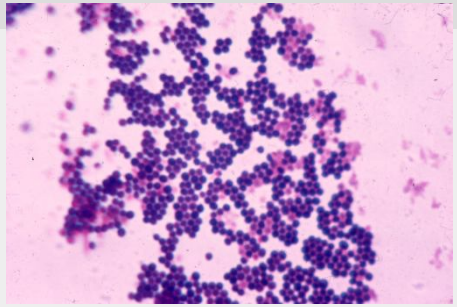
18 MRSA strains and 18 cfr -mediated MLRSA

Table 2 Cumulative frequency of MIC *in vitro* of tedizolid and linezolid against isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) and *cfr*-mediated methicillin- and linezolid-resistant *Staphylococcus aureus* (MLRSA).

		MIC (mg/L)							
		0.125	0.25	0.5	1	2	4	8	>8
MRSA	Linezolid				7	11			
	Tedizolid	2	11	5					
MLRSA	Linezolid							3	15
	Tedizolid		2	2	13	1			

Rev Esp Quimioter 2016;29(5): 255-258

Evaluation of tedizolid against *Staphylococcus aureus* and enterococci with reduced susceptibility to vancomycin, daptomycin or linezolid



- **302 MRSA** (75 DNS, 100 VISA, 120 hVISA and 7 LR) **and 220 VRE** [100 *E. faecalis* (all S to daptomycin and linezolid) and 120 *E. faecium* (25 DNS and 10 LR)]
- Tedizolid MIC90
  - **hVISA**, **VISA** and **DNS** were 0.5 mg/L (versus 4, 4 and 2 mg/L for linezolid)
  - **LR MRSA** was 0.063-1 mg/L. Two LR MRSA possessed the cfr gene with tedizolid MICs of 0.125 and 0.25 mg/L (linezolid MICs of 16 and 8 mg/L)
  - **Vancomycin-resistant *E. faecalis* and *E. faecium*** was 0.25 and 1 mg/L, respectively; three dilutions lower for *E. faecalis* and two dilutions lower for *E. faecium* compared with linezolid.
- Tedizolid may be a viable treatment option in clinical situations with **MDR Gram-positive pathogens**

Barber KE. JAC 2016.

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Tedizolid: Pharmacology

Variable	Linear pharmacokinetics
Route	Oral and IV (AUC igual con/sin comida). > 90% oral bioavailability
Formulations	200 mg tabs and single use vials
T max (single-dose)	**2.5 h** (oral), **1.1 h** (IV)
Distribution	**70-90% protein bound**
Metabolism	The prodrug tedizolid phosphate is rapidly converted to tedizolid by endogenous phosphatases; it is **not** a substrate, inhibitor, or inducer of **CYP450 enzymes**. Metabolized **via the liver**
Excretion	82% (feces), 18% (urine) as inactive metabolilte
Half-life (terminal)	**12 h**
Dosage	**200mg/day (oral OR IV)**
Renal or hepatic adjustment. Advanced age.	**NOT NEEDED**

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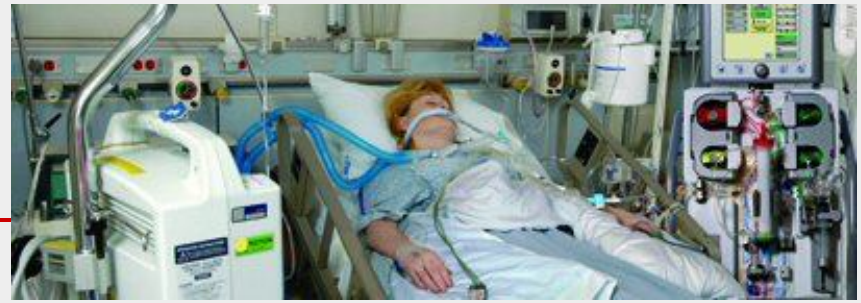
Stability of Crushed Tedizolid Phosphate Tablets for Nasogastric Tube Administration

- Difficulty swallowing and in whom venous access is not suitable.
- Crushed tablets dispersed in water and passed through NGT: 92.5 - 97.1 % tedizolid (acceptance 90-110%)
- Stable after 4 h of storage at room temperature (93.9 % initially and 94.7 % after 4 h)

Kennedy G. Drugs R D 2015

Tedizolid Adsorption and Transmembrane Clearance during in vitro Continuous Renal Replacement Therapy

- Transmembrane clearance (CLTM) and adsorption in continuous hemofiltration (CVVH) and continuous hemodialysis (CVVHD)
  - In vitro models (*polysulfone and AN69 hemodiafilters*). CLTM assessed at various ultrafiltrate (Quf) and dialysate rates (Qd). Adsorptiontested in a recirculating CVVH model over 4 h.
- **CLTM**
  - CVVH: did not differ between filter types
  - CVVHD, significantly higher with the polysulfone hemodiafilter at Qd 6 l/h ($p < 0.02$)
- **Adsortion:** irreversible adsorption to the CRRT apparatus and bound significantly higher to the polysulfone hemodiafilter



Lewis SJ. Blood Purif 2015

Tedizolid Adsorption and Transmembrane Clearance during in vitro Continuous Renal Replacement Therapy.

CONCLUSION:

- Tedizolid's CLTM is dependent on Qd, Quf, and hemodiafilter type.
- At conventional CRRT rates, tedizolid CLTM appears modest relative to total body clearance and is unlikely to require dose adjustments.
- CRRT adsorption in the clinical setting is likely less than what we observed in this in vitro, continuously recirculating blood model.

Lewis SJ. Blood Purif 2015

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SSTI: Inadequate initial treatment

Clinical and Economic Consequences of Failure of Initial Antibiotic Therapy for Hospitalized Patients With Complicated Skin and Skin-Structure Infections

47,219 patients with SSTIs

10,782 (22.8%) initial failures

Failures receive 5 days more IV Abx

5.4 extra days of hospital

> $ 5,285 of extra-cost

Edelsberg J. Infect.Cont.Hosp.Epidemiol 2008; 29: 160-169

Tedizolid: Clinical trials

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

The ESTABLISH-1 Randomized Trial

ITT 667 adult patients with ABSSSI's
Tedizolid: Non inferior than linezolid

10 d oral Linezolid	6 d oral Tedizolid
79.4%	79.5%

Prokocimer P. J.A.M.A. 2013; 309: 559-569.

Tedizolid. Piel y partes blandas

Comorbilidad

Criterio de valoración principal

48-72 hrs

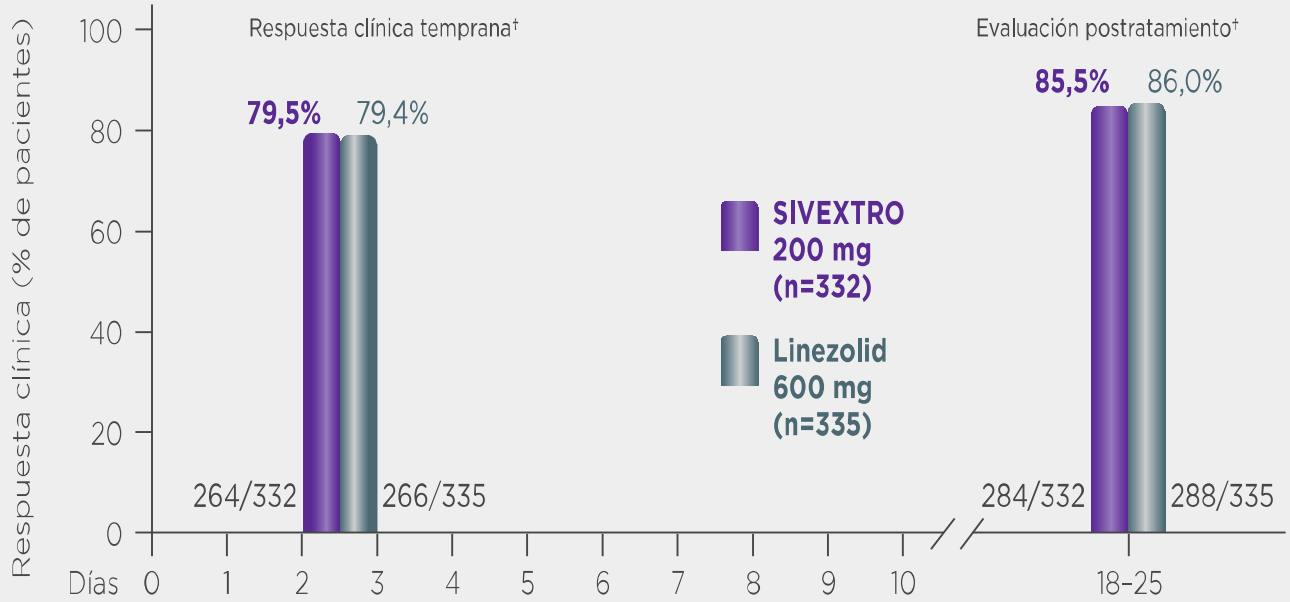
Respuesta clínica temprana†

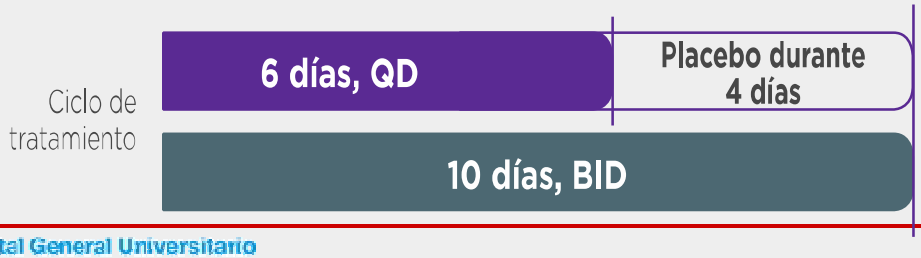
Factores de riesgo

Criterio de valoración secundario

Días 18-25

Evaluación postratamiento†





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Prokocimer P, et al. JAMA. 2013;309:559-569

Tedizolid

Clinical trials: **Complicated** SSTI (ESTABLISH 1-2)

Table 5. Tedizolid Clinical Trials

Study	Drug		Cessation of Lesion Spread[1]	Reduction in Lesion Area[2]
ESTABLISH-1 (n=649)	Tedizolid	6 d	79% (256/323)	78% (252/323)
	Linezolid	10 d	79% (258/326)	76% (246/326)
ESTABLISH-2 (n=666)	Tedizolid	6 d	86% (286/332)	85% (283/332)
	Linezolid	10 d	84% (281/334)	83% (276/334)

1. No increase from baseline in lesion surface area and temperature ≤37.6°C 48-72 hrs after the first dose.
2. Reduction from baseline of ≥20% in lesion surface area 48-72 hrs after the first dose.

Approved by FDA for cIPPB: Cost 235$/d

Med Lett Drugs Ther 2014; 56: 73

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- Caso clínico
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Tedizolid: Efecto

- Náuseas (8%)
- Cefalea (6%)
- Diarrea (4%)
- Vómitos (3%)
- Trombopenia (2%) < Line
- Interacción: IMAO (revers
- Embarazo=C

Table 2. Comparison of Adverse Events With Tedizolid and Linezolid From the ESTABLISH Studies

TEAEs	Tedizolid 200 mg Daily (n = 618)	Linezolid 600 mg Twice Daily (n = 617)
Discontinued due to adverse event	3 (0.5)	6 (0.9)
At least 1 serious adverse events	12 (1.8)	13 (2)
Gastrointestinal	106 (16)*	152 (23)
Nausea	54 (8)*	81 (12)
Vomiting	19 (2.9)*	37 (5.6)
Diarrhea	26 (3.9)	35 (5.3)
Dyspepsia	4 (0.6)	8 (1.2)
Hematologic		
Hb <10.1 g/dL in males, <9 g/dL in females	19 (3.1)	23 (3.7)
ANC <800 cells/μL	3 (0.5)	4 (0.6)
Platelets <112 500 cells/μL	7 (1.3)	20 (3.7)
Neurologic	65 (9.8)	67 (10.1)
Dizziness	12 (1.8)	14 (2.1)
Headache	41 (6.2)	39 (5.9)
Insomnia	10 (1.5)	5 (0.8)
Peripheral neuropathy	8 (1.2)	4 (0.6)
Optic nerve disorders	2 (0.3)	1 (0.2)
Dermatologic	47 (7.1)	40 (6)
Generalized pruritus	11 (1.7)	7 (1.1)

Med Lett Drugs Ther 2014; 56: 73;
Burdette SD. CID 2015:61

Tedizolid vs Linezolid.
Trombopenia

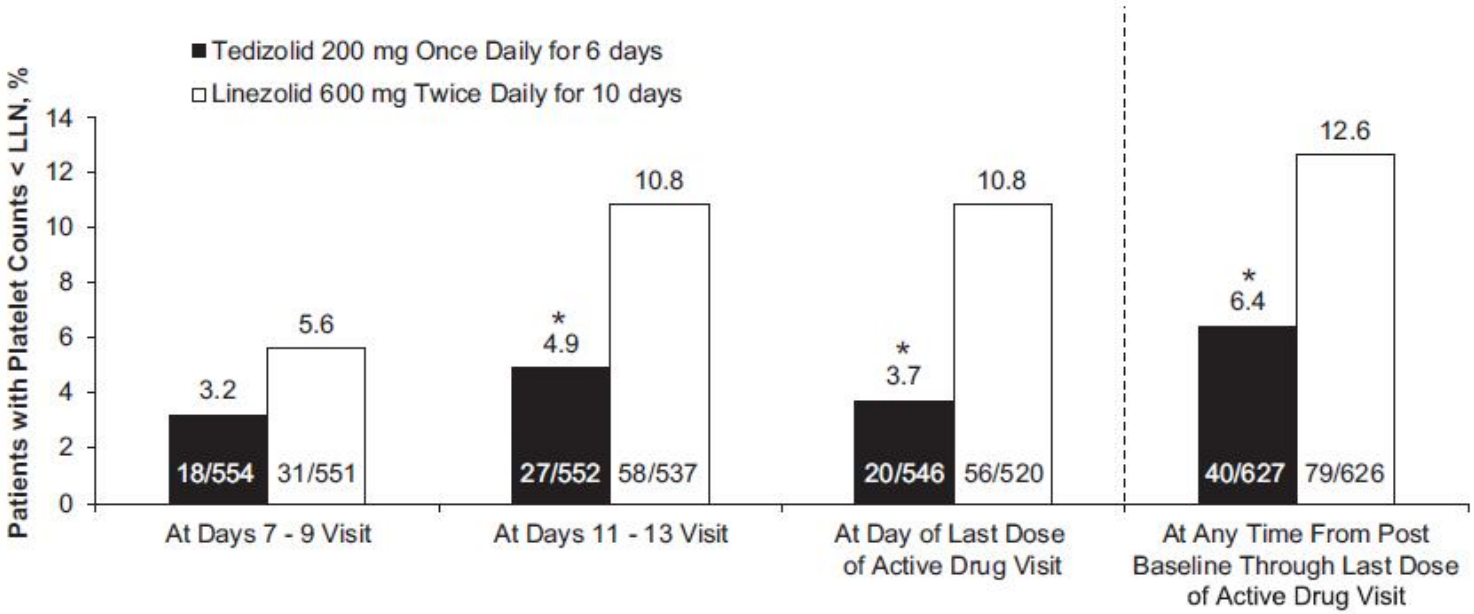


FIG 3 Patients with platelet counts below the lower limit of normal (LLN) (<150,000 cells/mm^3) over time. *, $P < 0.05$. EOT, end-of-therapy.

Shorr AF, et al. Antimicrob Agents Chemother. 2015;59:864-871

Nonclinical and pharmacokinetic assessments to evaluate the potential of tedizolid and linezolid to affect mitochondrial function.

- El **tratamiento prolongado con linezolid** se asocia a daño mitocondrial (mitochondrial protein synthesis -MPS)
  - Mielosupresión
  - Acidosis láctica
  - Neuropatía
- ¿Tedizolid?

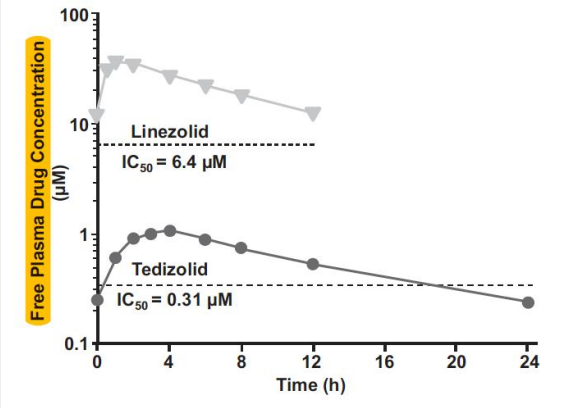
- **Mitocondrias cardíacas de ratón**: inhibición más potente de la MPS que linezolid

- **Modelo de rata** de 9 meses de altas dosis de tedizolid: **No neuropatía ni incremento de movimientos de cabeza**

Flanagan S. AAC 2015 y AAC 2013.

Nonclinical and pharmacokinetic assessments to evaluate the potential of tedizolid and linezolid to affect mitochondrial function.

- Why this discordance *in vitro / in vivo*
- **Murine macrophage (J774) cell fractionation studies**: NO stable association with eukaryotic mitochondria.
- **Monte Carlo simulations** on population PK models: during the intervals of standard treatment, free plasma concentrations below respective MPS IC50
  - 84% of tedizolid-treated pts (for a median duration of 7.94 h)
  - 38% of linezolid-treated pts (for a median duration of 0 h)



- Therapeutic doses of tedizolid, but not linezolid, may therefore allow for **mitochondrial recovery** during antibacterial therapy.

- Tedizolid has less potential to cause myelosuppression and neuropathy during prolonged treatment courses

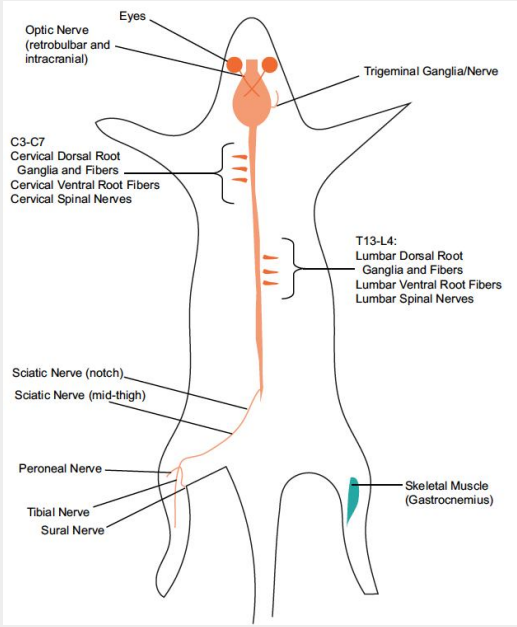
Flanagan S. Antimicrob Agents Chemother 2015.

Lack of neuropathological changes in rats administered tedizolid phosphate for nine months

- Long Evans rats. Up to 9 months at doses near the maximum tolerated dose (MTD) to evaluate for potential neurotoxicity.

- NO tedizolid-related adverse **neurobehavioral effects** or tedizolid-related **histopathologic changes** in the **central/peripheral** nervous systems, **including the optic nerve**.

- Results of this study indicate that tedizolid was **not neurotoxic** when administered long term to pigmented rats at doses near the MTD, which were up to **8-fold higher than the human therapeutic exposure**.



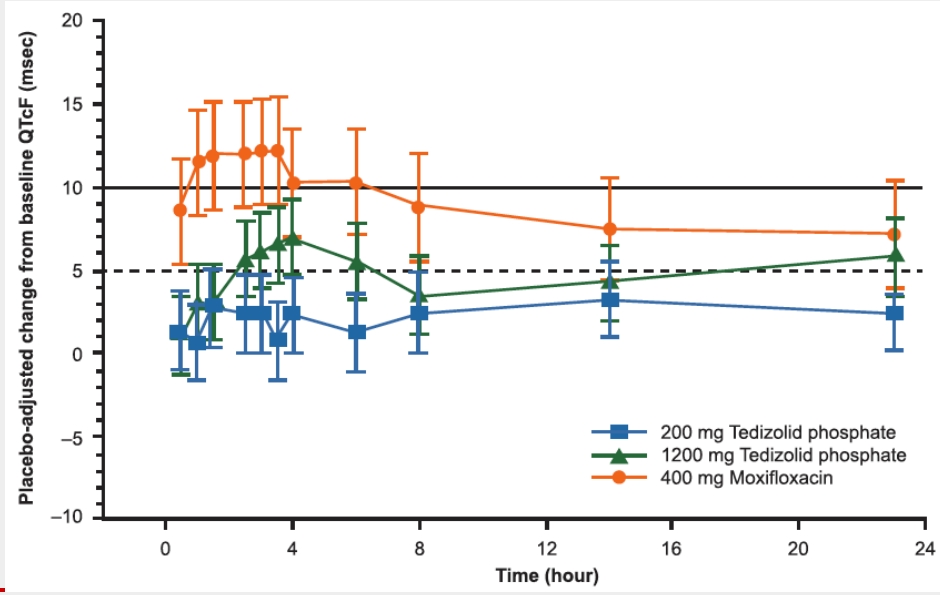
Schlosser MJ. Antimicrob Agents Chemother 2015.

Effects of therapeutic and supratherapeutic doses of oral tedizolid phosphate on cardiac repolarisation in healthy volunteers: a randomised controlled study

Shawn Flanagan [a], Jeffrey Litwin [b], Edward Fang [a], Philippe Prokocimer [a,*]

- Phase 1 study to analyzed effect on QT [ClinicalTrials.gov NCT01461460]
- 48 healthy adult patients received either
  - Tedizolid therapeutic dose (200 mg)
  - Tedizolid supra-therapeutic dose (1200 mg)
  - Moxifloxacin
  - Placebo

No clinically significant effect on QT interval in healthy adults



International Journal of Antimicrobial Agents 48 (2016) 33–40

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Future research

- Further research is needed
  - Longer duration of therapy
  - Concomitant serotonergic agents
  - Neutropenia
  - Pediatric patients (en marcha)
  - Other infections
    - Pneumonia (NCT02019420)
    - Osteoarticular
    - Bacteremia / Endocarditis
    - ....
  - Higher doses??

Bacteriemia y material protésico

- **Bacteriemia:** 11/11 pacientes de estudios ESTABLISH respondieron (4SAMS, 2SAMR, 5 otros)

In vitro activity of tedizolid against staphylococci isolated from prosthetic joint infections☆

Diagnostic Microbiology and Infectious Disease 85 (2016) 77–79

Suzannah M. Schmidt-Malan [b], Kerryl E. Greenwood Quaintance [b], Melissa J. Karau [b], Robin Patel

Comparative Efficacies of Tedizolid Phosphate, Linezolid, and Vancomycin in a Murine Model of Subcutaneous Catheter-Related Biofilm Infection Due to Methicillin-Susceptible and -Resistant *Staphylococcus aureus*

Antimicrob Agents Chemother 60:5092–5096.

Arnold S. Bayer,[a,b] Wessam Abdelhady,[a] Liang Li,[a] Rachelle Gonzales,[a] Yan Q. Xiong[a,b]

Tedi > Vanco y Line

Bacteriemia y material protésico

Activity of Tedizolid in Methicillin-Resistant *Staphylococcus aureus*

Experimental Foreign Body-Associated Osteomyelitis

AAC Accepted Manuscript Posted Online 22 August 2016

Kyung-Hwa Park,[1,3] Kerryl E. Greenwood-Quaintance,[1] Jayawant Mandrekar,[2] Robin Patel[1,3]

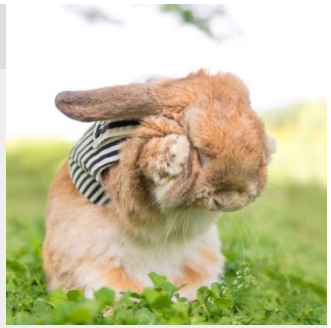
Conclusion: Tedizolid alone or combined with rifampin was active in a rat model of MRSA foreign body osteomyelitis. Emergence of rifampin resistance was noted in animals receiving tedizolid plus rifampin.

Open trials

☑ Include only open studies ☐ Exclude studies with Unknown status

Rank	Status	Study
1	Recruiting	A Study of Oral and Intravenous (IV) Tedizolid Phosphate in Hospitalized Participants, Ages 2 to <12 Years, With Confirmed or Suspected Bacterial Infection (MK-1986-013) **Condition:** Gram-Positive Bacterial Infections **Interventions:** Drug: Tedizolid Phosphate (IV); Drug: Tedizolid Phosphate (oral suspension)
2	Not yet recruiting	Tedizolid Tissue Penetration in Diabetic Patients With Wound Infections and Healthy Volunteers Via In Vivo Microdialysis **Conditions:** Diabetes; Wound Infection; Healthy Volunteers **Interventions:** Drug: Tedizolid; Procedure: Microdiaylsis Catheter Insertion
3	Not yet recruiting	Pharmacokinetics of Tedizolid Phosphate in Cystic Fibrosis **Condition:** Cystic Fibrosis **Interventions:** Drug: Tedizolid PO/IV; Drug: Tedizolid IV/PO
4	Recruiting	Study of Tedizolid Phosphate in Adolescents With Complicated Skin and Soft Tissue Infection (cSSTI) (MK-1986-012) **Conditions:** Skin Diseases, Infectious; Skin Diseases, Bacterial **Interventions:** Drug: Tedizolid Phophate 200 mg, IV and/or oral for 6 days; Drug: Antibiotic comparator
5	Recruiting	Safety and Efficacy of BAY1192631 in Japanese Patients With Methicillin-resistant Staphylococcus Aureus (MRSA) Infections **Condition:** Skin Diseases, Infectious **Interventions:** Drug: Tedizolid(BAY1192631); Drug: Linezolid
6	Recruiting	TR-701 FA vs Linezolid for the Treatment of Nosocomial Pneumonia **Condition:** Pneumonia **Interventions:** Drug: TR-701 FA IV; Drug: Linezolid

Comparative efficacies of tedizolid phosphate, vancomycin, and daptomycin in a rabbit model of MRSA endocarditis



- Tedizolid (15 mg/kg body weight intravenous [i.v.] twice a day [b.i.d.])
- Vancomycin (30 mg/kg i.v. b.i.d.)
- Daptomycin (18 mg/kg i.v. once a day [q.d.]) in a rabbit model of aortic valve endocarditis (AVE) caused by MRSA strain COL (infection inoculum of 10(7) CFU).

- **Vegetation titers**: Dapto < Tedi (P = 0.01); Tedi = Vanco
- **Organisms in spleen and kidney**: similar in all groups

- Lower doses of tedizolid were less efficacious
  - The 15 mg/kg dose used produced 5 times AUC of the 200 mg/d in humans
  - Higher doses needed for this indication?

Chan LC. Antimicrob Agents Chemother 2015

Coste

New Antibiotic			Comparator			Cost Ratio
Drug	**Dose and Duration**	**Cost Range, $***	**Drug**	**Dose and Duration**	**Cost Range, $***	
Ceftaroline	CABP: 600 mg every 12 h for 5–7 d	CABP: 1666.30–2332.82	CABP: ceftriaxone	CABP: 1 g of ceftriaxone once daily for 5–7 d	CABP: 9.00–329.35	CABP: 185:1 to 7:1
	ABSSSI: 600 mg every 12 h for 5–14 d	ABSSSI: 1666.30–4665.64	ABSSSI: vancomycin + aztreonam	ABSSSI: 1 g of vancomycin twice daily and 1 g of aztreonam twice daily for 5–14 d	ABSSSI: 470.10–1681.68	ABSSSI: 4:1 to 3:1
Fidaxomicin	200 mg twice daily for 10 d	3969.20	Vancomycin†	125-mg capsule 4 times daily for 10 d	1252.00–1392.00	3:1
Bedaquiline	400 mg daily for 2 wk, then 200 mg 3 times/wk for 22 wk	36 000.12	Placebo (both groups received a background multidrug anti–TB treatment regimen)	-‡	-‡	-‡
Dalbavancin	1 dose of 1000 mg, then 500 mg 8 d later	5364.00	Vancomycin or linezolid	1 g of vancomycin twice daily for 3–14 d, with optional switch to 600 mg of linezolid twice daily for 8 d	Vancomycin: 44.82–574.56 Linezolid: 2938.72	Vancomycin: 120:1 to 9:1 Linezolid: 2:1
Tedizolid	200 mg once daily for 6 d	Oral: 2124 IV: 1692	Linezolid	600 mg twice a day for 10 d	3673.40	Oral: 0.5:1 IV: 0.5:1
Oritavancin	1200 mg dose administered by IV once	3480.00	Vancomycin	1 g every 12 h for 7–10 d	104.58–410.40	33:1 to 9:1
Ceftolozane–tazobactam	CUTI: 1.5 g every 8 h for 7 d	CUTI: 2091.60	CUTI: levofloxacin	CUTI: 750 mg levofloxacin daily for 7 d	CUTI: 0.35–0.70	CUTI: 5976:1 to 2988:1
	CIAI:1.5 g every 8 h for 4–14 d	CIAI: 1195.20–4183.20	CIAI: meropenem	CIAI: 1 g of meropenem every 8 h for 4–10 d	CIAI: 154.20–2111.10	CIAI: 8:1 to 2:1
Ceftazidime–avibactam	CUTI: 2.5 g every 8 h for 7–14 d	CUTI: 7182–14 364	CUTI: imipenem–cilastatin	CUTI: 500 mg imipenem–cilastatin every 6 h for 7–14 d (optional switch to ciprofloxacin after 4 d)	CUTI: 352.80–1680.00	CUTI: 20:1 to 9:1
	CIAI: 2.5 g every 8 h for 5–14 d + MTZ	CIAI: 5130–14 364	CIAI: meropenem	CIAI: 1 g of meropenem every 8 h for 5–14 d	CIAI: 192.75–2955.54	CIAI: 27:1 to 5:1

INVITED ARTICLE REVIEWS OF ANTI-INFECTIVE AGENTS

Louis D. Saravolatz, Section Editor

Tedizolid: The First Once-Daily Oxazolidinone Class Antibiotic

Steven D. Burdette[1] and Robin Trotman[2]

[1]Wright State University Boonshoft School of Medicine, Dayton, Ohio; and [2]CoxHealth Infectious Diseases, Springfield, Missouri

Tedizolid phosphate is the second commercially available oxazolidinone antibiotic, although the first one in class that is dosed once daily. It is a prodrug that is rapidly converted to the active compound tedizolid. Tedizolid has activity against a wide range of gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus*. It is approved to treat acute bacterial skin and skin structure infections (ABSSSIs). In 2 randomized controlled phase 3 trials, 6 days of tedizolid (200 mg once daily) has been proven to be noninferior to 10 days of linezolid (600 mg twice daily). These 2 ABSSSI studies have positioned tedizolid among the growing armamentarium of newer, novel, anti-gram-positive agents. Tedizolid appears to differ from linezolid in the incidence of gastrointestinal and hematologic side effects and appears to lack drug interactions with selective serotonin reuptake inhibitors. Conditions other than ABSSSI are currently being evaluated in clinical studies.

Keywords. tedizolid; oxazolidinone; linezolid; MRSA; ABSSSI.

En resumen

VENTAJAS frente a Linezolid	DESVENTAJAS
Bactericida	Solo una indicación por ahora
Mayor potencia	Precio
Dosis única al día	
Tratamiento más corto	
No mielosupresión	
No neurotoxicidad	
No efecto MAO	

Muchas gracias

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- Spanish Group for the Management of Infectious Endocarditis (**GAMES**) and the Hospital General Universitario Gregorio Marañón **GAME**