
# Dalbavancina y oritavancina y su potencial en bacteriemia y endocarditis infecciosa.

Juan Manuel Pericàs
Servicio de Enfermedades Infecciosas
Hospital Clínic de Barcelona

No COIs

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# 1. Generalidades Nuevos (Lipo) glicopéptidos

LISTADO DE PRINCIPIOS ACTIVOS E INCORPORACIÓN DEL PICTOGRAMA DE LA CONDUCCIÓN.

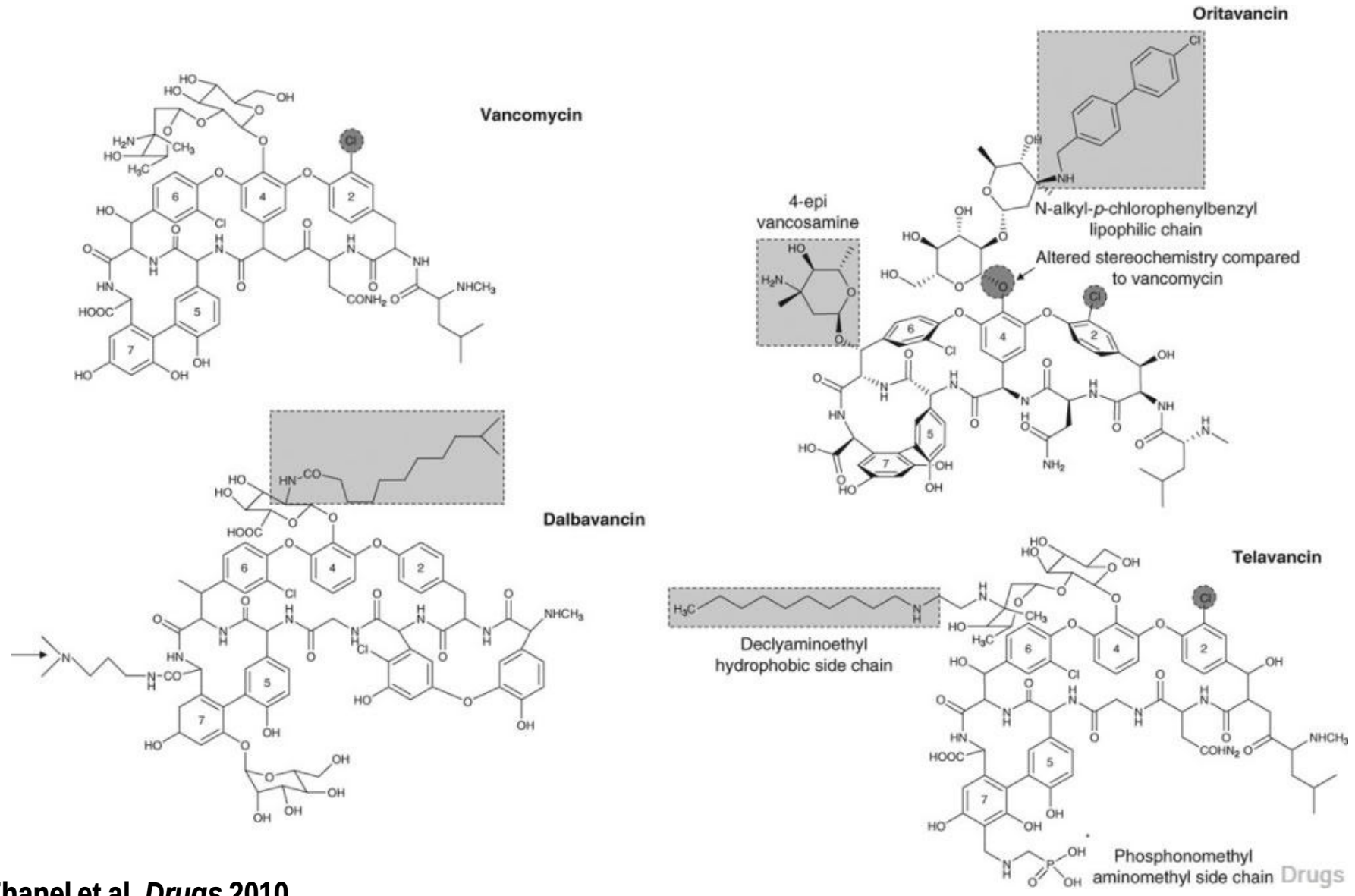
**Grupo J** – Antiinfecciosos para uso sistémico. **Subgrupo J01** – Antibacterianos para uso sistémico. Fecha de publicación 12.03.14. Versión 002

| SUBGRUPO | P. ACTIVOS | PICTOGRAMA | PROPUESTA DE REDACTADO |
|---|---|---|---|
| **J01X: OTROS ANTIBACTERIANOS** | | | |
| **J01XA** Glicopéptidos antibacterianos | Vancomicina | No | |
| | Teicoplanina | | |
| | Telavancina | | |
| | Dalbavancina | | |
| | Oritavancina | | |
| **J01XB** Poliximinas | Colistina | | |
| | Polimixina B | | |
| **J01XC** Esteroides antibacterianos | Ácido fusídico | | |
| **J01XD** Derivados Imidazólicos | Metronidazol | | |
| | Tinidazol | | |
| | Ornidazol | | |
| **J01XE** Derivados del nitrofurano | Nitrofurantoína | | |
| | Nifurtoinol | | |
| **J01XX** Otros antibacterianos | Fosfomicina | | |
| | Xibornol | | |
| | Clofoctol | | |
| | Espectinomicina | | |
| | Metenamina | | |
| | Ácido mandélico | | |
| | Nitroxolina | | |
| | Linezolid | | |
| | Daptomicina | | |
| | Bacitracina | | |

# Nuevos (lipo)glucopéptidos

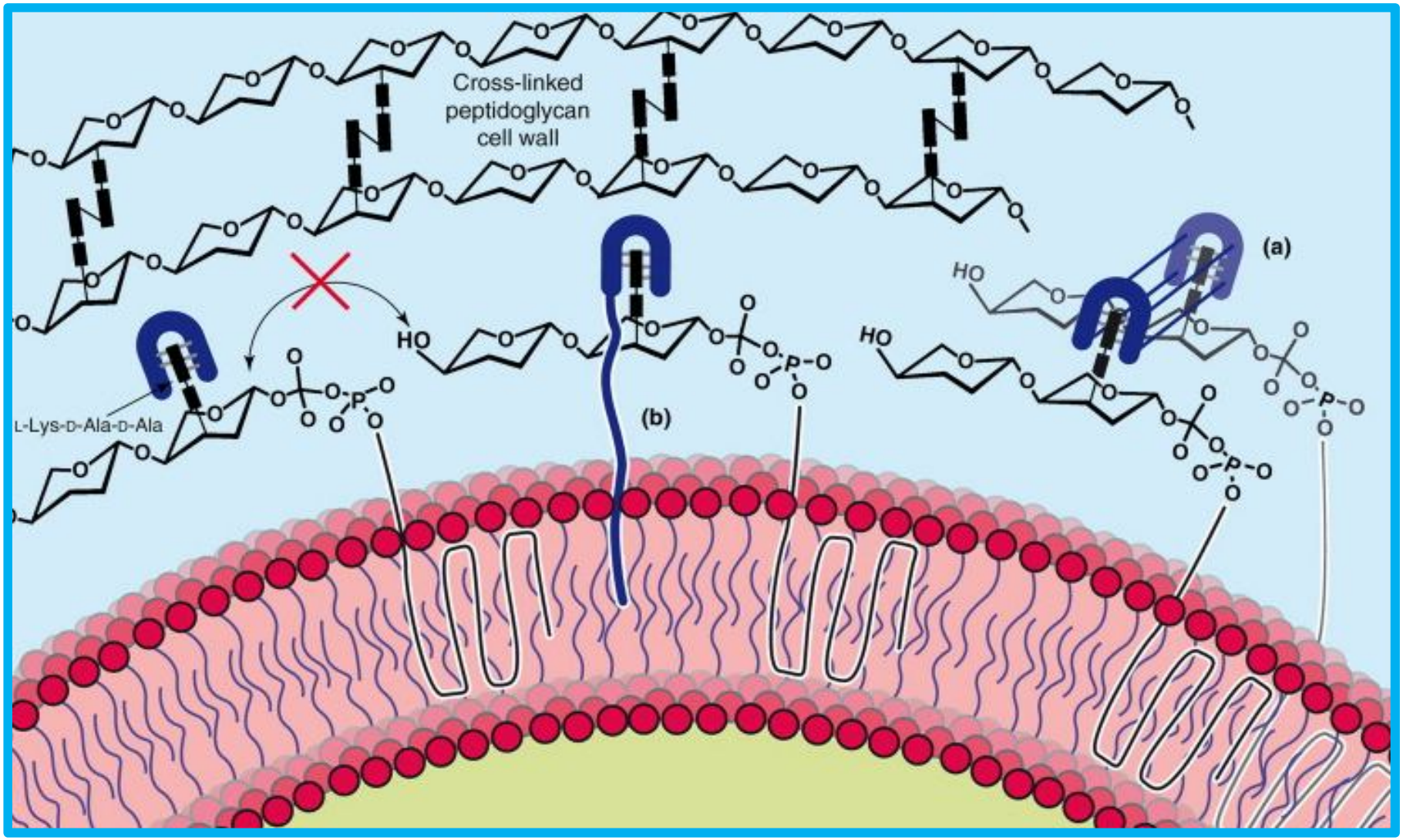
- Justificación para su desarrollo
- Moléculas precursoras y primeros estudios in vitro.
  - **LY333328 (orit), 1996---cloroeremomicina**
  - **BI397 (dal),1999---teicoplanina**
  - **TD-6424 (tel), 2003---vancomicina**
- Moléculas comerciales:
  - Dalbavancina: Xydalba®
  - Oritavancina: Orbactiv®
  - Telavancina: Vibatib®

# Estructura química



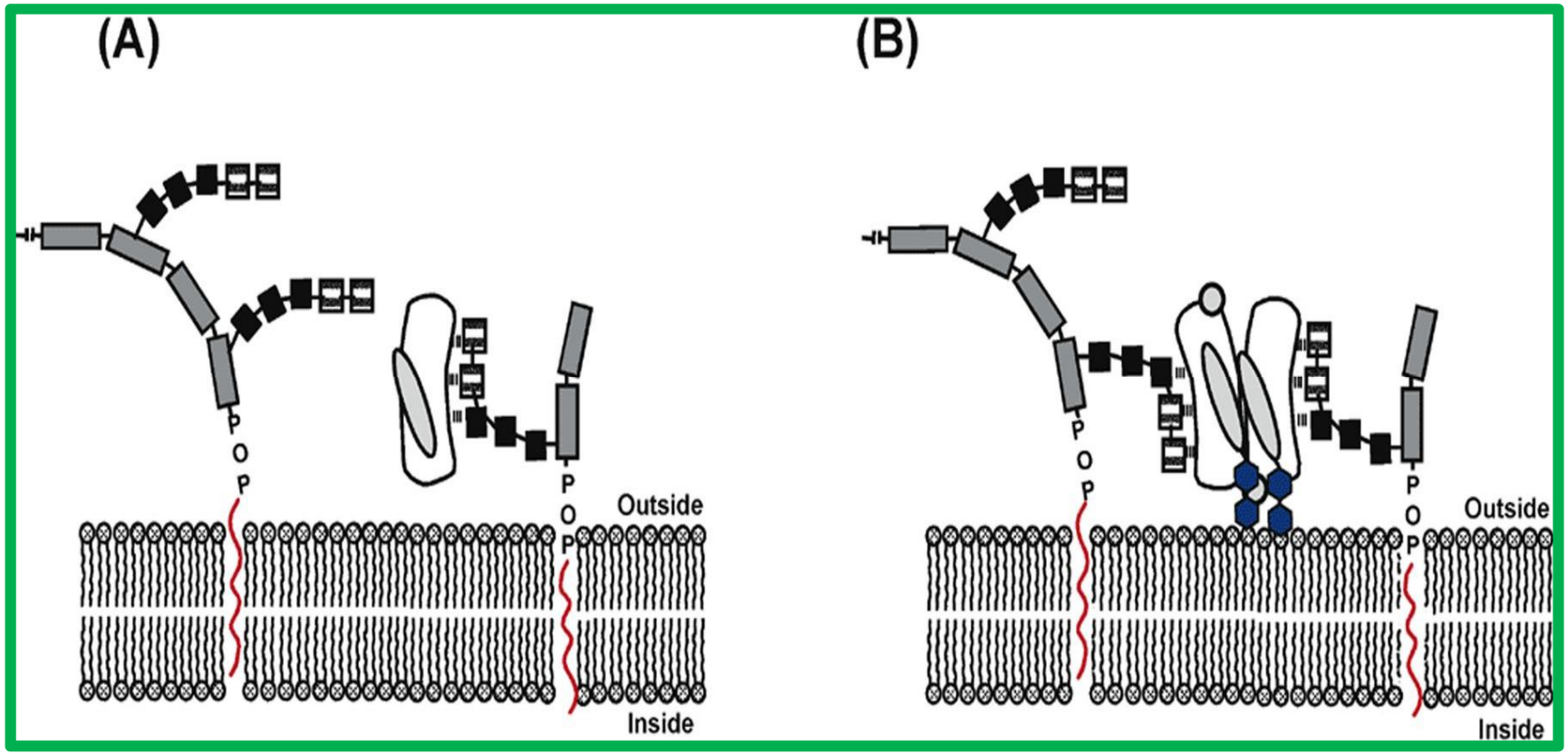

Zhanel et al, *Drugs* 2010

# Mecanismo de acción




Jovetic S et al, *Trends Biotech* 2010

# Mecanismo de acción




Allen NE & Nicas, *FEMS Microbiol Rev* 2003

# Espectro antimicrobiano

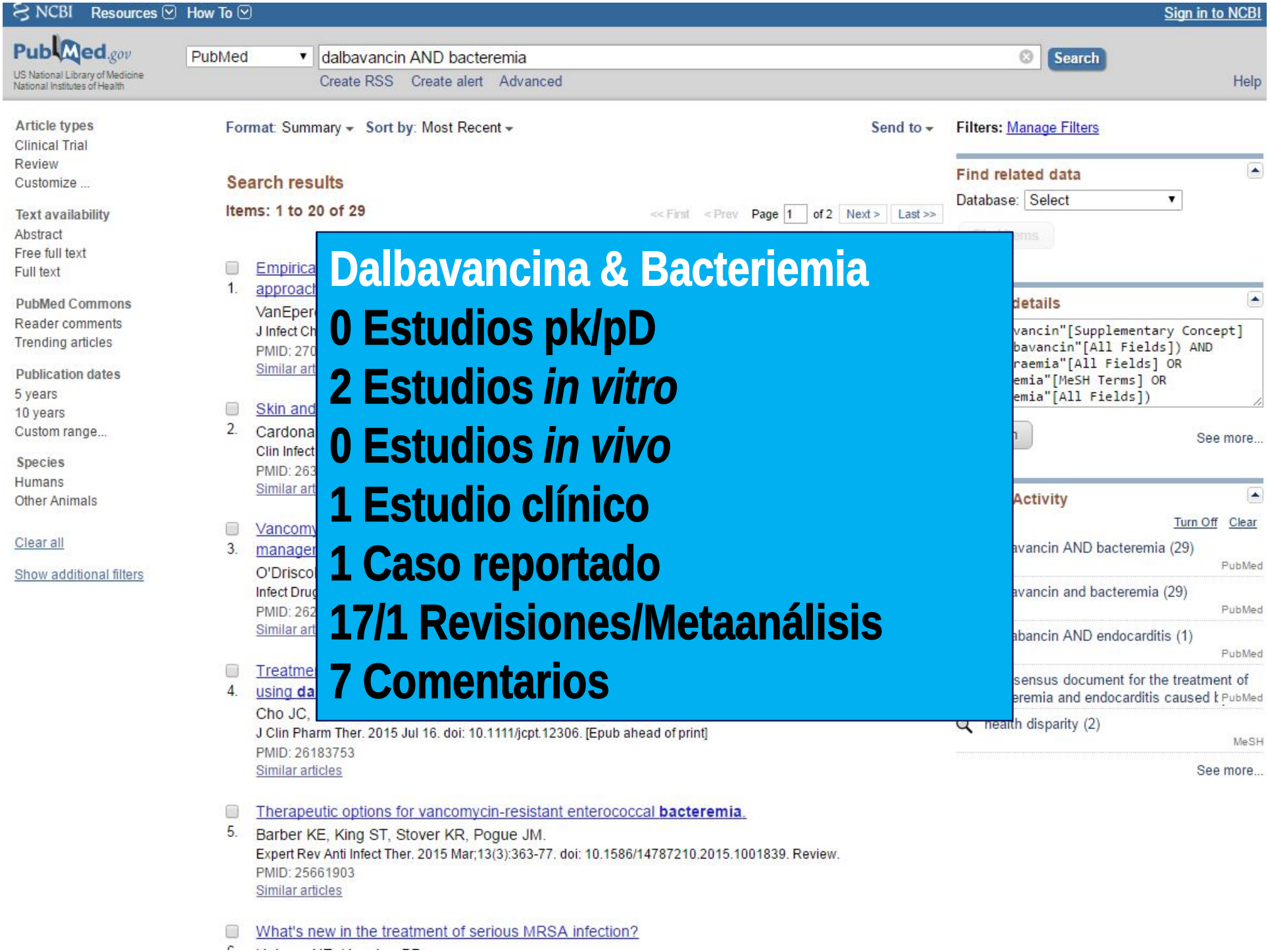
- ***S. aureus*** **(SASM, SARM, hVISA/GISA y VRSA)**
- ***S. epidermidis*** **(SESM y SERM)**
- ***Enterococcus spp*** **(también VRE, DAL no van A)**
- ***Streptoccus spp.***
- ***Clostridium spp.***

# Mecanismos de resistencia

- van A: dalbavancina (oritavancina in vitro)
- van B: oritavancina en enterococos
- van Z: oritavancina
- C, D, E y G

Jones et al, AAC 2015

# 2. Resumen de la evidencia actual en bacteriemia y endocarditis infecciosa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7 Comentarios
Therapeutic options for vancomycin-resistant enterococcal bacteremia.
Barber KE, King ST, Stover KR, Pogue JM.
Expert Rev Anti Infect Ther. 2015 Mar;13(3):363-77. doi: 10.1586/14787210.2015.1001839. Review.
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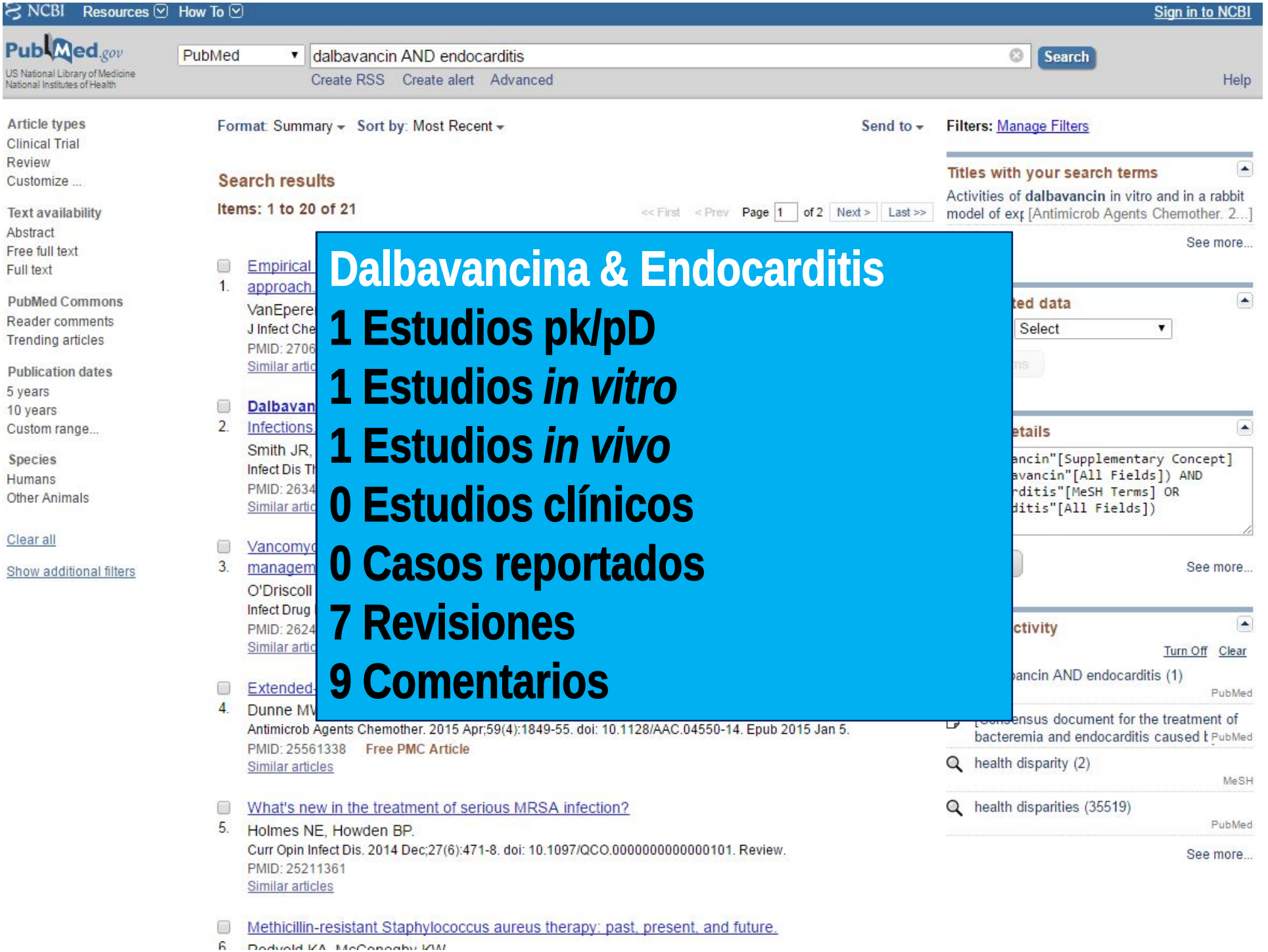
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0 Casos reportados
7 Revisiones
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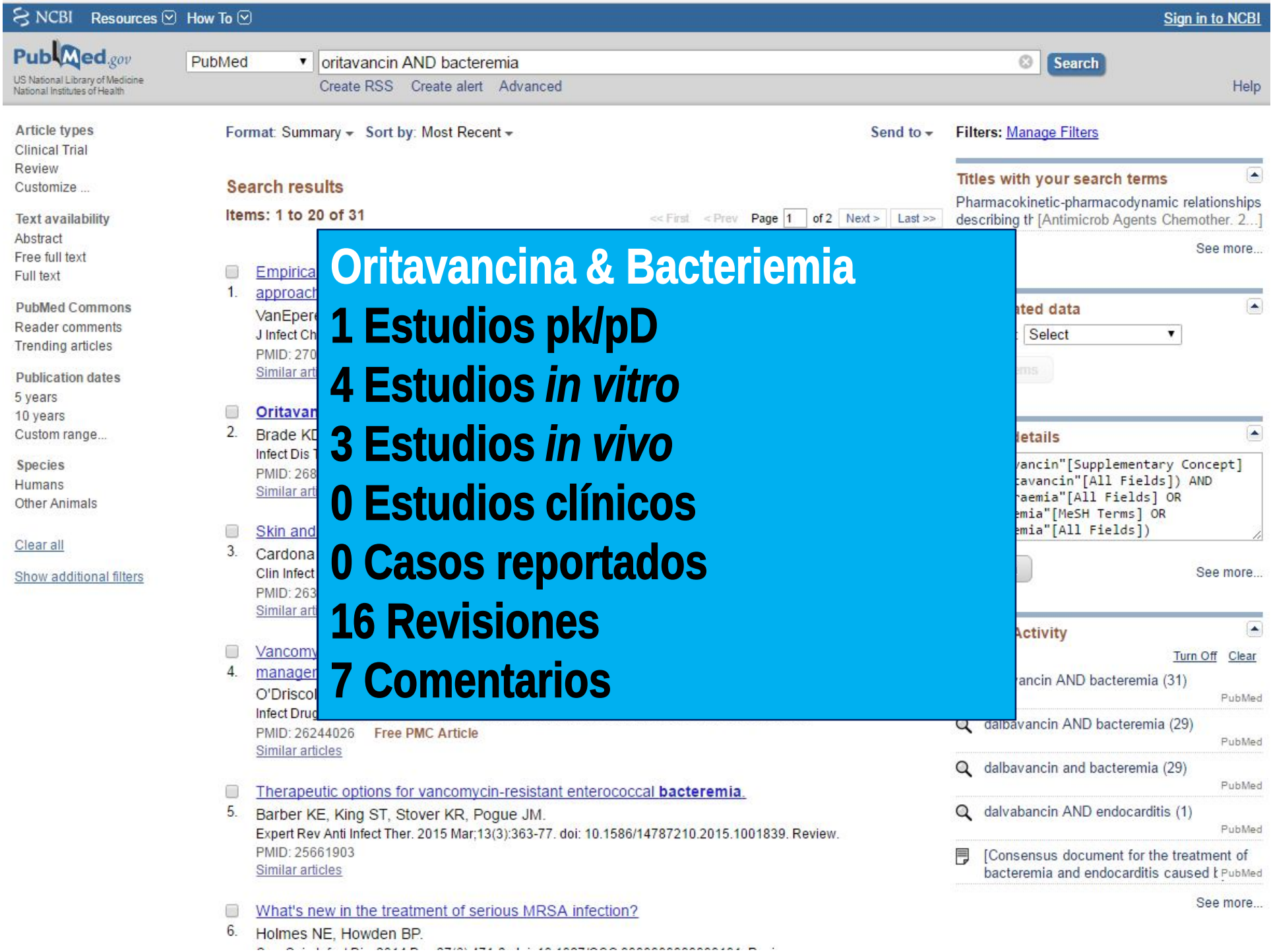
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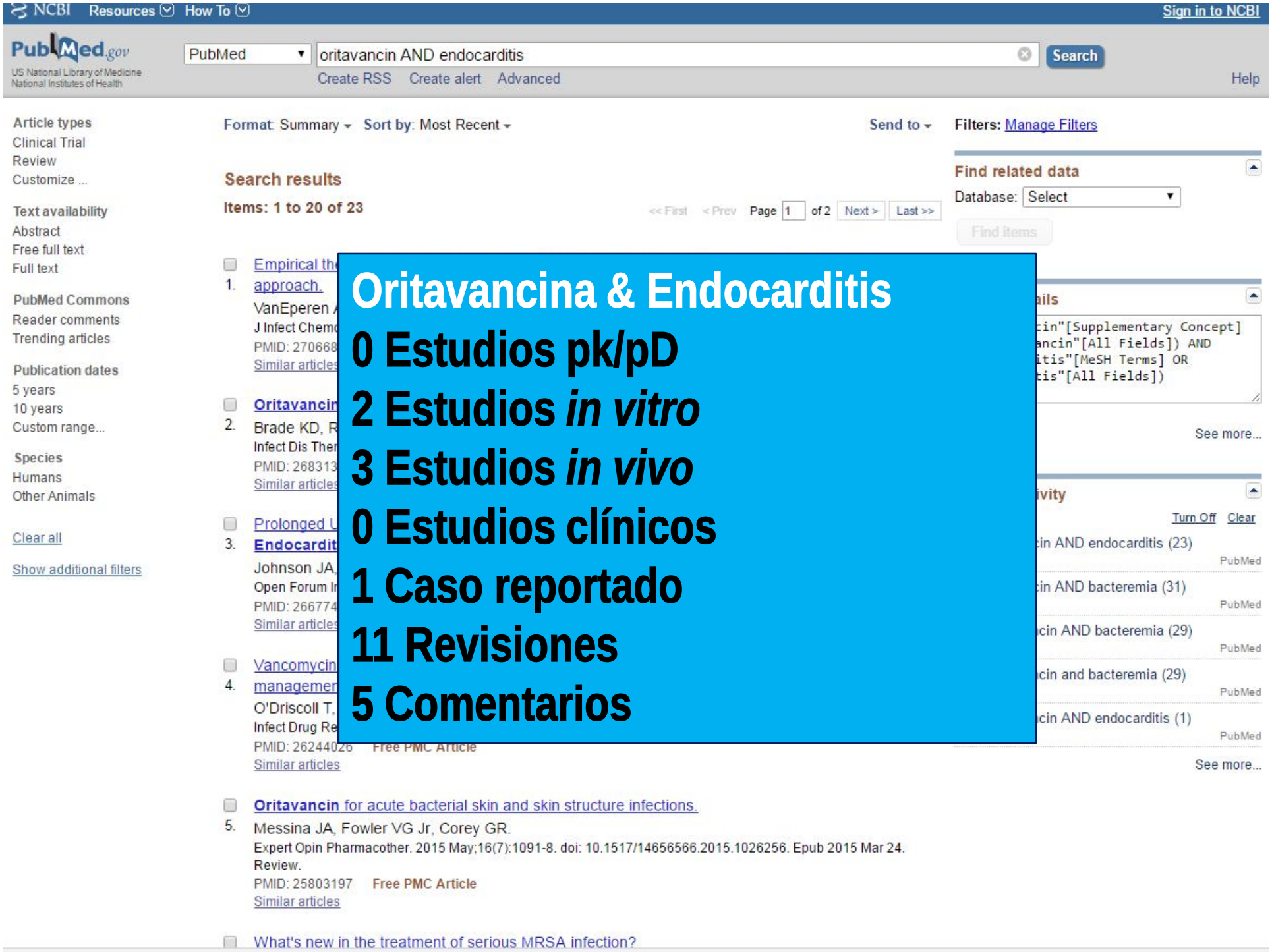
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Messina JA, Fowler VG Jr, Corey GR.
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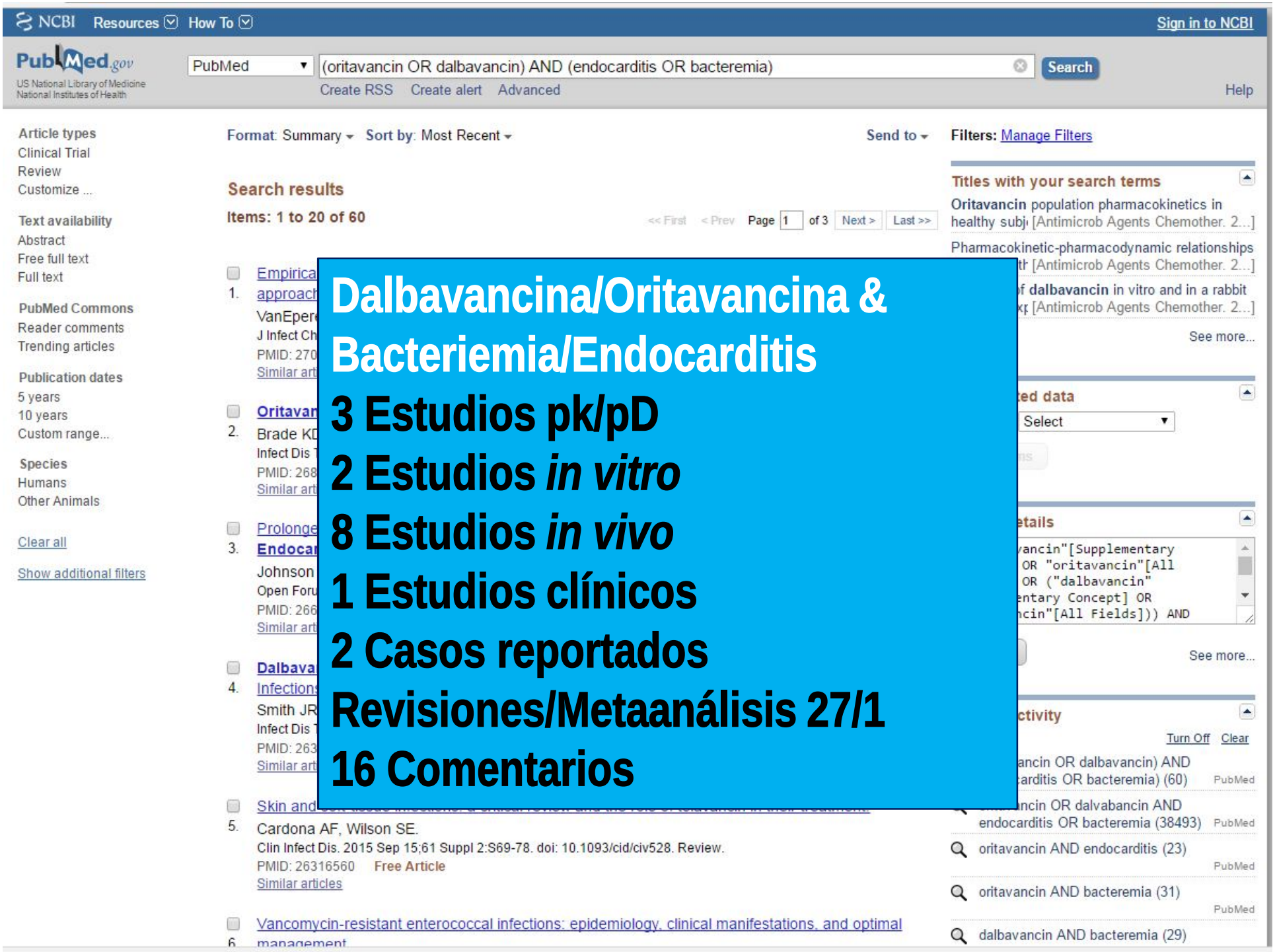
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# 3. Dalbavancina

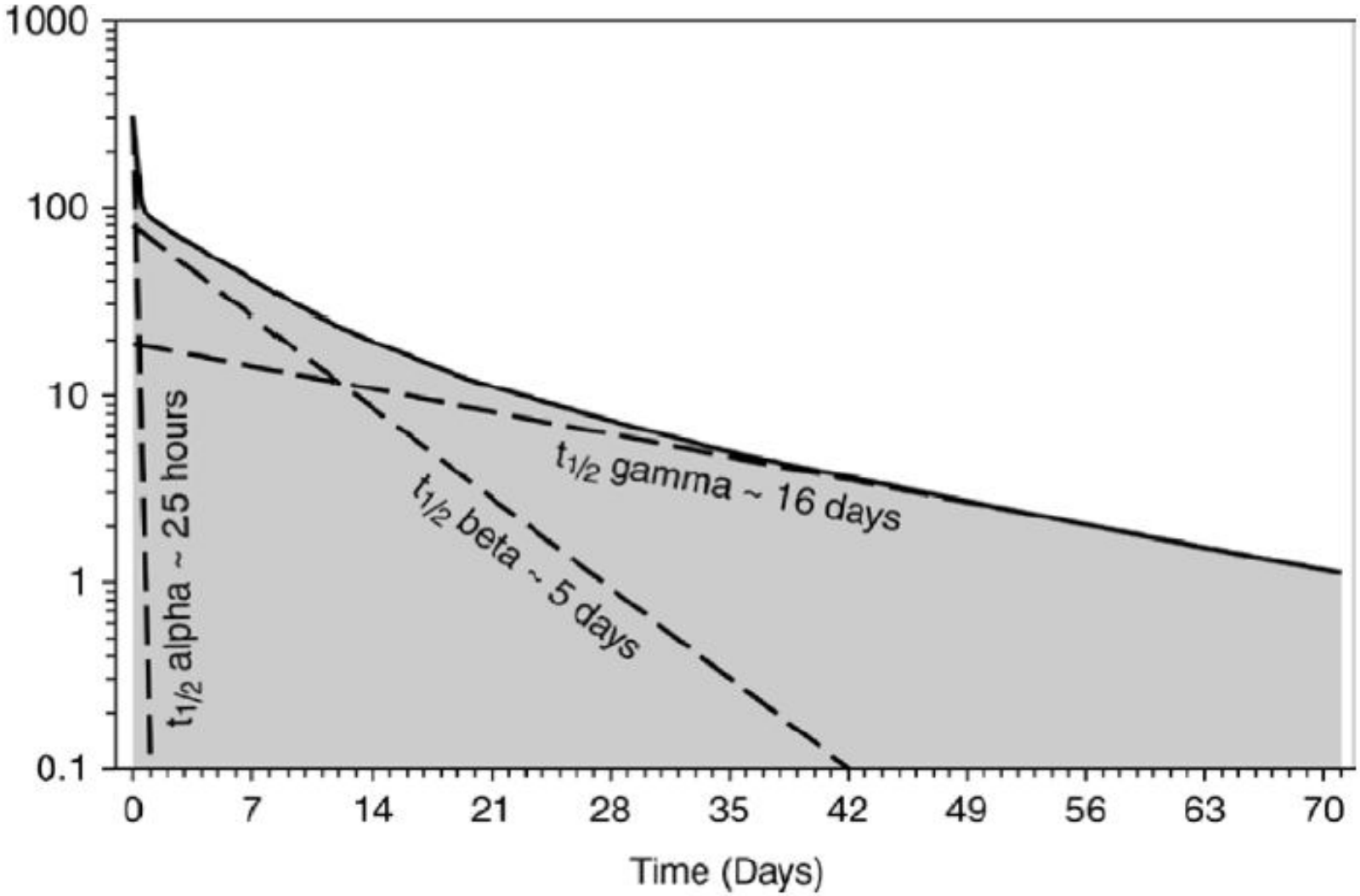
# DAL. Principales Características PK/PD-1

| Parameter | Two-dose regimen[2] | Single-dose regimen[3] |
|---|---|---|
| $C_{max}$ (mg/L) | Day 1: 281 (52)<br>Day 8: 141 (26) | Day 1: 411 (86) |
| $AUC_{0\text{-}Day14}$ (mg•h/L) | 18100 (4600) | 20300 (5300) |
| CL (L/h) | 0.048 (0.0086) | 0.049 (0.0096) |

[1] Source: DAL-MS-01.
[2] 1000 mg on Day 1 + 500 mg on Day 8; Study DUR001-303 subjects with evaluable PK sample.
[3] 1500 mg; Study DUR001-303 subjects with evaluable PK sample.

Ficha técnica EMA, Actualización 2016

# DAL. Perfil PK tras una dosis de 1000mg

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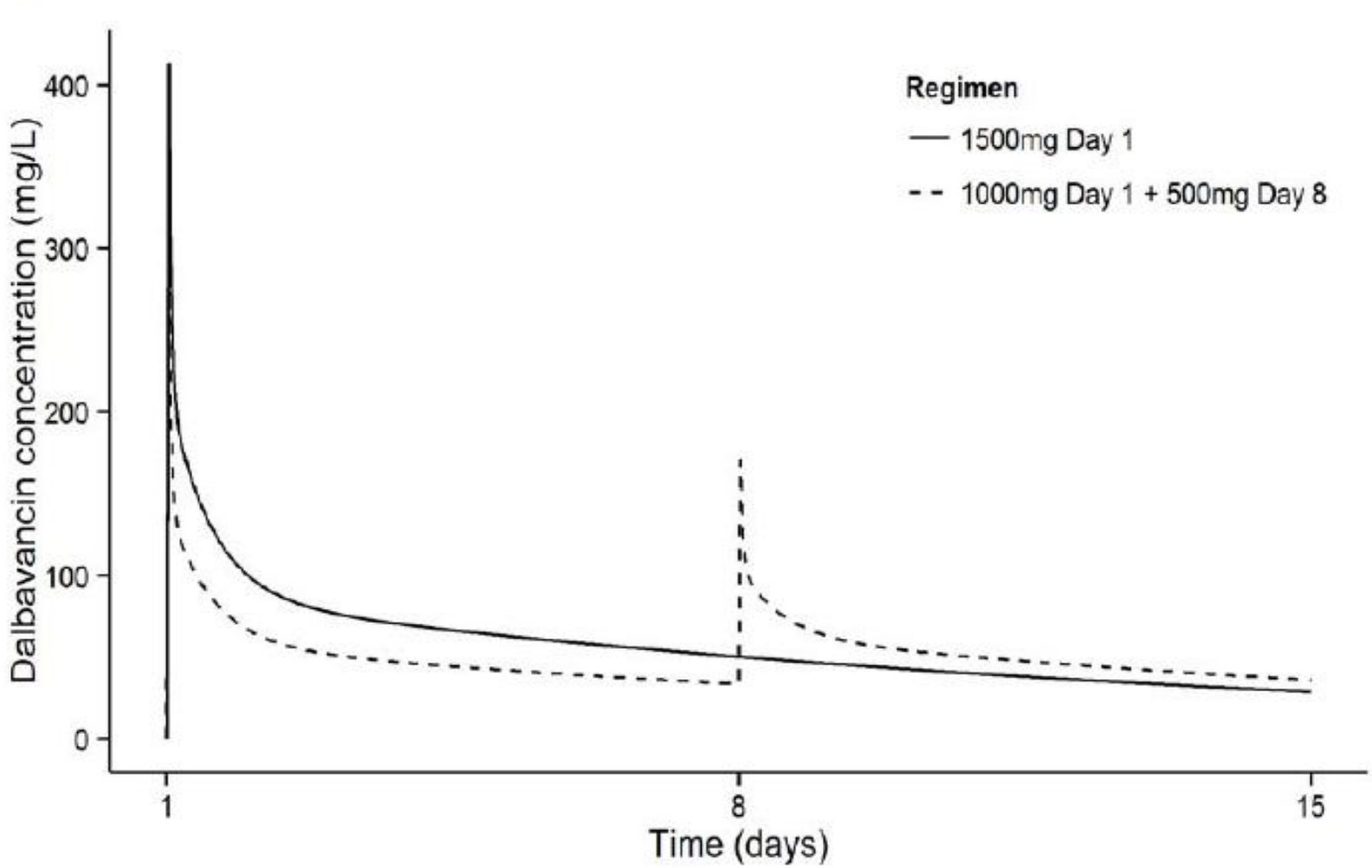
# DAL. Niveles plasmáticos 1-2 dosis/semana

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# DAL. Principales Características PK/PD-2

**Unión a proteínas 93%**

**Vd 0,1-0,2 l/kg**

| | |
|---|---|
| **Metabolismo** | **15% hidroxilación** |
| | **No es sustrato P450** |
| **Eliminación** | **20% heces** |
| | **19-33% renal no modificada y 8-12% renal en forma de hidroxi-dalbavancina.** |
| **Poblaciones especiales** | |
| | **Insuf. Renal** |
| | **Insuf. Hepática** |
| | **Sexo** |
| | **Ancianos** |
| | **Población pediátrica** |

Ficha técnica EMA, Actualización 2016

# DAL. Espectro Antimicrobiano-1

***Staphylococcus* spp.**

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

| Glycopeptides and lipoglycopeptides[1] | MIC breakpoint (mg/L) | | Disk content (µg) | Zone diameter breakpoint (mm) | | Notes |
|---|---|---|---|---|---|---|
| | S ≤ | R > | | S ≥ | R < | Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method. |
| Dalbavancin[2] | | | | | | |
| Oritavancin, *S. aureus*[2] | | | | | | |
| Teicoplanin, *S. aureus*[2] | | | | | | |
| Teicoplanin, Coagulase-negative staphylococci[2] | | | | | | |
| Telavancin, MRSA[2] | | | | | | |
| Vancomycin, *S. aureus*[2] | | | | | | |
| Vancomycin, Coagulase-negative staphylococci[2] | | | | | | |

**MIC Breakpoints**

***Staphylococcus spp.***

**0,125 mg/L**

***Enterococcus spp***

**IE (datos insuficientes)**

***Enterococcus* spp.**

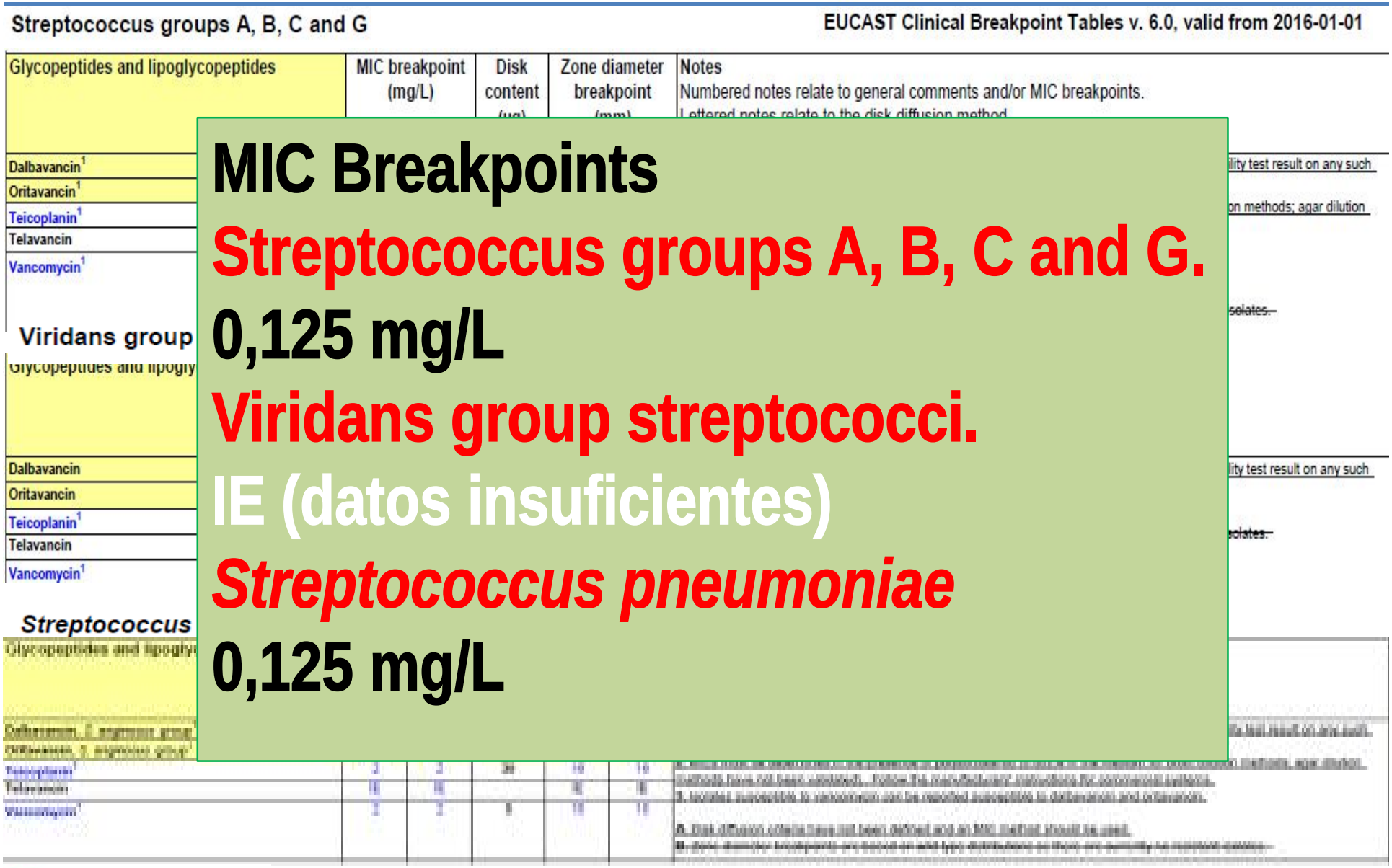
**oint Tables v. 6.0, valid from 2016-01-01**

| Glycopeptides and lipoglycopeptides | | | | | | C breakpoints. |
|---|---|---|---|---|---|---|
| Dalbavancin | IE | IE | | IE | IE | A. Vancomycin susceptible enterococci exhibit sharp zone edges and do not exhibit colonies in the inhibition zone. Examine zone edges with transmitted light (plate held up to light). If the zone edge is fuzzy, colonies grow within the zone or if you are uncertain, then perform confirmatory testing with PCR or report resistant (**see pictures below**) even if the zone diameter is ≥ 12 mm. Isolates must not be reported susceptible before 24 h incubation. |
| Oritavancin | IE | IE | | IE | IE | |
| Teicoplanin | 2 | 2 | 30 | 16 | 16 | |
| Telavancin | IE | IE | | IE | IE | |
| Vancomycin | 4 | 4 | 5 | 12^ | 12^ | |

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

# DAL. Espectro Antimicrobiano-2




**MIC Breakpoints**

**Streptococcus groups A, B, C and G.**

**0,125 mg/L**

**Viridans group streptococci.**

**IE (datos insuficientes)**

***Streptococcus pneumoniae***

**0,125 mg/L**

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

# Actividad de DAL frente a VRE

| Organism or group and resistance phenotype or serogroup (no. tested) | Cumulative % inhibited at MIC (μg/ml) of: | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ≤0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 |
| *E. faecalis* | | | | | | | | |
| VanA (230) | 0.4 | 0.9 | 2.6 | 3.9 | 4.3 | 4.3 | 7.4 | 14.8 |
| VanB (84) | 9.5 | 33.3 | 70.2 | 70.2 | 75.0 | 78.6 | 85.7 | 91.7 |
| *E. faecium* | | | | | | | | |
| VanA (1,744) | 0.1 | 0.3 | 1.2 | 3.1 | 6.6 | 11.5 | 18.3 | 33.1 |
| VanB (134) | 26.1 | 56.0 | 71.6 | 77.6 | 85.1 | 90.3 | 94.0 | 97.8 |

**Biedebenbach et al, *AAC* 2009**

# DAL. Principales Efectos Adversos

| System Organ Class | <1/10->1/100 | <1/100-≥1/1,000 | <1/1,000-≥1/10,000 |
|---|---|---|---|
| **Infections and infestations** | | vulvovaginal mycotic infection, urinary tract infection, fungal infection, *Clostridium difficile* colitis, oral candidiasis | |
| **Blood and lymphatic system disorders** | | anaemia, thrombocytosis, eosinophilia, leucopenia, neutropenia | |
| **Immune system disorders** | | | anaphylactoid reaction |
| **Metabolism and nutrition disorders** | | decreased appetite | |
| **Psychiatric disorders** | | insomnia | |
| **Nervous system disorders** | headache | dysgeusia, dizziness | |
| **Vascular disorders** | | flushing, phlebitis | |
| **Respiratory, thoracic and mediastinal disorders** | | cough | bronchospasm |
| **Gastrointestinal disorders** | nausea, diarrhoea, | constipation, abdominal pain, dyspepsia, abdominal discomfort, vomiting | |
| **Skin and subcutaneous tissue disorders** | | pruritus, urticaria, rash | |
| **Reproductive system and breast disorders** | | vulvovaginal pruritus | |
| **General disorders and administration site conditions** | | infusion-related reactions | |
| **Investigations** | | blood lactate dehydrogenase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood uric acid increased, liver function test abnormal, transaminases increased, blood alkaline phosphatase increased, platelet count increased, body temperature increased, hepatic enzyme increased | |

Ficha técnica EMA. Actualización 2016

# DAL. Indicaciones Aprobadas

- **Alternativa en Infecciones de piel y partes blandas, en adultos.**
  - **FDA 2014**
  - **EMA 2015**

  **(1500mg administrados como perfusión única o 1000mg + 500mg una semana después).**

# Randomized, Double-Blind Comparison of Once-Weekly Dalbavancin versus Twice-Daily Linezolid Therapy for the Treatment of Complicated Skin and Skin Structure Infections

Luis E. Jauregui,[1] Simon Babazadeh,[2] Elyse Seltzer,[5] Lisa Goldberg,[5] Dainis Krievins,[7] Mark Frederick,[3] David Krause,[5] Igors Satilovs,[8] Zilvinas Endzinas,[9] Jeffrey Breaux,[6] and William O'Riordan[4]

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.

# A Randomized Clinical Trial of Single-Dose Versus Weekly Dalbavancin for Treatment of Acute Bacterial Skin and Skin Structure Infection

Michael W. Dunne,[1] Sailaja Puttagunta,[1] Philip Giordano,[2] Dainis Krievins,[3] Michael Zelasky,[1] and James Baldassarre[4]

# DAL. Estudios pK/pD

Extended-Duration Dosing and Distribution of Dalbavancin into Bone and Articular Tissue **AAC 2015**

Michael W. Dunne,[a] Sailaja Puttagunta,[a] Craig R. Sprenger,[c*] Chris Rubino,[b] Scott Van Wart,[b] James Baldassarre[a]

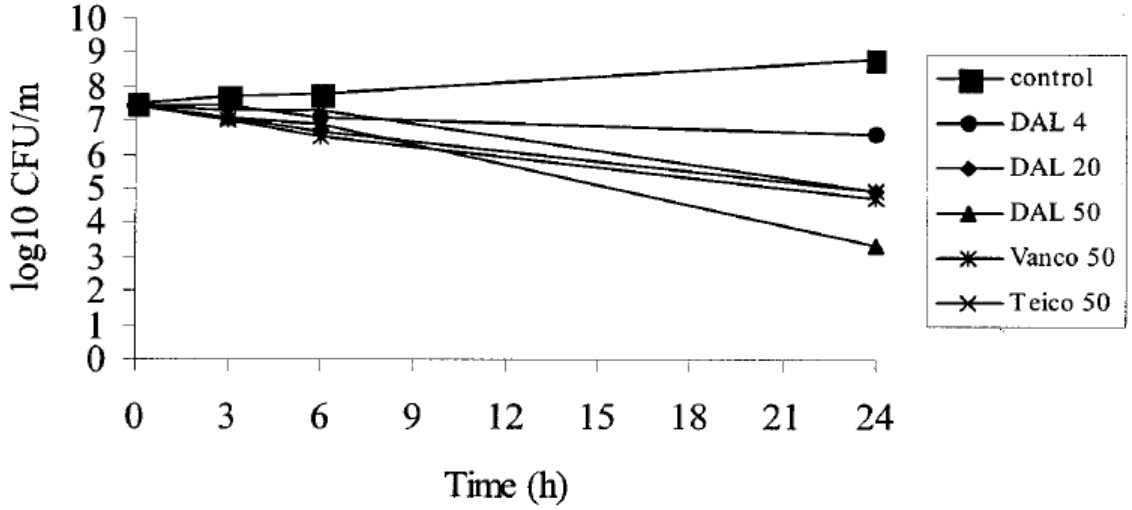
- **Fase I,1000mg+500mg hasta 8sem (4,6,8). N=18**
- **Fase I, 1000 mg antes cirugía. N=30**
- **Bien tolerado, no acumulación.**
- **Niveles en hueso y articulación >CMI *S. aureus*.**

# DAL. Modelos animales en Bact/EI-1

## Activities of Dalbavancin In Vitro and in a Rabbit Model of Experimental Endocarditis Due to *Staphylococcus aureus* with or without Reduced Susceptibility to Vancomycin and Teicoplanin

**AAC, 2004**

Agnès Lefort,* Juliette Pavie, Louis Garry, Françoise Chau, and Bruno Fantin




| Regimen | Antibiotic levels in serum, μg/ml (mean ± SD) | | $Log_{10}$ CFU/g of vegetation (mean ± SD) (no. of sterile/treated animals) | |
|---|---|---|---|---|
| | Peak (h) | Trough (h) | Lim-1 | Lim-2 |
| Controls | | | 9.1 ± 1.3 (0/17) | 9.4 ± 1.1 (0/15) |
| DAL 10 mg/kg q.d.i.v., 4 days | 114 ± 17 (0.5) | 19 ± 9 (24) | 5.6 ± 1.6[b] (0/7) | 5.5 ± 2.1[b] (1/10) |
| DAL 40 mg/kg i.v., single dose | 255 ± 53 (0.5) | 3 ± 2 (96) | 7.0 ± 1.4[b] (0/8) | 6.9 ± 2.1[b] (0/10) |

# DAL. Estudios clínicos en Bact/EI-1

## Efficacy and Safety of Weekly Dalbavancin Therapy for Catheter-Related Bloodstream Infection Caused by Gram-Positive Pathogens

**2005**

Issam Raad,[1] Rabih Darouiche,[2] Jose Vazquez,[3] Arnold Lentnek,[4] Ray Hachem,[1] Hend Hanna,[1] Beth Goldstein,[5] Tim Henkel,[5] and Elyse Seltzer[5]

**1000mg día 1 + 500mg día 8 vs. 1000mg/12h**

| | Dalbavancin group | Vancomycin group |
|---|---|---|
| Study population | | |
| ITT population | 33 | 34 |
| MicroITT population[a] | 23 (70) | 28 (82) |
| Evaluable population at EOT | 17 (52) | 21 (62) |
| Evaluable population at TOC | 14 (42) | 20 (59) |
| Demographic characteristic[b] | | |
| No. of patients | 23 | 28 |
| Age, mean years (range) | 54 (20–78) | 58 (19–85) |
| Male sex | 13 (57) | 11 (39) |
| Probable CR-BSI | 18 (78) | 20 (71) |
| Definite CR-BSI | 5 (22) | 8 (29) |
| ICU stay during study[c] | | |
| Yes | 8 (24) | 8 (24) |
| No | 25 (76) | 26 (76) |

# DAL. Estudios clínicos en Bact/EI-2

| Type of isolate | No. (%) of isolates | |
|---|---|---|
| | Dalbavancin group[a] ($n$ = 26) | Vancomycin group ($n$ = 28) |
| *Staphylococcus aureus* | | |
| All | 11 (42.3) | 12 (42.9) |
| MRSA[b] | 5 (19.2) | 9 (32.1) |
| CoNS | 13 (50.0) | 13 (46.4) |
| *Enterococcus faecalis* | 2 (7.7) | 3 (10.7) |

**Raad I et al, *CID* 2005**

# DAL. Estudios clínicos en Bact/EI-3

| Population and visit, response | Dalbavancin group | Vancomycin group |
|---|---|---|
| microITT population at EOT | | |
| Overall success | 21/23 (91.3) | 18/28 (64.3) |
| Clinical success | 21/23 (91.3) | 18/28 (64.3) |
| Microbiological success | 22/23 (95.6) | 26/28 (92.9) |
| microITT population at TOC | | |
| Overall success[a] | 20/23 (87.0)[b] | 14/28 (50.0)[c] |
| By catheter status | | |
| Retained at baseline | 6/8 (75.0) | 4/10 (40.0) |
| Removed at or before baseline | 14/15 (93.3) | 10/18 (55.6) |
| By catheter type | | |
| Tunneled | 6/7 (85.7) | 5/ 5 (100.0) |
| Nontunneled | 14/16 (87.5) | 9/22 ( 41.0) |
| Clinical success | 20/23 (87.0) | 14/28 (50.0) |
| Microbiological success | 22/23 (95.7) | 22/28 (78.6) |
| Evaluable population at EOT | | |
| Overall success | 16/17 (94.12) | 13/21 (61.9) |
| Clinical success | 16/17 (94.12) | 13/21 (61.9) |
| Microbiological success | 17/17 (100.0) | 20/21 (95.2) |
| Evaluable population at TOC | | |
| Overall success | 13/14 (92.9) | 9/20 (45.0) |
| Clinical success | 13/14 (92.9) | 9/20 (45.0) |
| Microbiological success | 14/14 (100.0) | 16/20 (80.0) |

***P*<0.05**

**Raad I et al, *CID* 2005**

# DAL. Estudios clínicos en Bact/EI-4

| | DISCOVER 1 | | DISCOVER 2 | | BOTH STUDIES | |
|---|---|---|---|---|---|---|
| **Characteristic** | **Dalbavancin** | **Vancomycin/ Linezolid** | **Dalbavancin** | **Vancomycin/ Linezolid** | **Dalbavancin** | **Vancomycin/ Linezolid** |
| SIRS n, (%)* | 175 (61.6) | 175 (61.6) | 157 (42.7) | 161 (43.8) | 332 (50.9) | 336 (51.5) |
| Area of infection, median $cm^2$, ( range)** | 333.0 (25.6, 3400.0) | 367.8 (77.6, 3675.0) | 313.50 (85.1, 5100.0) | 362.40 (72.0, 3922.0) | 324.0 (25.6, | 366.8 (72.0, 3922.0) |
| Gram-positive bacteremia, n**** | 8 | 6 | 20 | 11 | 28 | 17 |
| *S. aureus*, n | 4 | 3 | 7 | 6 | 11 | 9 |
| *S. pyogenes*, n | 1 | 0 | 3 | 1 | 4 | 1 |
| *S. agalactiae*, n | 3 | 0 | 2 | 1 | 5 | 1 |
| Other, n | 0 | 3 | 9 | 3 | 9 | 6 |
| **Success** | | | | | **100%** | **85,7%** |

23 pacientes

Boucher H et al, NEJM 2014 (Suppl. Material)

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD
agencia española de medicamentos y productos sanitarios

INFORME DE POSICIONAMIENTO TERAPÉUTICO
PT-DALBAVANCINA/V1/21012016

# Informe de Posicionamiento Terapéutico de dalbavancina (Xydalba®)

**Fecha de publicación: 21 de enero de 2016**

## CONCLUSIÓN

Dalbavancina, a la dosis de 1000 mg en el día 1 y 500 mg en día 8, ha demostrado su eficacia, en base a criterios de no inferioridad, frente a vancomicina (1000 mg/ 12 h/ 14 días) con posibilidad de cambio a terapia oral con linezolid (600 mg/12 h) a partir del tercer día.

Respecto al perfil de seguridad, es aceptable y similar al que presentan los comparadores.

Este antibiótico constituye una alternativa terapéutica válida al tratamiento actual con glicopéptidos y otros antibióticos comercializados para esta finalidad (daptomicina, tigeciclina, linezolid y ceftarolina), en aquellos casos de infección bacteriana aguda de la piel y sus estructuras en los que haya una alta sospecha clínica o una alta prevalencia local de infección por SARM en adultos. En aquellas situaciones clínicas en las que se plantee un tratamiento parenteral prolongado, dalbavancina, ofrecería como ventaja, su régimen de administración (dos dosis espaciadas 7 días), que potencialmente reduciría el riesgo de complicaciones asociadas a la terapia parenteral en múltiples dosis.

En aquellas situaciones en las que, tras un período de hospitalización, se contemple el manejo extrahospitalario de la infección, dalbavancina constituye una alternativa terapéutica al tratamiento secuencial con linezolid oral.

## CONSIDERACIONES FINALES DEL GCPT

*Dado que no se han encontrado diferencias clínicamente relevantes entre la eficacia y seguridad del medicamento evaluado y sus alternativas, la elección entre ellos se basará fundamentalmente en criterios de eficiencia.*

# DAL. Micro-resumen

- No suficiente evidencia clínica (s.t. EI, microorganismo)
- Necesarios más estudios en modelo animal
- Datos in vitro (enterococos, VGS)
- Datos pK/pD y seguridad para tratamientos prolongados >14 días.
- Comodidad
- Seguridad
- Perfil microbiológico
- Buena penetración hueso (artritis séptica 1ª o embólica)

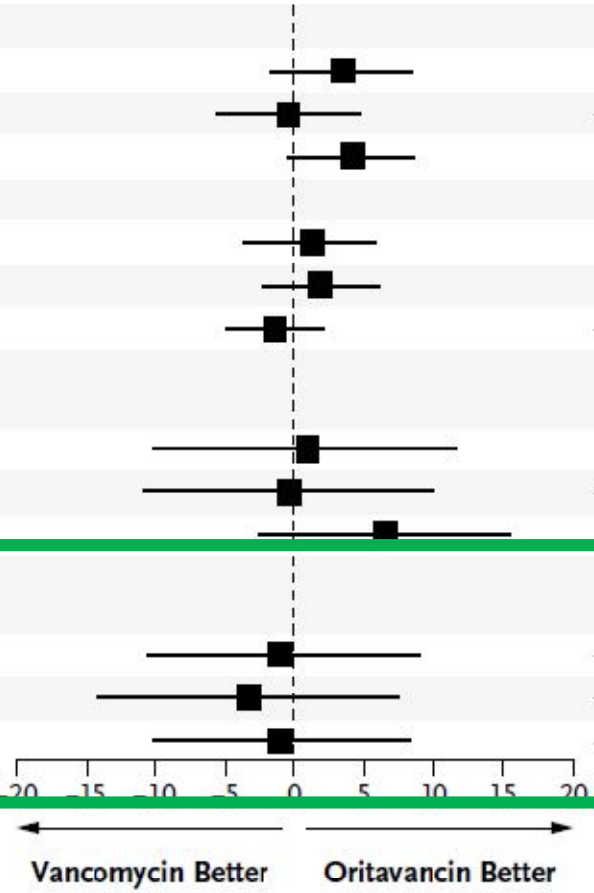
# 4. Oritavancina

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

| Subgroup | Oritavancin | Vancomycin | Percentage-Point Difference (95% CI) |
|---|---|---|---|
| | *no. of events/total no. (%)* | | |
| Modified intention-to-treat population | | | |
| Primary efficacy outcome at ECE | 391/475 (82.3) | 378/479 (78.9) | 3.4 (−1.6 to 8.4) |
| Investigator-assessed clinical cure at PTE | 378/475 (79.6) | 383/479 (80.0) | −0.4 (−5.5 to 4.7) |
| Lesion size reduction ≥20% at ECE | 413/475 (86.9) | 397/479 (82.9) | 4.1 (−0.5 to 8.6) |
| CE population | | | |
| Primary efficacy outcome at ECE | 344/394 (87.3) | 342/397 (86.1) | 1.2 (−3.6 to 5.9) |
| Investigator-assessed clinical cure at PTE | 357/394 (90.6) | 352/397 (88.7) | 1.9 (−2.3 to 6.2) |
| Lesion size reduction ≥20% at ECE | 362/394 (91.9) | 370/397 (93.2) | −1.3 (−5.0 to 2.3) |
| Patients infected with MRSA in intention-to-treat population with microbiologic evaluation | | | |
| Primary efficacy outcome at ECE | 84/104 (80.8) | 80/100 (80.0) | 0.8 (−10.1 to 11.7) |
| Investigator-assessed clinical cure at PTE | 86/104 (82.7) | 83/100 (83.0) | −0.3 (−10.7 to 10.0) |
| Lesion size reduction ≥20% at ECE | 94/104 (90.4) | 84/100 (84.0) | 6.4 (−2.8 to 15.5) |
| Patients infected with MSSA in intention-to-treat population with microbiologic evaluation | | | |
| Primary efficacy outcome at ECE | 96/116 (82.8) | 92/110 (83.6) | −0.9 (−10.6 to 8.9) |
| Investigator-assessed clinical cure at PTE | 89/116 (76.7) | 88/110 (80.0) | −3.3 (−14.0 to 7.4) |
| Lesion size reduction ≥20% at ECE | 98/116 (84.5) | 94/110 (85.5) | −1.0 (−10.3 to 8.3) |



The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

# Dalbavancin or Oritavancin for Skin Infections

# ORI. Indicaciones Aprobadas

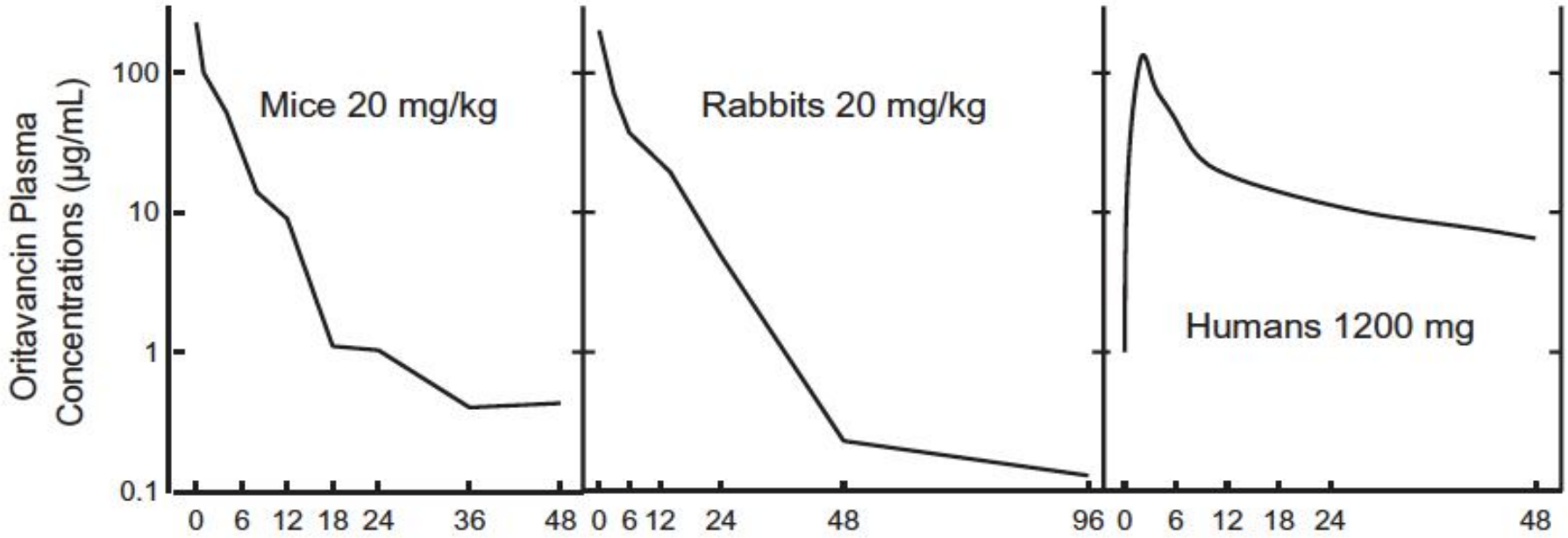
- **Alternativa en Infecciones de piel y partes blandas, en adultos.**
  - **FDA 2014**
  - **EMA 2015**

  **(1200mg iv en dosis única a pasar en 3h)**

# ORI. Características pK/pD-1

**Concentración-dependiente:**
**$AUC_{0-24}$/MIC, *C*max/MIC**

**Distribución en 3 comp**
**$t_{1/2}$ 393h**
**Unión a proteínas 85%**
**Vd 100L**
**No se metaboliza**



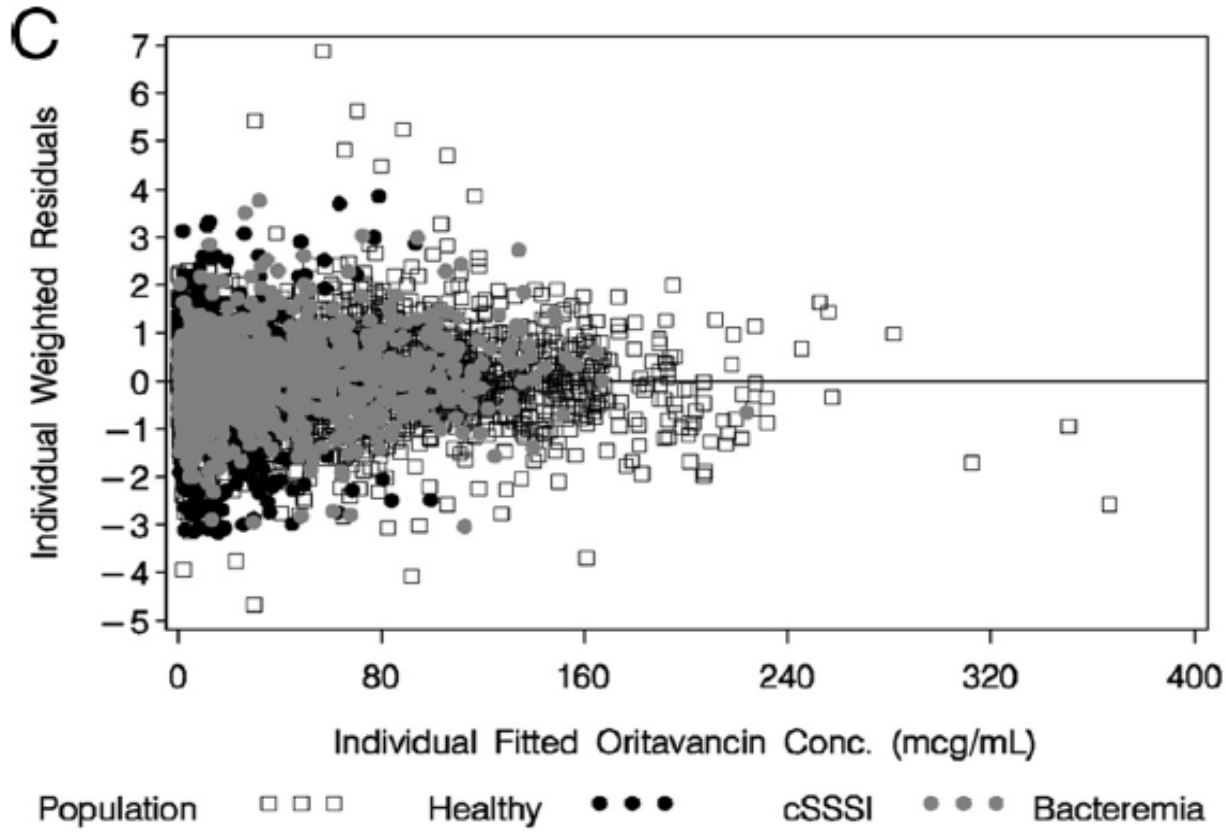

**Ambrose P et al, *CID* 2012**

# ORI. Estudios pK/pD Bact/EI-2

## Oritavancin Population Pharmacokinetics in Healthy Subjects and Patients with Complicated Skin and Skin Structure Infections or Bacteremia▽

Christopher M. Rubino,[1,2]* Scott A. Van Wart,[1,2] Sujata M. Bhavnani,[1,2] Paul G. Ambrose,[1,2] Jill S. McCollam,[3]† and Alan Forrest[1,2]

*Institute for Clinical Pharmacodynamics, Ordway Research Institute, Inc., Albany, New York[1]; SUNY at Buffalo, School of Pharmacy and Pharmaceutical Sciences, Buffalo, New York[2]; and Targanta Therapeutics, Cambridge, Massachussetts[3]*



# ORI. Estudios pK/pD Bact/EI-3

## Pharmacokinetic-Pharmacodynamic Relationships Describing the Efficacy of Oritavancin in Patients with *Staphylococcus aureus* Bacteremia

Sujata M. Bhavnani,[1,2]* Julie A. Passarell,[1] Joel S. Owen,[1,3] Jeffrey S. Loutit,[4] Steven B. Porter,[4] and Paul G. Ambrose[1,2]†

| Parameter | Estimate | SE | Odds ratio | 95% CI[e] for odds ratio | | *P* |
|---|---|---|---|---|---|---|
| | | | | Lower limit | Upper limit | |
| $AUC_{0-24}$ (μg · h/ml) | −0.0005 | 0.0016 | 1.00 | 0.996 | 1.00 | 0.77 |
| $AUC_{0-24}$/MIC | 0.0001 | 0.0029 | 1.00 | 0.995 | 1.00 | 0.96 |
| $C_{max}$ (μg/ml) | 0.0015 | 0.0145 | 1.00 | 0.973 | 1.03 | 0.92 |
| $C_{max}$/MIC | 0.0120 | 0.0235 | 1.01 | 0.967 | 1.06 | 0.61 |
| % Time > MIC (%) | −0.0014 | 0.0368 | 0.999 | 0.929 | 1.07 | 0.97 |
| Free-drug % time > MIC (%) | 0.0007 | 0.0208 | 1.00 | 0.961 | 1.04 | 0.97 |
| Free-drug % time > MIC ≥ 22%[a] | 0.743 | 0.434 | 4.42 | 0.805 | 24.3 | 0.09 |
| Preexisting diabetes[b] | −0.634 | 0.397 | 0.281 | 0.059 | 1.34 | 0.11 |
| Ideal body wt[c] (kg) | 0.743 | 0.434 | 4.42 | 0.805 | 24.3 | 0.09 |
| Wt[d] (kg) | — | — | — | — | — | — |
| Age (yr) | −0.0068 | 0.0207 | 0.993 | 0.954 | 1.03 | 0.74 |

# ORI. Espectro Antimicrobiano-1

***Staphylococcus* spp.**

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

| Glycopeptides and lipoglycopeptides[1] | MIC breakpoint (mg/L) | | Disk content (µg) | Zone diameter breakpoint (mm) | | Notes |
|---|---|---|---|---|---|---|
| | S ≤ | R > | | S ≥ | R < | Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method. |
| Dalbavancin[2] | | | | | | by broth microdilution (reference ISO 20776). *S. aureus* |
| Oritavancin, *S. aureus*[2] | | | | | | distribution and there may be an impaired clinical |
| Teicoplanin, *S. aureus*[2] | | | | | | reporting "GISA" isolates intermediate as serious |
| Teicoplanin, Coagulase-negative staphyl | | | | | | vancomycin or teicoplanin. |
| Telavancin, MRSA[2] | | | | | | n and antimicrobial susceptibility test result on any such |
| Vancomycin, *S. aureus*[2] | | | | | | in the medium for broth dilution methods: agar dilution |
| Vancomycin, Coagulase-negative staphy | | | | | | s for commercial systems. |
| | | | | | | tible to dalbavancin and oritavancin. |
| | | | | | | e to telavancin. |
| | | | | | | solates and those with non-*vanA*-mediated glycopeptide |

**MIC Breakpoints**

***Staphylococcus spp.***

**0,125 mg/L**

***Enterococcus spp***

**IE (datos insuficientes)**

***Enterococcus* spp.**

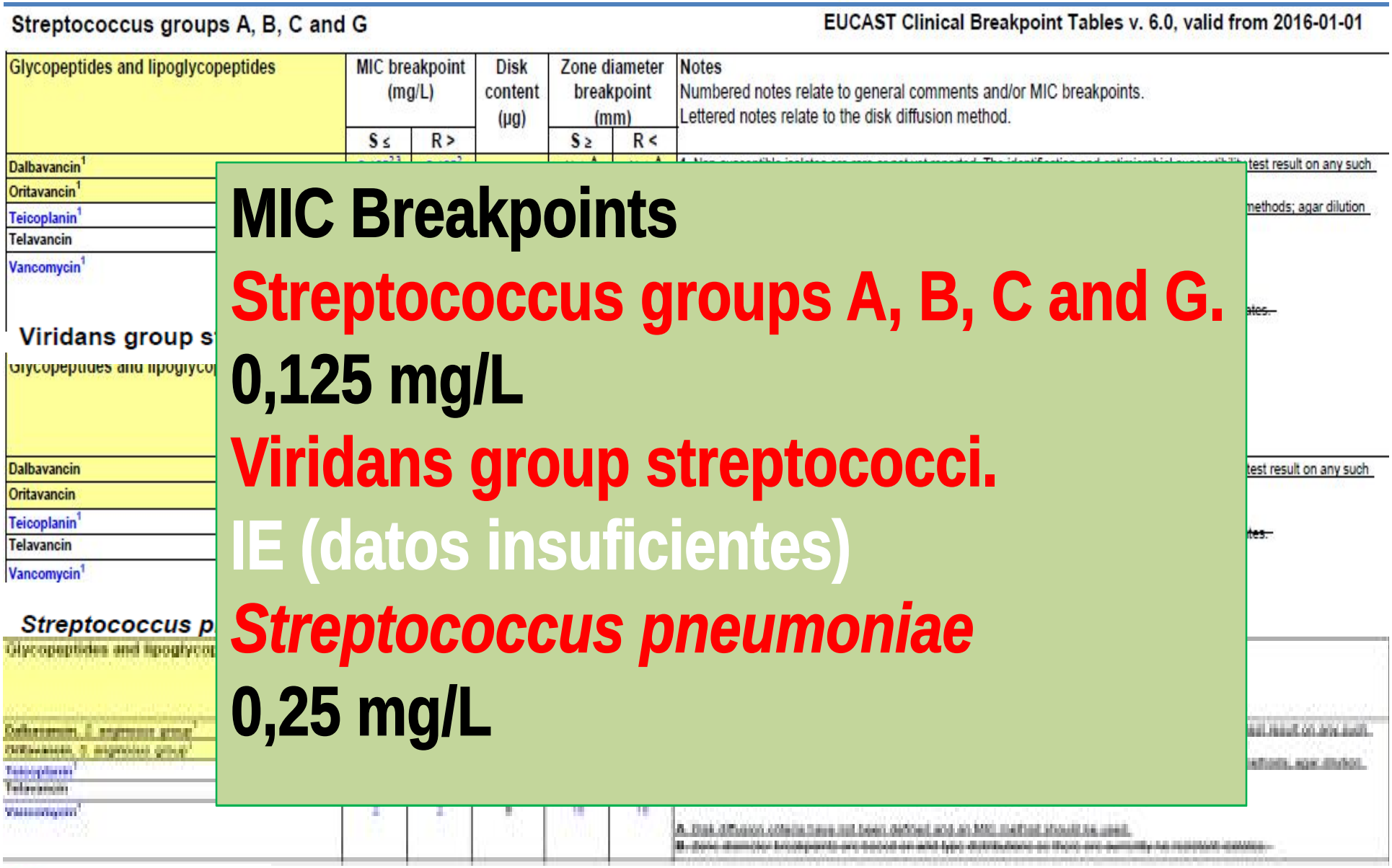
**t Tables v. 6.0, valid from 2016-01-01**

| Glycopeptides and lipoglycopep | S ≤ | R > | | S ≥ | R < | reakpoints. |
|---|---|---|---|---|---|---|
| Dalbavancin | IE | IE | | IE | IE | A. Vancomycin susceptible enterococci exhibit sharp zone edges and do not exhibit colonies in the inhibition zone. Examine zone |
| Oritavancin | IE | IE | | IE | IE | edges with transmitted light (plate held up to light). If the zone edge is fuzzy, colonies grow within the zone or if you are uncertain, |
| Teicoplanin | 2 | 2 | 30 | 16 | 16 | then perform confirmatory testing with PCR or report resistant (**see pictures below**) even if the zone diameter is ≥ 12 mm. |
| Telavancin | IE | IE | | IE | IE | Isolates must not be reported susceptible before 24 h incubation. |
| Vancomycin | 4 | 4 | 5 | 12^ | 12^ | |

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

# ORI. Espectro Antimicrobiano-2



Streptococcus groups A, B, C and G

EUCAST Clinical Breakpoint Tables v. 6.0, valid from 2016-01-01

| Glycopeptides and lipoglycopeptides | MIC breakpoint (mg/L) | | Disk content (µg) | Zone diameter breakpoint (mm) | | Notes |
|---|---|---|---|---|---|---|
| | S ≤ | R > | | S ≥ | R < | Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method. |
| Dalbavancin[1] | | | | | | |
| Oritavancin[1] | | | | | | |
| Teicoplanin[1] | | | | | | |
| Telavancin | | | | | | |
| Vancomycin[1] | | | | | | |

**MIC Breakpoints**

**Streptococcus groups A, B, C and G.**

**0,125 mg/L**

**Viridans group streptococci.**

**IE (datos insuficientes)**

***Streptococcus pneumoniae***

**0,25 mg/L**

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

# ORI. Estudios *in vitro* Bact/EI-1

## Oritavancin Activity against Vancomycin-Susceptible and Vancomycin-Resistant Enterococci with Molecularly Characterized Glycopeptide Resistance Genes Recovered from Bacteremic Patients, 2009-2010

Rodrigo E. Mendes,[a] Leah N. Woosley,[a] David J. Farrell,[a] Helio S. Sader,[a] and Ronald N. Jones[a,b]

AAC, 2011

| Organism and resistance (no. tested) | MIC (μg/ml) 50% | MIC (μg/ml) 90% | Number[a] (cumulative %) inhibited at MIC (μg/ml) of[a]: ≤0.008 | 0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 |
|---|---|---|---|---|---|---|---|---|---|
| *E. faecalis* (1,312) | | | | | | | | | |
| Vancomycin susceptible (1,275) | 0.015 | 0.03 | | | | | | 99.9) | 1 (100.0) |
| *vanA* (27) | 0.25 | 0.5 | | | | | | (81.5) | 5 (100.0) |
| *vanB* (10) | 0.015 | 0.015 | | | | | | | – |
| *E. faecium* (869) | | | | | | | | | |
| Vancomycin susceptible (383) | ≤0.008 | ≤0.008 | 374 (97.7) | 7 (99.5) | 2 (100.0) | – | – | – | – |
| *vanA* (470) | 0.03 | 0.06 | 76 (16.2) | 74 (31.9) | 146 (63.0) | 133 (91.3) | 37 (99.1) | 4 (100.0) | – |
| *vanB* (16) | ≤0.008 | ≤0.008 | 16 (100.0) | – | – | – | – | – | – |
| *E. casseliflavus* (15) and *E. gallinarum* (24) | | | | | | | | | |
| *vanC* (39) | ≤0.008 | 0.015 | 34 (87.2) | 5 (100.0) | – | – | – | – | – |

**Sinergia con DAP frente a VRE (no cepas bacteriemia)**

# ORI. Estudios *in vitro* Bact/EI-2

**Activities of antistaphylococcal antibiotics towards the extracellular and intraphagocytic forms of *Staphylococcus aureus* isolates from a patient with persistent bacteraemia and endocarditis** **CMI, 2008**

*S. Lemaire[1], K. Kosowska-Shick[2], K. Julian[2], P. M. Tulkens[1], F. Van Bambeke[1] and P. C. Appelbaum[2]*

| Antibiotic | Strain | Regression parameter value (95% confidence intervals)[a] $E_{max}$ (mg/L)[c,d] | $EC_{50}$ (mg/L)[d,e] | $R^2$ | Bacteriostatic concentration (mg/L)[b] | $C_{max}$/bacteriostatic concentration ratio |
|---|---|---|---|---|---|---|
| Vancomycin | ATCC 25923 | −0.87 (−1.14 to −0.60) a,A | 0.99 (0.62 1.59) a,A | 0.995 | 2.9 | 17 |
| | HMC 546 | −0.87 (−1.27 to −0.47) a,A | 1.33 (0.70 2.51) a,A | 0.979 | 3.1 | 16 |
| | HMC 549 | −0.68 (−1.32 to −0.04) a,A | 3.79 (1.47–9.78) a,A | 0.974 | 12 | 4.2 |
| Daptomycin | ATCC 25923 | −1.64 (−2.04 to −1.26) b,B,E | 1.13 (0.59–2.16) a,A | 0.980 | 1.4 | 55 |
| | HMC 546 | −0.61 (−1.16 to −0.06) a,A | 3.20 (1.66–12.5) a,A | 0.971 | 20 | 3.8 |
| | HMC 549 | −0.59 (−1.14 to −0.05) a,A | 4.56 (1.11–9.16) a,A | 0.967 | 14 | 5.4 |
| Quinupristin–dalfopristin | ATCC 25923 | −2.42 (−3.27 to −1.58) a,C,E | 0.34 (0.12–0.94) a,C | 0.973 | 0.46 | 21.7 |
| | HMC 546 | −2.01 (−2.25 to −1.78) a,C,E | 0.16 (0.11–0.25) a,C | 0.995 | 0.19 | 53 |
| | HMC 549 | −1.82 (−2.24 to −1.50) a,C,E | 0.26 (0.05–1.27) a,C,E | 0.934 | 0.38 | 26 |
| Oritavancin | ATCC 25923 | −2.46 (−3.50 to −1.42) a,C | 2.95 (1.02–8.49) a,A | 0.976 | 2.6 | 15 |
| | HMC 546 | −2.54 (−3.79 to −1.57) a,C | 3.24 (0.93–11.2) a,A | 0.967 | 2.7 | 15 |
| | HMC 549 | −1.61 (−2.44 to −0.77) a,C,B | 1.51 (0.46–4.81) a,A,D | 0.968 | 2.0 | 20 |

# ORI. Estudios *in vivo* Bact/EI-1

## VRE y VSE

### CONEJO

Activity and Diffusion of LY333328 in Experimental Endocarditis Due to Vancomycin-Resistant *Enterococcus faecalis*

AZZAM SALEH-MGHIR,[1] AGNÈS LEFORT,[1] YOLANDE PETEGNIEF,[2] SOPHIE DAUTREY,[3] JEAN-MARIE VALLOIS,[1] DOMINIQUE LE GULUDEC,[2] CLAUDE CARBON,[1] AND BRUNO FANTIN[1]*

**AAC 1999**

Activity of LY333328 Combined with Gentamicin In Vitro and in Rabbit Experimental Endocarditis Due to Vancomycin-Susceptible or -Resistant *Enterococcus faecalis*

AGNÈS LEFORT,[1] AZZAM SALEH-MGHIR,[1] LOUIS GARRY,[1] CLAUDE CARBON,[1,2] AND BRUNO FANTIN[1,3]*

**AAC 2000**

# ORI. Estudios *in vivo* Bact/EI-2

**MRSA**

**CONEJO**

Efficacy of LY333328 against Experimental Methicillin-Resistant *Staphylococcus aureus* Endocarditis

GLENN W. KAATZ,[1,2,3]* SUSAN M. SEO,[1,2] JEFFREY R. AESCHLIMANN,[3,4] HEATHER H. HOULIHAN,[3,4] RENEE-CLAUDE MERCIER,[3,4] AND MICHAEL J. RYBAK[1,3,4]

**AAC 1998**

**MSSA**

**RATA**

Xiong YQ, Yin L, Hady WA, et al. Efficacy of oritavancin (ORI), a lipoglycopeptide antibiotic, in a rat *Staphylococcal aureus* endocarditis (IE) model: microbiological and bioluminescent assessments [abstract B-1011]. In: 48th Interscience Conference on Antimicrobial Agents and Chemotherapy/Infectious Diseases Society of America 46th Annual Meeting. Washington, DC: American Society for Microbiology, **2008.**

# In Vivo Activity of Oritavancin in Animal Infection Models and Rationale for a New Dosing Regimen in Humans

**CID 2012**

Paul G. Ambrose,[1,2] George L. Drusano,[3] and William A. Craig[4]

**EI:**

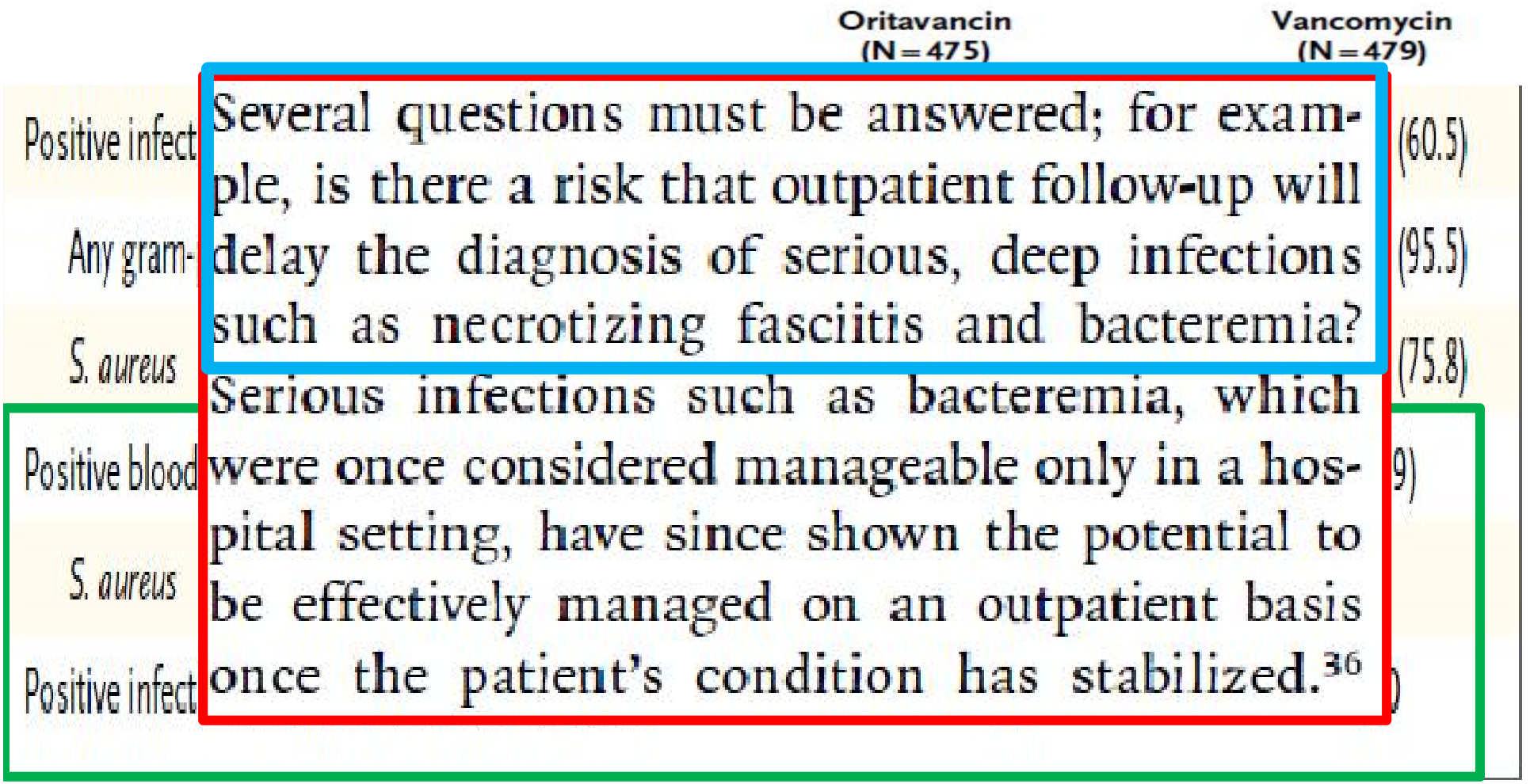
**MRSA: eficacia similar a vancomicina. Limitación: humanización de las dosis.**
**MSSA: eficacia similar a daptomicina y cloxacilina (<% HC+ día 3). Superior a vancomicina.**

**VSE: eficacia similar a vancomicina y teicoplanina.**
**VRE (van A y B): mayor eficacia. No desarrollo de resistencias.**
**Sinergia con gentamicina.**
**No datos en *E. faecium***

**Bacteriemia:**

**Efecto bactericida a las 72h; buena penetración en bazo.**
**Buena actividad intracelular, tb frente a SCV.**
**En el modelo de CRB en rata (tanto en VRE como en MRSA): mayor eficacia dosis grandes infrecuentes.**

# ORI. Estudios clínicos en Bact/EI-1




Several questions must be answered; for example, is there a risk that outpatient follow-up will delay the diagnosis of serious, deep infections such as necrotizing fasciitis and bacteremia?

Serious infections such as bacteremia, which were once considered manageable only in a hospital setting, have since shown the potential to be effectively managed on an outpatient basis once the patient's condition has stabilized.[36]

**Corey R et al, *NEJM* 2014**

# ORI. Estudios clínicos en Bact/EI-1

## Prolonged Use of Oritavancin for

| Antibiotic | Initial Presentation | First Recurrence (5 mo Later) | Second Recurrence (8 mo Later) |
|---|---|---|---|
| Ampicillin | KBD 6 mm (R) | KBD 6 mm (R)<br>MIC > 256 µg/mL (R) | KBD 6 mm (R)<br>MIC 256 µg/mL (R) |
| Vancomycin | KBD 6 mm (R) | KBD 6 mm (R) | KBD 6 mm (R) |
| Gentamicin | KBD 26 mm (Syn) | KBD 26 mm (Syn) | KBD 28 mm (Syn) |
| Streptomycin | KBD 21 mm (Syn) | KBD 22 mm (Syn) | KBD 26 mm (Syn) |
| Tetracycline | KBD 6 mm (R) | KBD 6 mm (R) | KBD 6 mm (R) |
| Doxycycline | – | KBD 12 mm | – |
| Telavancin | – | Initial: MIC > 32 µg/mL<br>Repeat: MIC 0.19 µg/mL | Initial: MIC 32 µg/mL |
| Linezolid | KBD 30 mm (S) | KBD 31 mm (S) | KBD 35 mm (R)<br>MIC 0.75 µg/mL (S) |
| Daptomycin | MIC 4 µg/mL (S) | Initial: MIC 4 µg/mL (S)<br>Repeat: MIC 6 µg/mL (R) | Initial: MIC 4 µg/mL (S) |
| Quinupristin/dalfopristin | – | MIC 1.5 µg/mL (I) | – |
| Tigecycline | MIC 0.25 µg/mL | Initial: MIC 0.19 µg/mL<br>Repeat: MIC 0.25 µg/mL | MIC 0.094 µg/mL |
| Oritavancin | – | MIC 0.5 µg/mL | MIC 0.5 µg/mL |

# ORI. Micro-resumen

- No suficiente evidencia clínica (s.t. EI, microorganismo)
- Más datos en el modelo animal, pero muchas dudas en el modelo. ¿Datos en combinación?
- Datos *in vitro* (enterococos, VGS)
- Datos pK/pD para tratamientos prolongados >14 días.
- Rápida actividad bactericida
- Buena penetración tisular
- Perfil microbiológico
- Actividad frente a biofilm

# 5. Potencialidades en bacteriemia/EI

- **Tratamiento domiciliario**
- **Tratamiento supresivo en casos refractarios**
- **Dosis inicial + otro tratamiento para reducir el tiempo de bacteriemia inicial + complicaciones.**
- **Dosis antes de cirugía (¿repetir?)**
- **Explorar actividad ORI frente a EI sobre DIC**
- **Uso en recidivas debidas SCV**
- **...**

# 6. Conclusiones

1. Por su espectro y su escaso riesgo de nefrotoxicidad, tanto DAL como ORI son antibióticos cuyas características los hacen interesantes para tratar pacientes graves como son los afectos de bacteriemia complicada o endocarditis infecciosa (como alternativa a VAN)
2. Su larga vida media y facilidad de administración los convierte en fármacos con una potencial aplicación en domicilio, centros convalescencia, etc.
3. Otros usos y su eficacia en combinación con otros fármacos (st MRSA y VRE) deben ser todavía explorados.
4. La evidencia disponible para ambos fármacos a día de hoy no permite recomendarlos off-label. Se requieren nuevos estudios experimentales y clínicos.

# ¡Gracias!