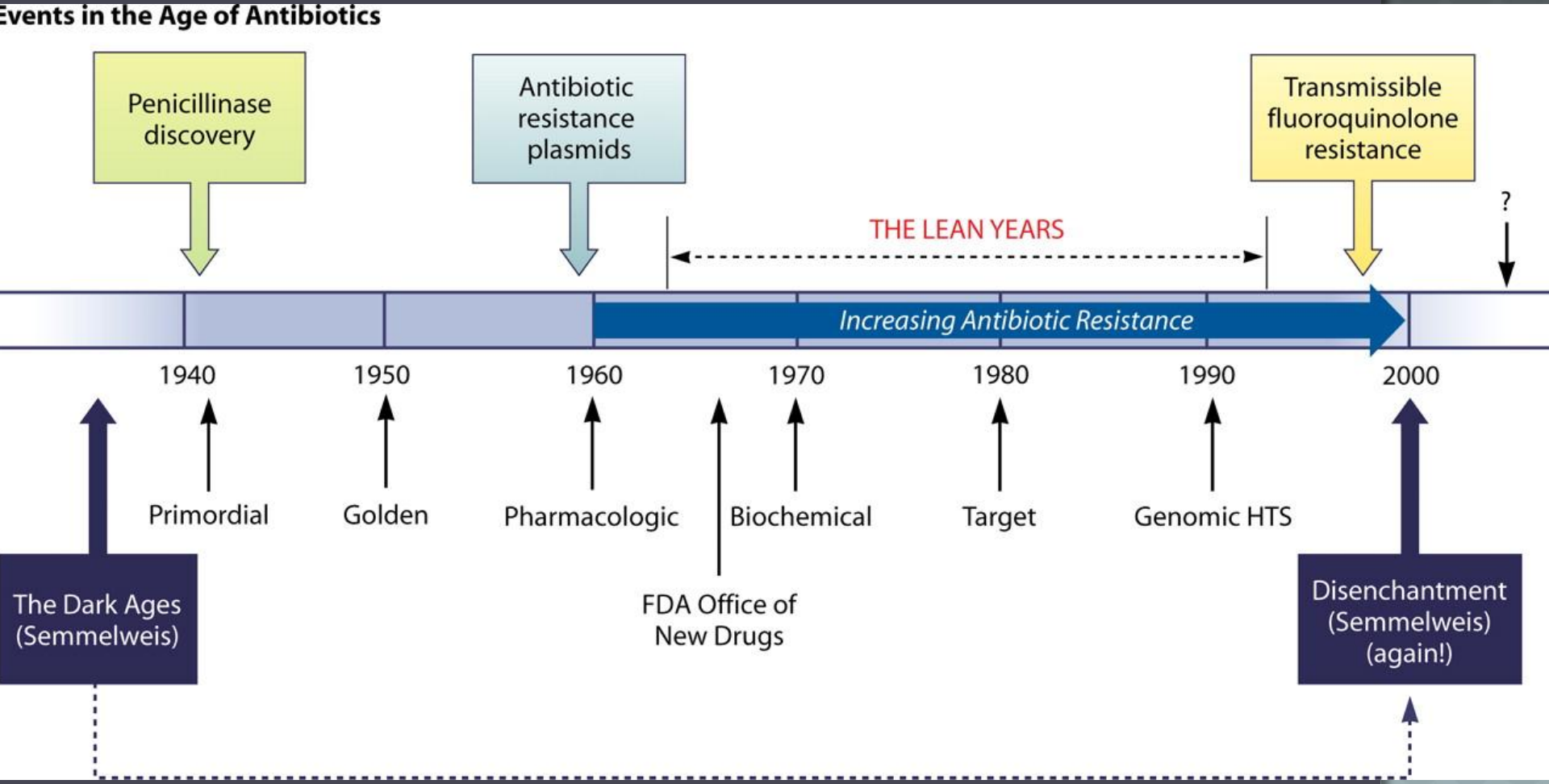
XXVI CURSO DE AVANCES EN ANTIBIOTERAPIA

NUEVOS ANTIBIOTICOS Y MICROORGANISMOS RESISTENTES.

Dra. Teresa Alarcón
Hospital Universitario de La Princesa
MADRID.

History of antibiotic discovery and concomitant development of antibiotic resistance.



Davies J , Davies D Microbiol. Mol. Biol. Rev. 2010;74:417-433

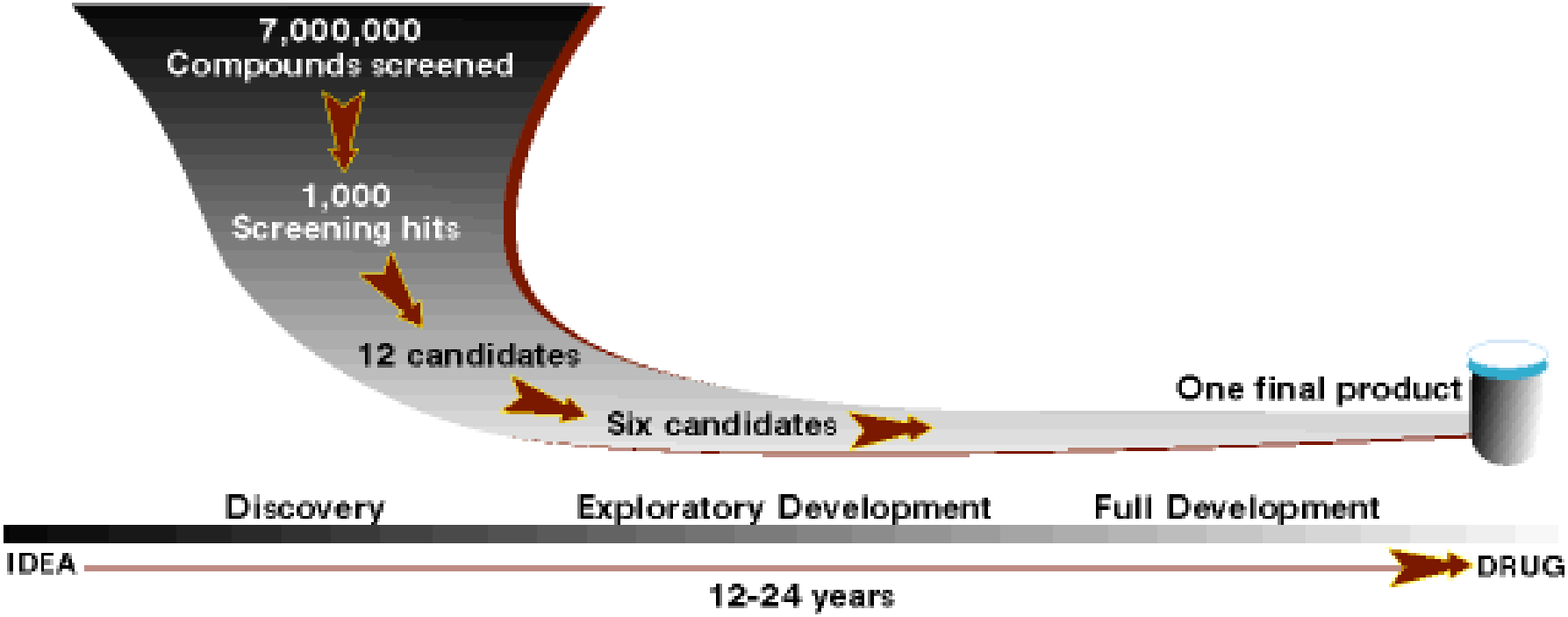
Microbiology and Molecular Biology Reviews

RESISTENCIA A ANTIBIÓTICOS

Antibiotic	Year Deployed	Resistance Observed
Sulfonamides	1930s	1940s
Penicillin	1943	1946
Streptomycin	1943	1959
Chloramphenicol	1947	1959
Tetracycline	1948	1953
Erythromycin	1952	1988
Vancomycin	1956	1988
Methicillin	1960	1961
Ampicillin	1961	1973
Cephalosporins	1960s	late 1960s

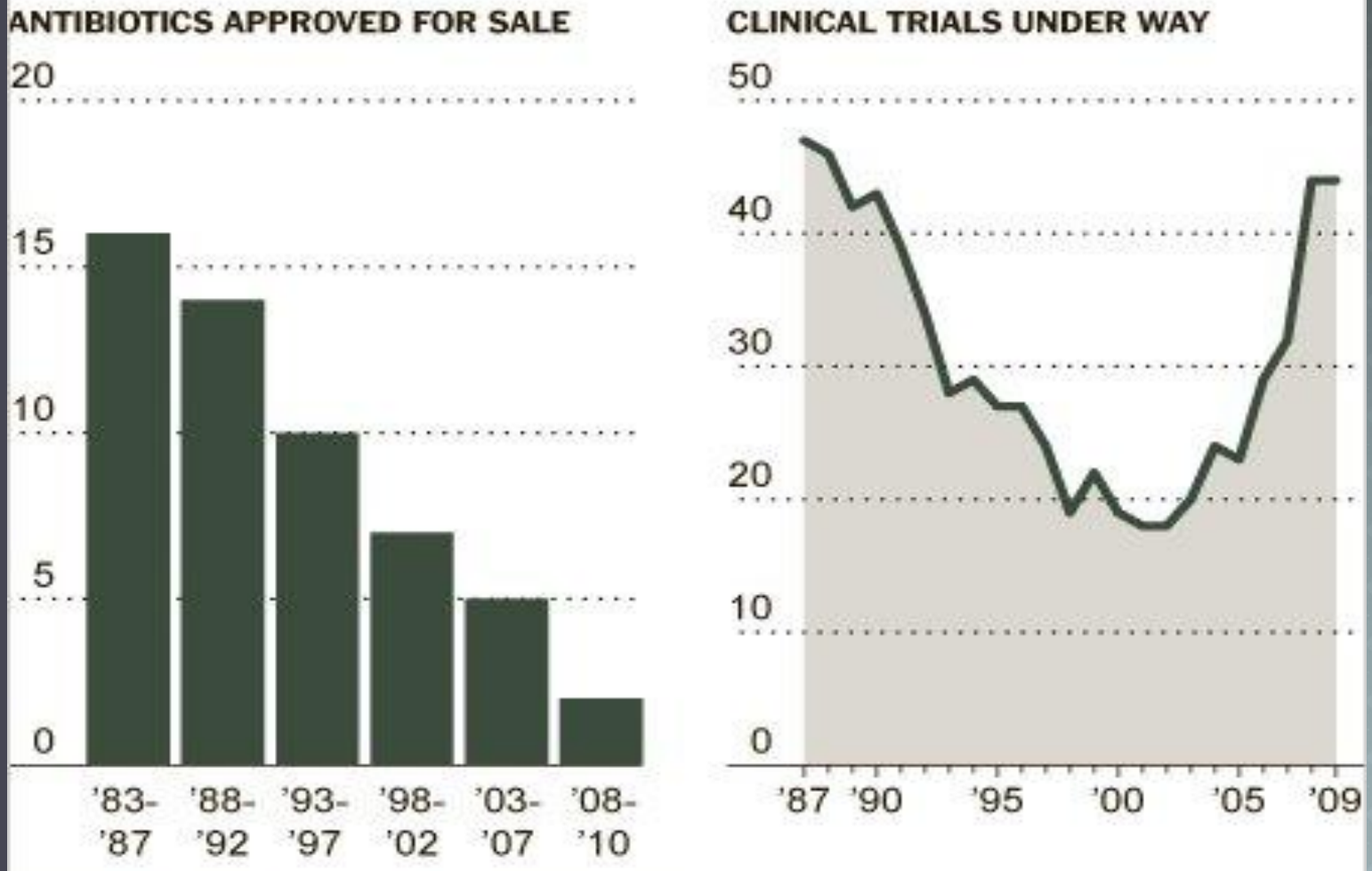
Table 20.2 Microbiology: A Clinical Approach (© Garland Science)

ATTRITION ON THE ROAD: Research and development of new drugs



Searching for New Antibiotics

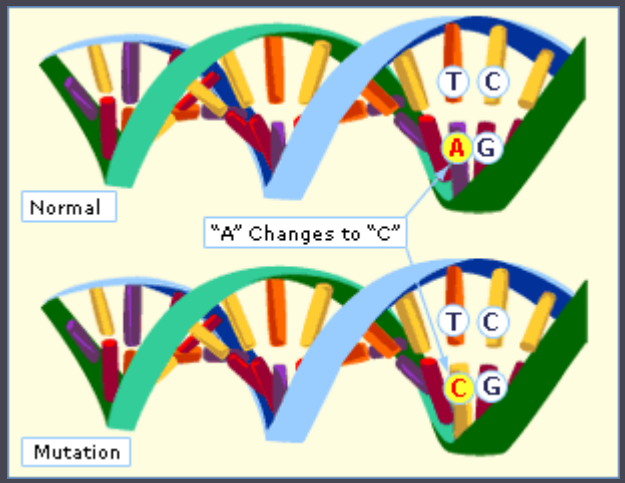
The number of new antibiotics approved for sale in the United States has steadily declined, leading some pharmaceutical executives and infectious disease specialists to call for federal subsidies to stimulate development. But others say that the rising number of clinical studies indicates that companies are stepping up research on their own.

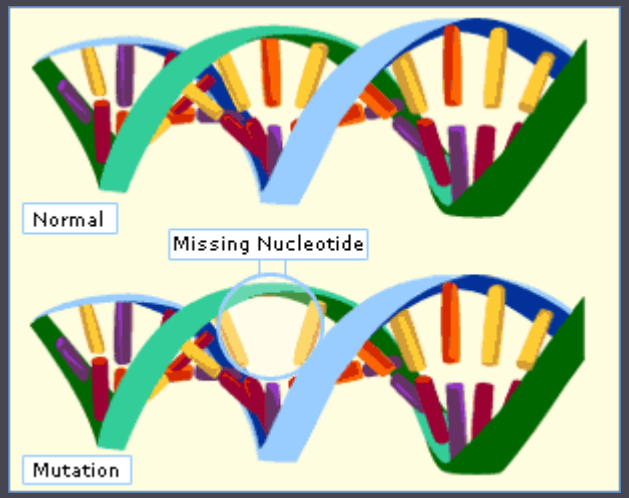


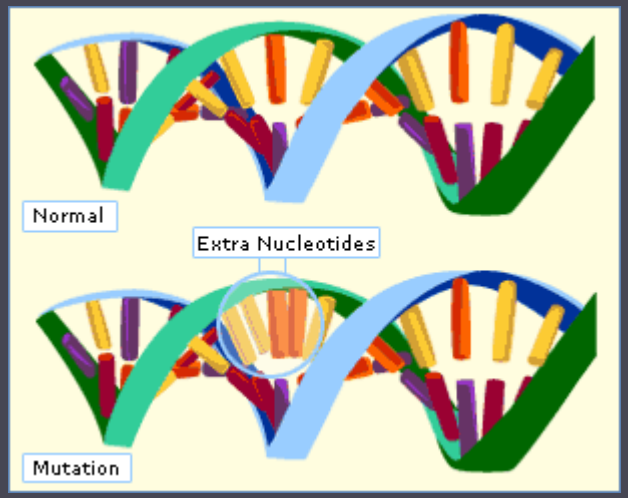
Sources: Infectious Diseases Society of America; Food and Drug Administration

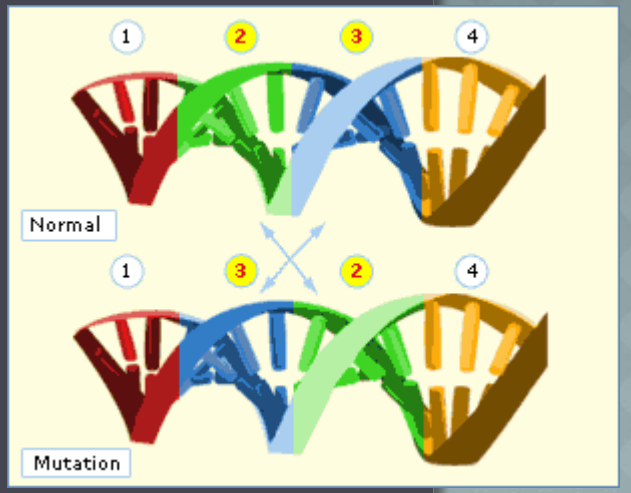
¿POR QUÉ SE HACEN RESISTENTES?

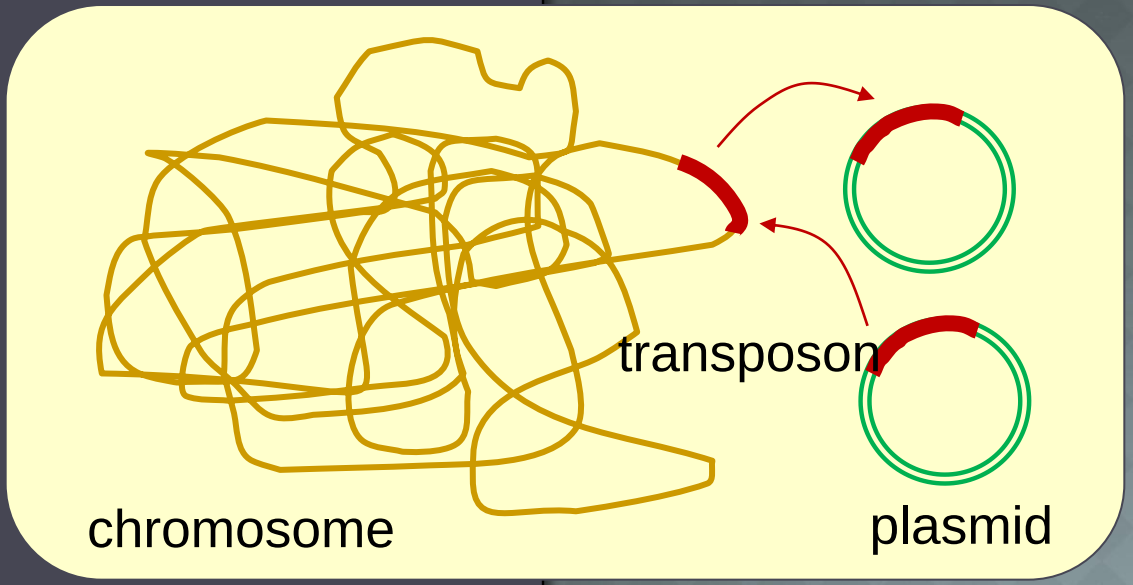
Mutaciones:



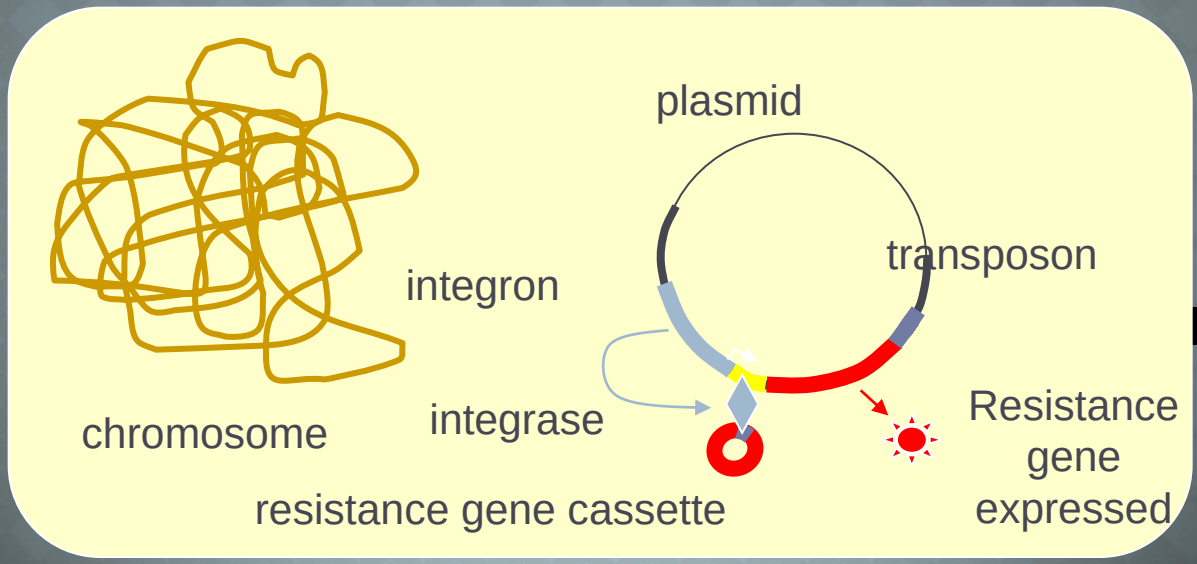




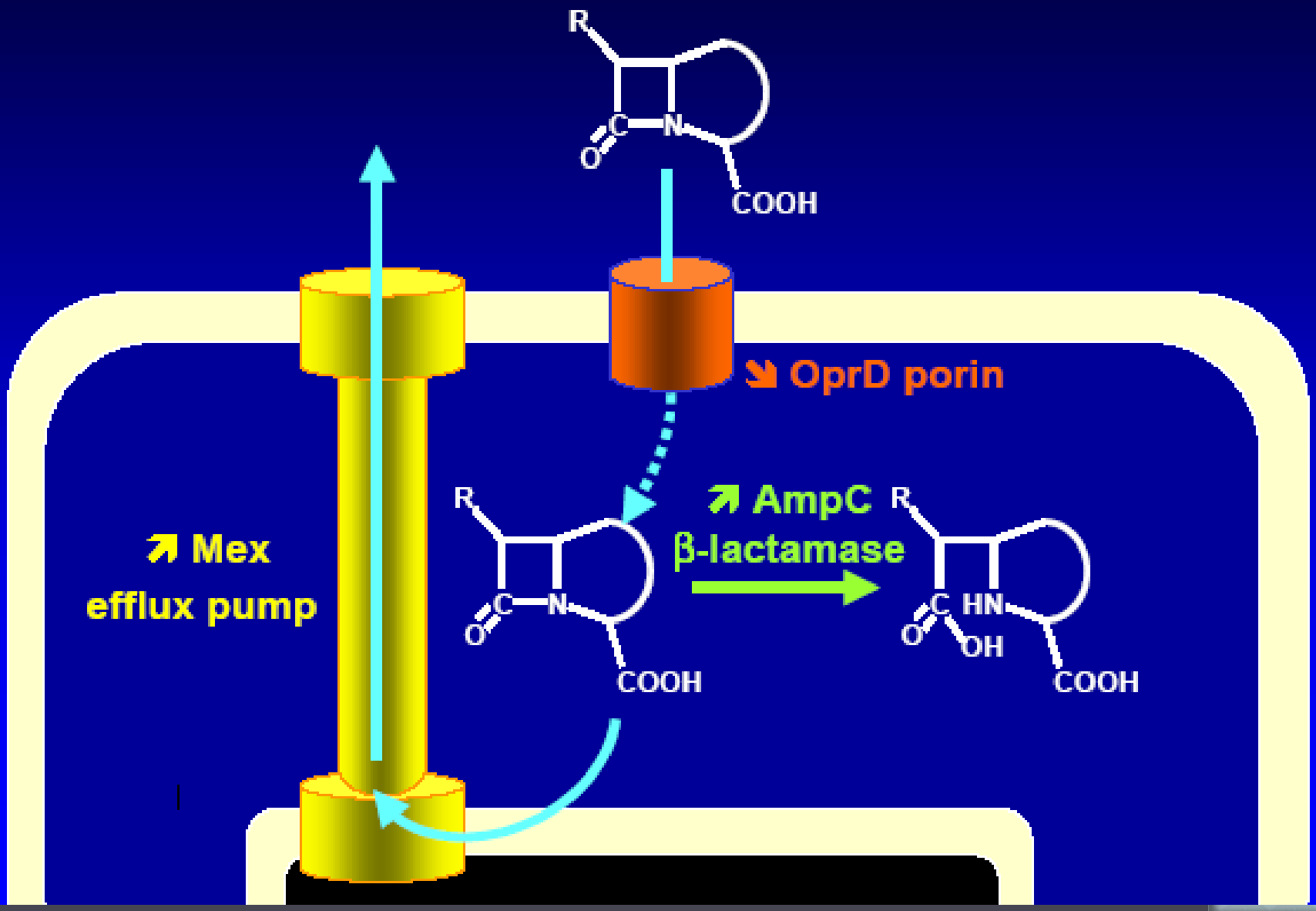




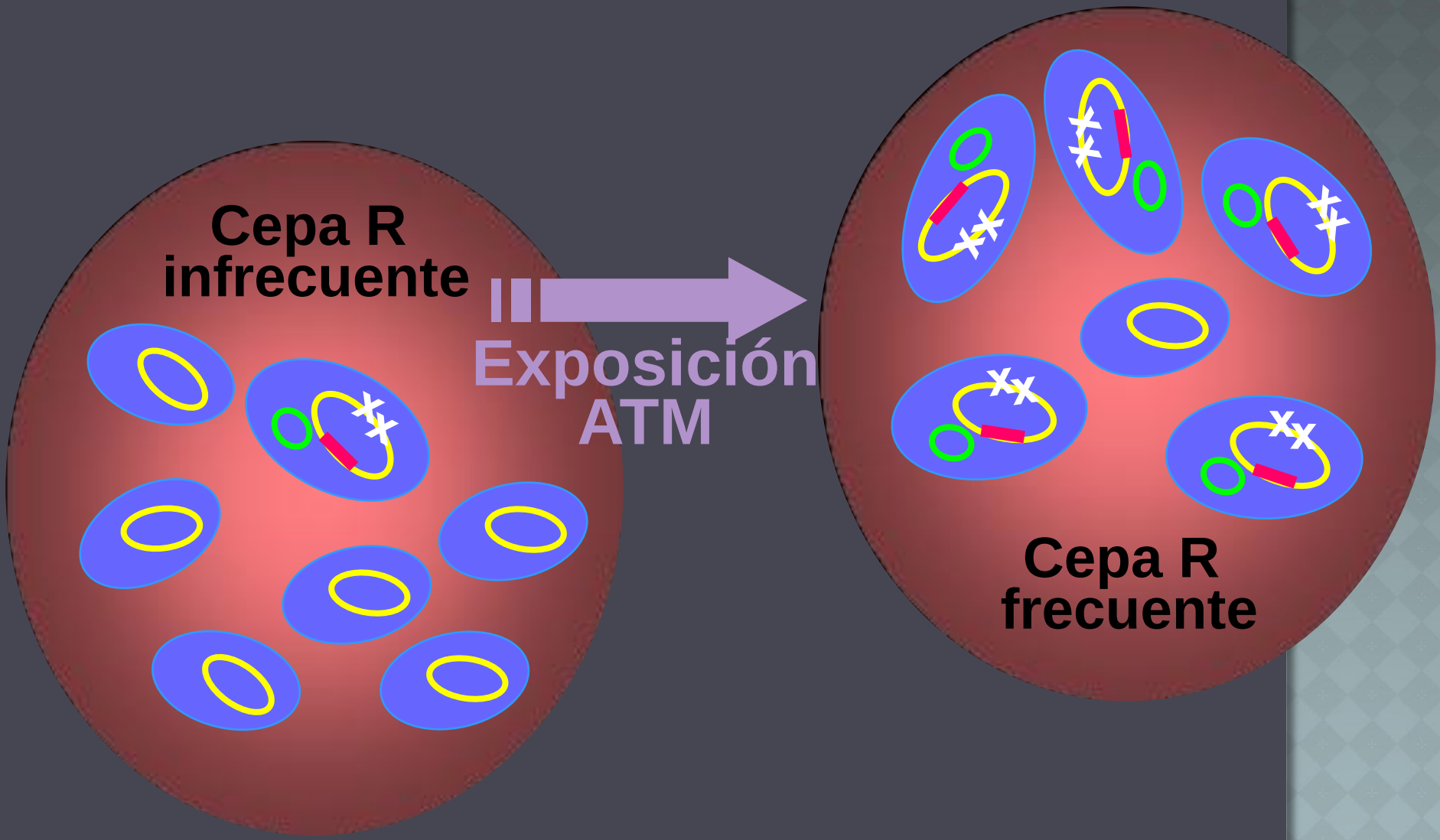
“jumping genes”



Combined mechanisms of resistance in *Pseudomonas*



SELECCIÓN DE RESISTENCIA



RESISTENCIA ANTIBIOTICA

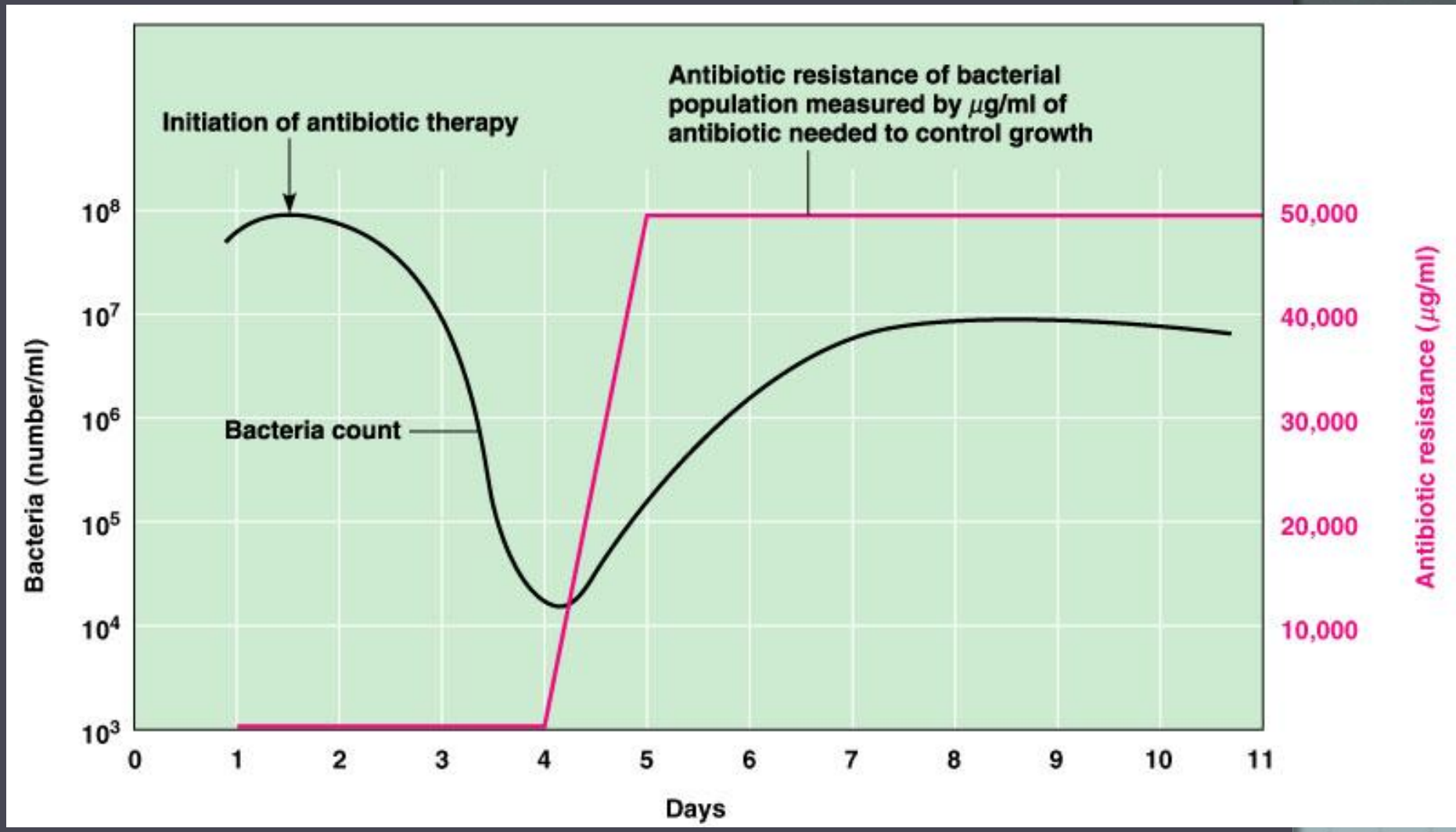


Figure 20.20

BACTERIAS MULTIRRESISTENTES (DATOS HOSP. UNIV. LA PRINCESA)

Bacteria	Característica	2010	2011	2012
E. coli	Productor de BLEE	10,3%	8,6%	8.8%
K pneumoniae	Productor de BLEE	6,7%	12,0%	16,2%
P. aeruginosa	R-imipenem	25,8%	24,0%	22,1%
S. maltophilia	R-cotrimoxazol	14,28%	21,0%	11,8%S
S. aureus	R- meticilina	29,05%	24,0%	22,9%

MECANISMOS DE R: β-LACTAMASAS

DATOS SOBRE β-LACTAMASAS

1940 : Introducción de penicillnas

1940 : Primera publicación de β-lactamasa

1944 : Cepas de *S. aureus* productor de β-lactamasa

1960s : Uso clínico de penicilinas de amplio espectro (ampicilina y carbenicilina)

1970s : β-lactamasas codificadas en plásmidos en Enterobacteriaceae y otros Gram-negativos

1980-90 : Desarrollo de cefalosporinas cefamicinas, monobactamas y carbapenémicos

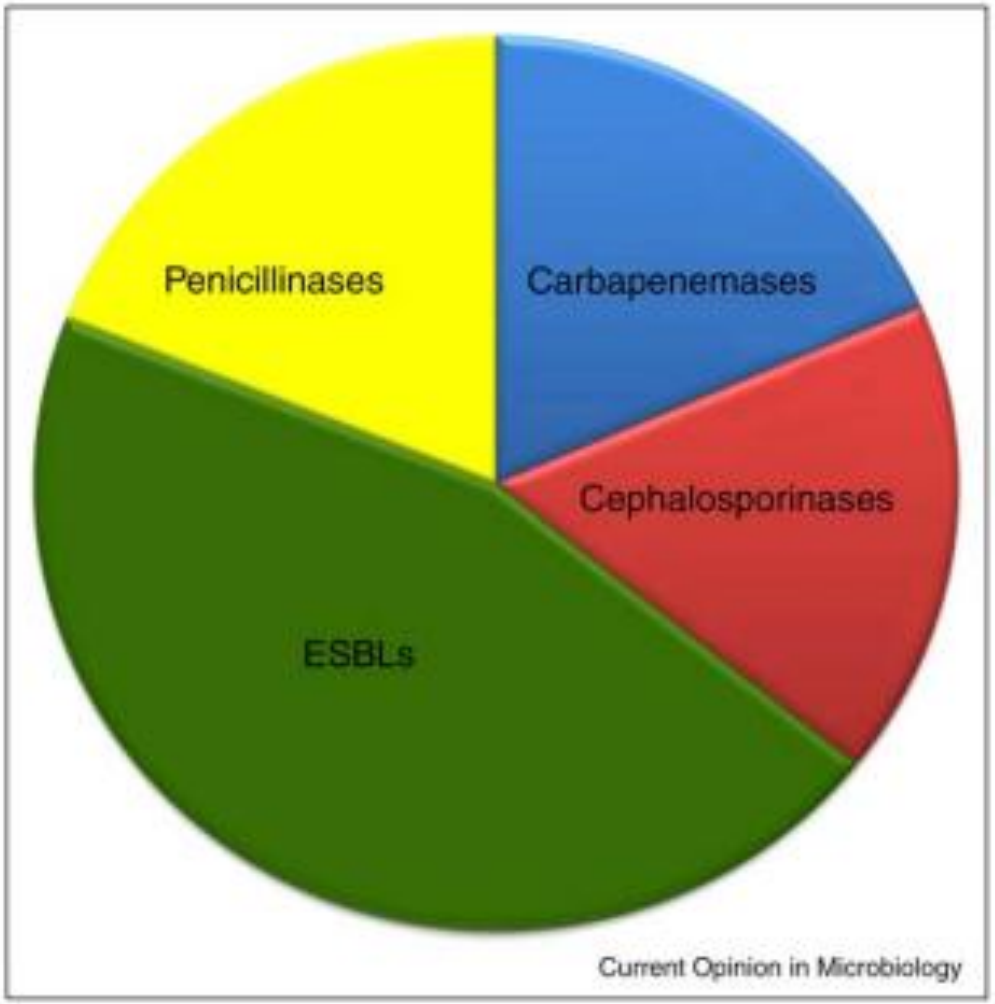
1990 : Aumento de R entre bacterias Gram-negativas

CLASIFICACIÓN DE B-LACTAMASAS

- Clase molecular:
  - **A**:
    - TEM
    - SHV
    - other
  - **B**:
    - Metaloenzimas (carbapenemasas)
  - **C**:
    - Prototipo: *ampC*
  - **D**:
    - OXA (hidrolizan oxacilina)

- Tipo de enzima (perfil sustrato):
  - Penicilinasas
  - Amplio espectro
  - Espectro extendido
  - Carbapenemasas

http://www.lahey.org/studies/webt.asp



Distribution of β-lactamases according to functionality [4]. Penicillinases primarily include functional groups 2, 2a, 2b, 2c, and 2d β-lactamases. Carbapenemases include functional groups 2df, 2f, and group 3 β-lactamases. Cephalosporinases include functional groups 1, 1e, and 2e enzymes. ESBLs include functional groups 2be, 2ber, and 2de β-lactamases.

Bush, K. Curr Op Microbi 2010

B-LACTAMASAS TRANSFERIBLES EN ENTEROBACTERIAS

β-lactamasas de amplio espectro o penicilinasas

CLASE A: TEM, SHV

CLASE D: OXA

β-lactamasas de espectro extendido (BLEE)

CLASE A: TEM, SHV, CTX-M

CLASE D: OXA

Cefamicinasas o β-lactamasas tipo AmpC

CLASE C: ACC, ACT, CMY, DHA, FOX

Carbapenemasas

CLASE A: KPC

CLASE B: VIM, IMP, NDM

CLASE D: OXA-48

Dra. Carmen Conejo. Univ Sevilla

CARBAPENEMASAS TRANSFERIBLES EN ENTEROBACTERIAS

Clase A

KPC, IMI, GES)

Hidrolizan todos los ß-lactámicos.

Son inhibidas por ácido borónico.

Clase B (MBL)

VIM, IMP, NDM

Perfil hidrólisis: Todos los ß-lactámicos, excepto aztreonam.

Son inhibidas por quelantes de Zn (EDTA).

Clase D u Oxacilinasas

OXA-48 y dvdas

Hidrolizan penicilinas y carbapenémicos >>>>>> cefalosporinas de amplio espectro

No inhibidores efectivos.

Dra. Carmen Conejo.
Univ Sevilla

CARBAPENEMASAS TRANSFERIBLES EN ENTEROBACTERIAS. ESPAÑA 2009

35 hospitales

Prevalencia global:
0,04% (43/100.132)
VIM-1 (77%), IMP (23%)

Dra. Carmen Conejo. Univ Sevilla

Miró et al. Eur J Clin Microbiol Infect Dis. 2013; 32:253–259

DISTRIBUCIÓN MUNDIAL DE KPC

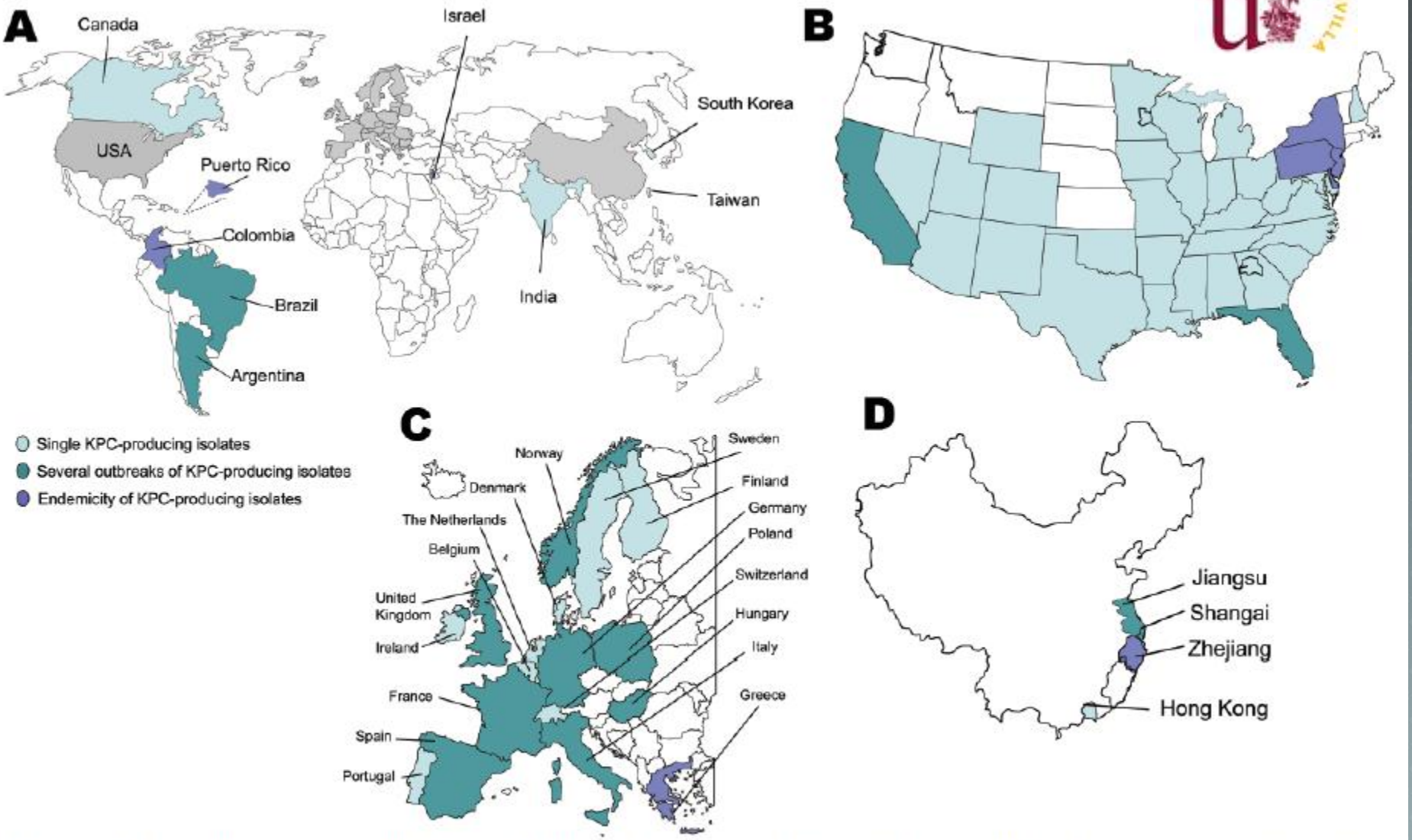


Figure 1. A) Worldwide geographic distribution of *Klebsiella pneumoniae* carbapenemase (KPC) producers. Gray shading indicates regions shown separately: B) distribution in the United States; C) distribution in Europe; D) distribution in China.

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Nordmann et al. Emerg Infect Dis 2011; 17: 1791 -1798

DISTRIBUCIÓN MUNDIAL DE VIM E IMP

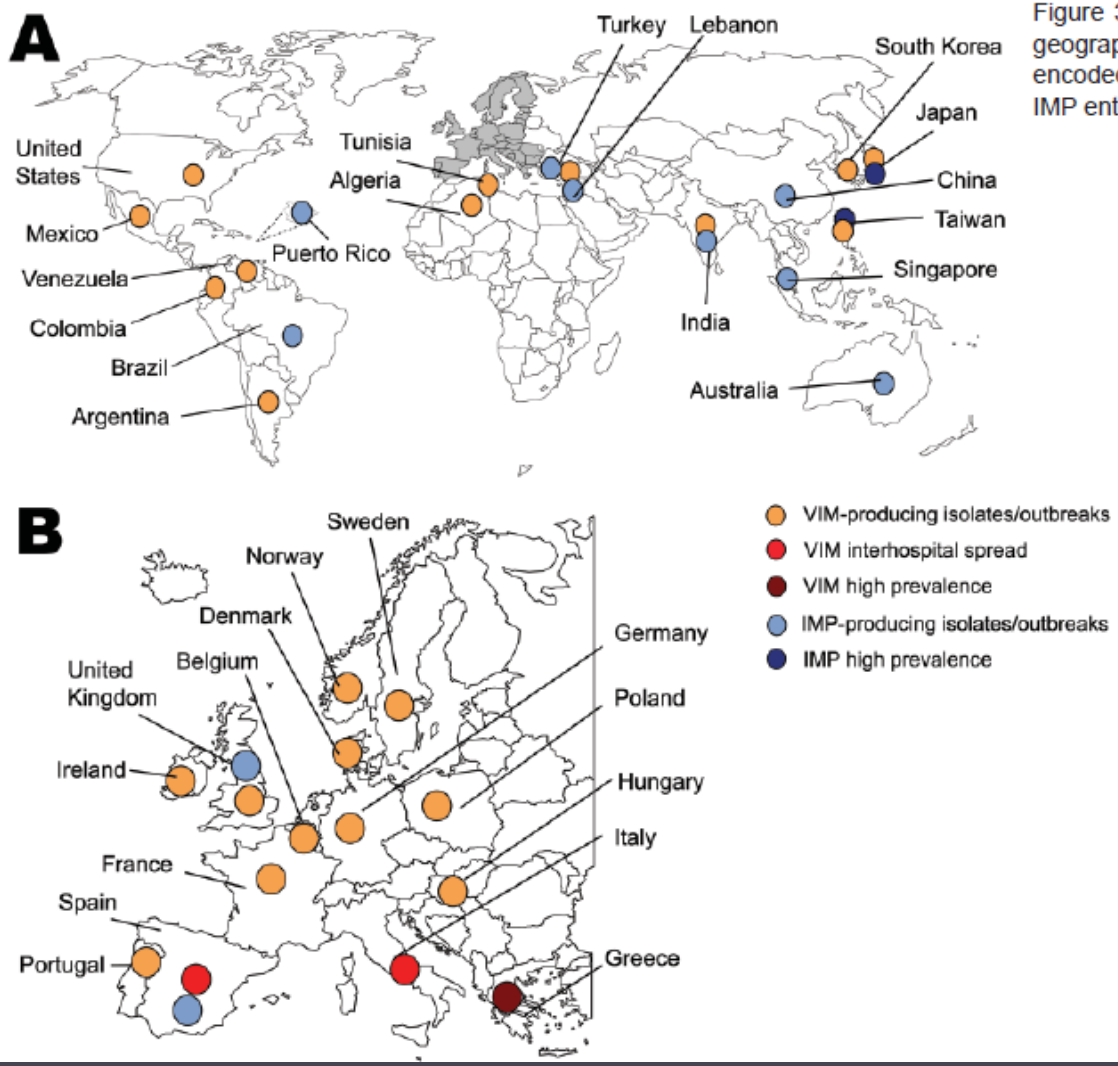

Figure 3. Worldwide (A) and European (B) geographic distribution of Verona integron–encoded metallo-β-lactamase (VIM) and IMP enterobacterial producers.

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Nordmann et al. Emerg Infect Dis 2011; 17: 1791 -1798

DISTRIBUCIÓN MUNDIAL DE NDM-1

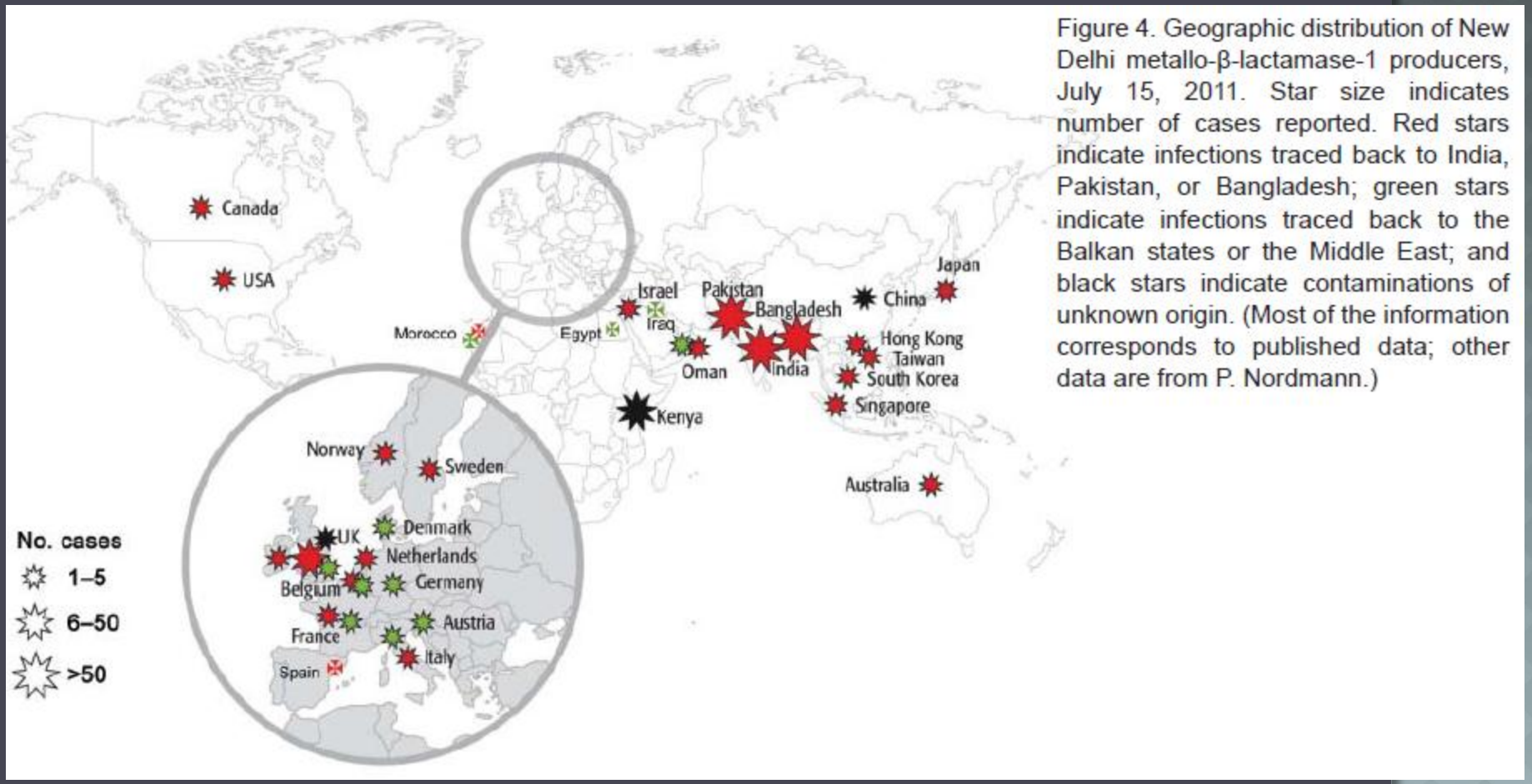


Figure 4. Geographic distribution of New Delhi metallo-β-lactamase-1 producers, July 15, 2011. Star size indicates number of cases reported. Red stars indicate infections traced back to India, Pakistan, or Bangladesh; green stars indicate infections traced back to the Balkan states or the Middle East; and black stars indicate contaminations of unknown origin. (Most of the information corresponds to published data; other data are from P. Nordmann.)

Dra. Carmen Conejo. Univ Sevilla

Nordmann et al. Emerg Infect Dis 2011; 17: 1791 -1798

DISTRIBUCIÓN MUNDIAL DE OXA-48

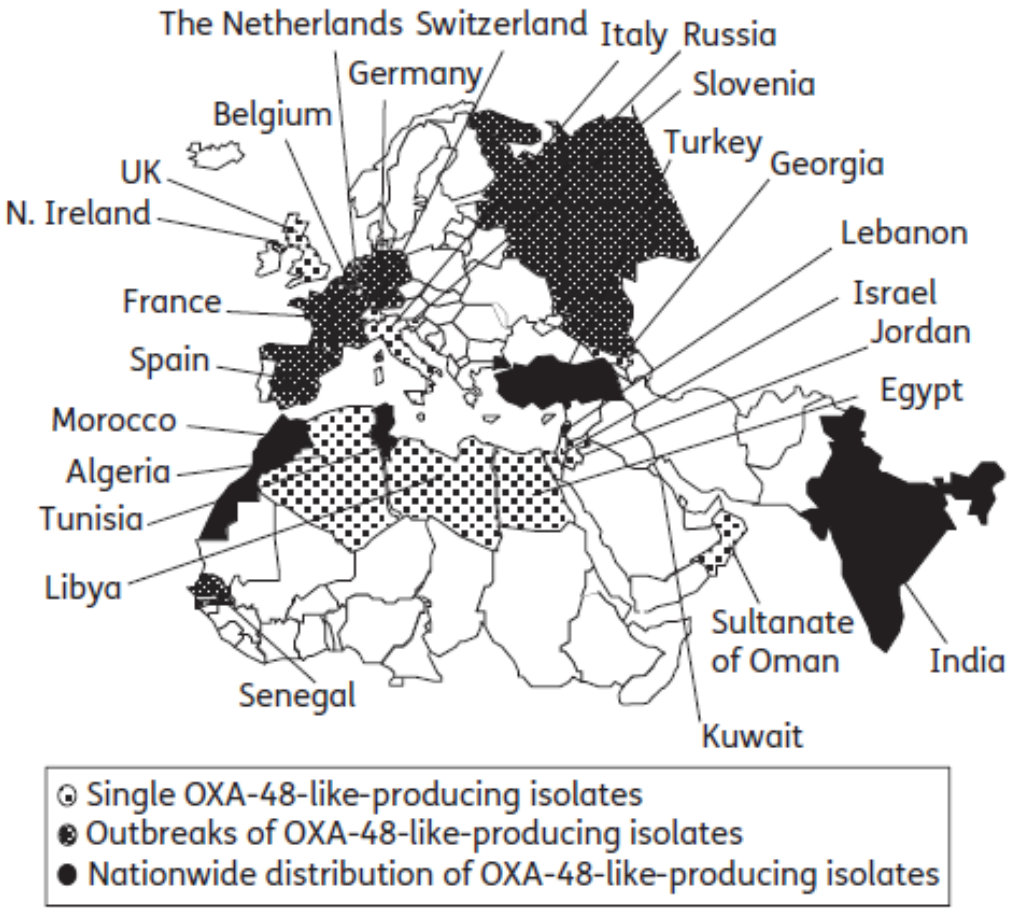
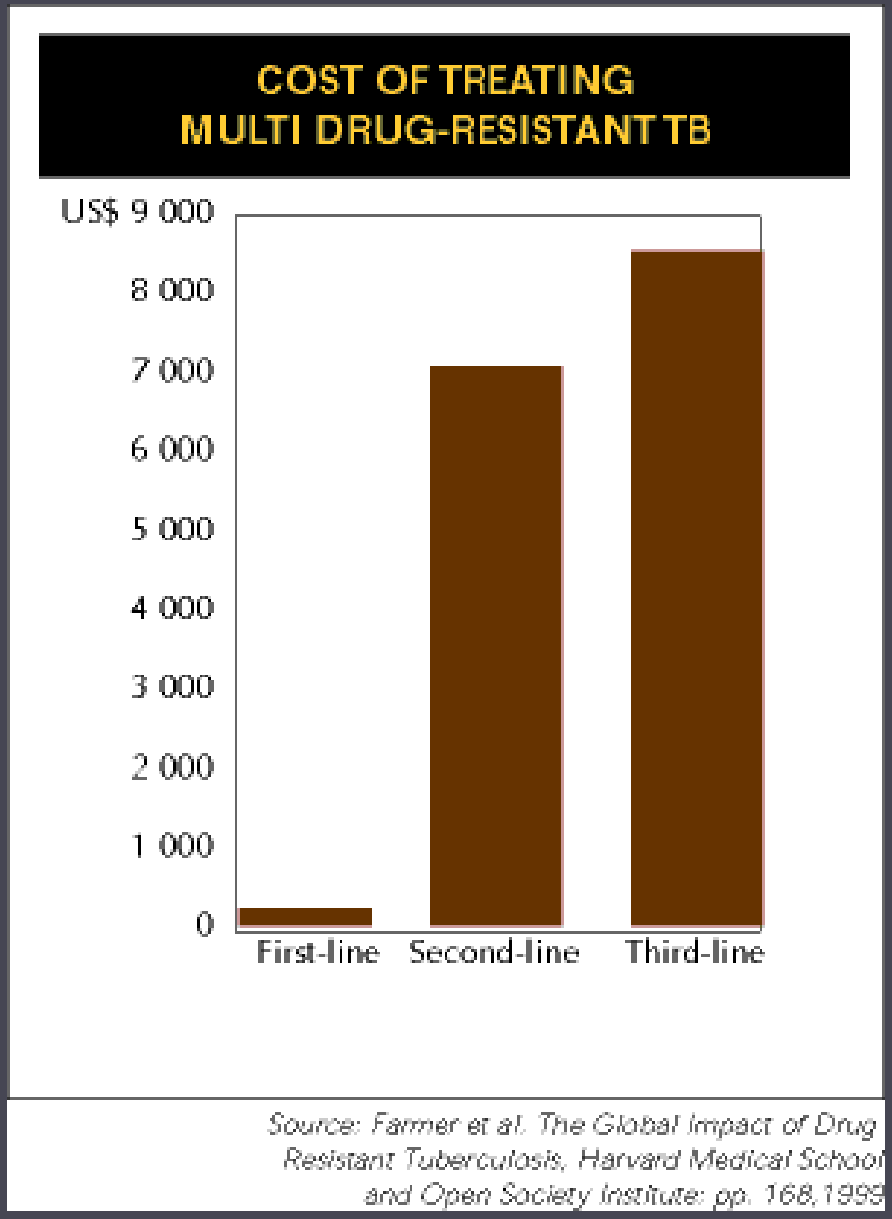


Figure 1. Geographical distribution of OXA-48-like-producing enterobacterial isolates. The country corresponds to that where the other studies. Argentina, New Zealand and South Africa are countries where OXA-48-like producers have been detected, but are not included on the map.

Y también en EEUU

Poirel et al. J Antimicrob Chemother. 2012; 67: 1597-1606



CONSECUENCIAS DE LA RESISTENCIA ANTIMICROBIANA

- Infecciones resistentes a los antimicrobianos disponibles
- Tratamientos más caros

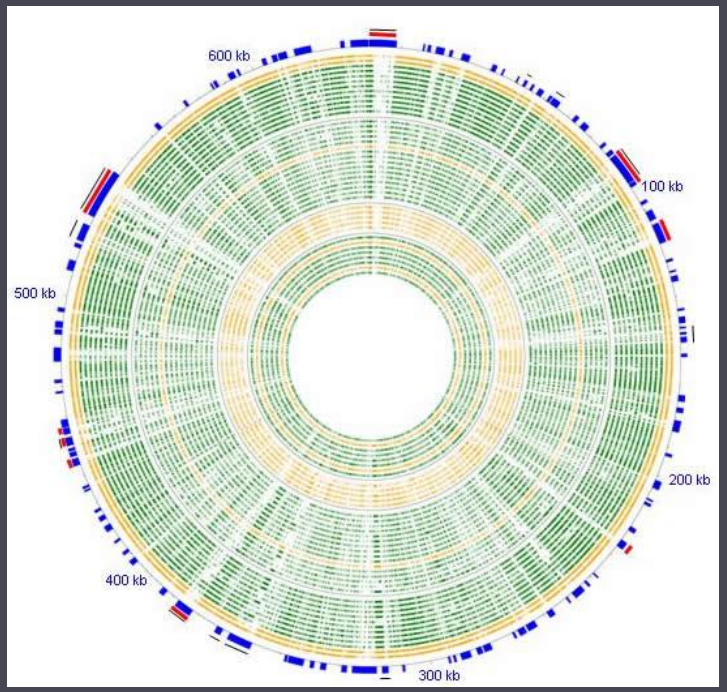
DESCUBRIMIENTO DE NUEVOS ATB

Screening empírico →

La mayoría de los ATB que utilizamos

DESCUBRIMIENTO DE NUEVOS ATB

Búsqueda de nuevos ATB en la era de la genómica, bioinformática, biología molecular y estructural, etc



BLOQUEANTES DE FACTORES DE VIRULENCIA

- Antitoxinas: toxinas de *Bacillus anthracis*, *Corynebacterium diphtheriae*, *Clostridium tetani*
- Inhibidores de moléculas extracelulares y receptores implicados en el Quorum sensing y biofilm
- Sistemas de secreción especializados como dianas (los utilizan las bacterias para crecer en el hombre pero no en el ambiente)

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 Recent Patents on Anti-Infective Drug Discovery, 2013, 8, 68-83

Bacterial Quorum Sensing Inhibitors: Attractive Alternatives for Control of Infectious Pathogens Showing Multiple Drug Resistance

Ashima K. Bhardwaj*, Kittappa Vinothkumar and Neha Rajpara

Department of Human Health and Diseases, Indian Institute of Advanced Research, Koba Institutional Area, Gandhinagar 382 007, Gujarat, India

Received: December 13, 2012; Revised: January 31, 2013; Accepted: January 31, 2013

Abstract: Quorum sensing (QS) is a bacterial communication process that depends on the bacterial population density. It involves small diffusible signaling molecules which activate the expression of myriad genes that control diverse array of functions like bioluminescence, virulence, biofilm formation, sporulation, to name a few. Since QS is responsible for virulence in the clinically relevant bacteria, inhibition of QS appears to be a promising strategy to control these pathogenic bacteria. With indiscriminate use of antibiotics, there has been an alarming increase in the number of antibiotic resistant pathogens. Antibiotics are no longer the magic bullets they were once thought to be and therefore there is a need for development of new antibiotics and/or other novel strategies to combat the infections caused by multidrug resistant organisms. Quorum sensing inhibition or quorum quenching has been pursued as one of such novel strategies. While antibiotics kill or slow down the growth of bacteria, quorum sensing inhibitors (QSIs) or quorum quenchers (QQs) attenuate bacterial virulence. A large body of work on QS has been carried out in deadly pathogens like *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Vibrio fischeri*, *V. harveyi*, *Escherichia coli* and *V. cholerae* etc to unravel the mechanisms of QS as well as identify and study QSIs. This review describes various aspects of QS, QSI, different model systems to study these phenomena and recent patents on various QSIs. It suggests QSIs as attractive alternatives for controlling human, animal and plant pathogens and their utility in agriculture and other industries.

Keywords: Biofilms, multidrug resistance, patents, *Pseudomonas aeruginosa*, quorum sensing, quorum sensing inhibitors, *Staphylococcus aureus*, *Vibrio cholerae*.

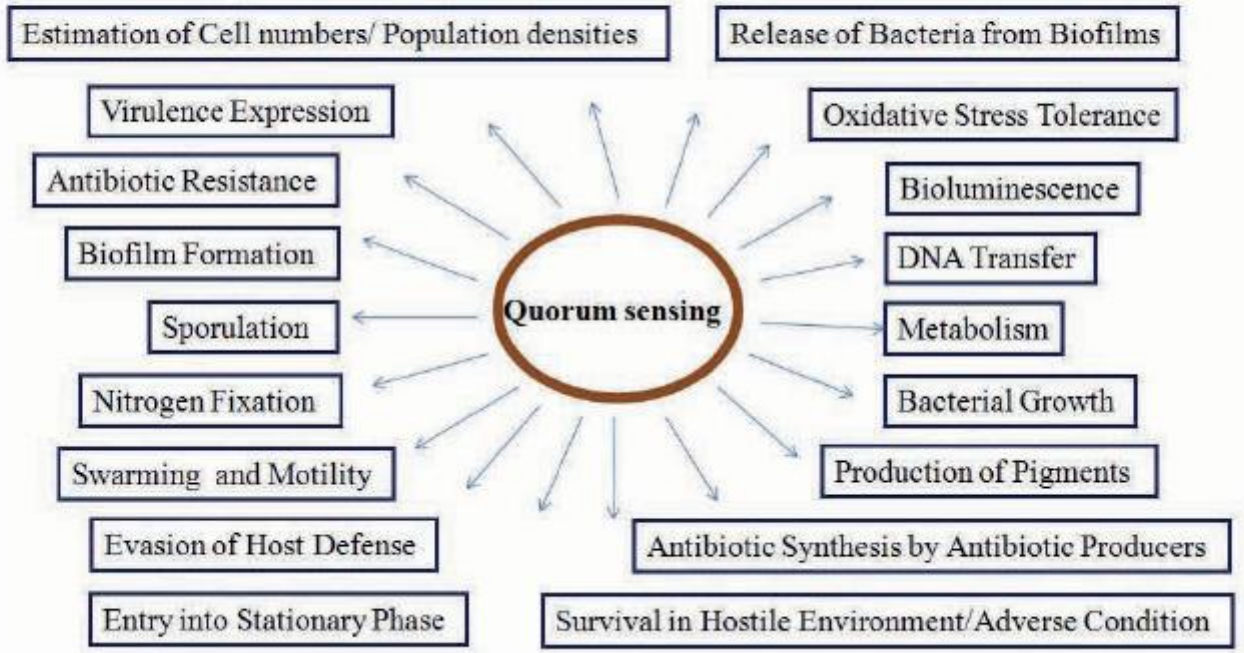
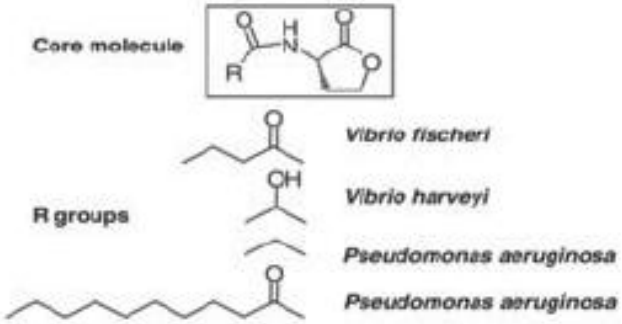


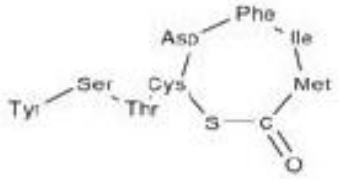
Fig. (1). Quorum sensing: A central component of multiple functions in bacterial communities.

A. QS Signals

Acyl homoserine lactone autoinducers

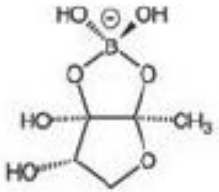


Oligopeptide autoinducers

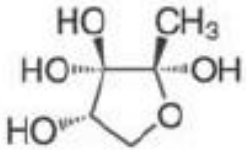


Staphylococcus aureus

Autoinducer 2 (*Vibrio harveyi*)
(2S,4S)-2-methyl-2,3,3,4-
Tetrahydroxytetrahydrofuran borate
(S-THMF-borate)



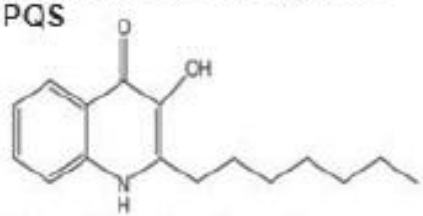
(2R,4S)-2-methyl-2,3,3,4-
tetrahydroxytetrahydrofuran (R-THMF)



Other QS signals

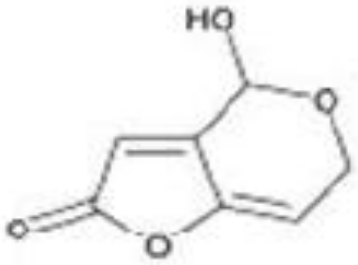
Bacillus subtilis
ComX
Ala-Asp-Pro-Ile-Thr-Arg-Gln-Trp*-Gly-Asp

Pseudomonas aeruginosa
PQS

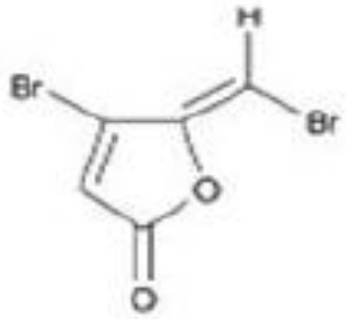


Streptococcus pneumoniae
CSP
Glu-Met-Arg-Leu-Ser-Lys-Phe-Phe- Arg-Asp-Phe-Ile-Leu-Gln-Arg-Lys-Lys

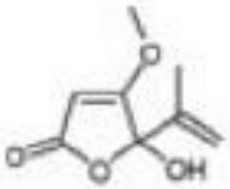
B. QS Inhibitors



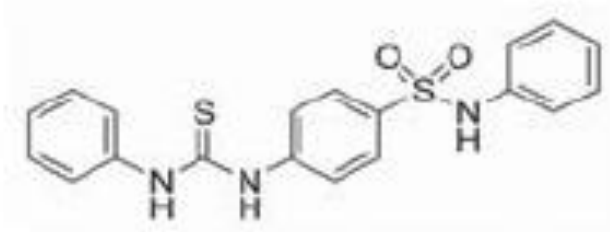
Patulin



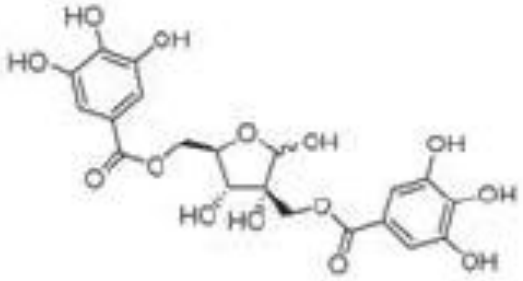
Furanone compound 30



Penicillic acid



N-phenyl-4-(3-phynylthiourido) benzenesulfonamide
LED209



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ORIGINAL RESEARCH

Antibacterial and antibiofilm properties of yttrium fluoride nanoparticles

This article was published in the following Dove Press journal:
International Journal of Nanomedicine
2 November 2012
Number of times this article has been viewed

Jonathan Lellouche[1,2]
Alexandra Friedman[2]
Aharon Gedanken[2]
Ehud Banin[1]

[1]Biofilm Research Laboratory, The Mina and Everard Goodman Faculty of Life Sciences, [2]Kanbar Laboratory for Nanomaterials, Department of Chemistry, Institute for Nanotechnology and Advanced Materials, Bar-Ilan University, Ramat-Gan, Israel

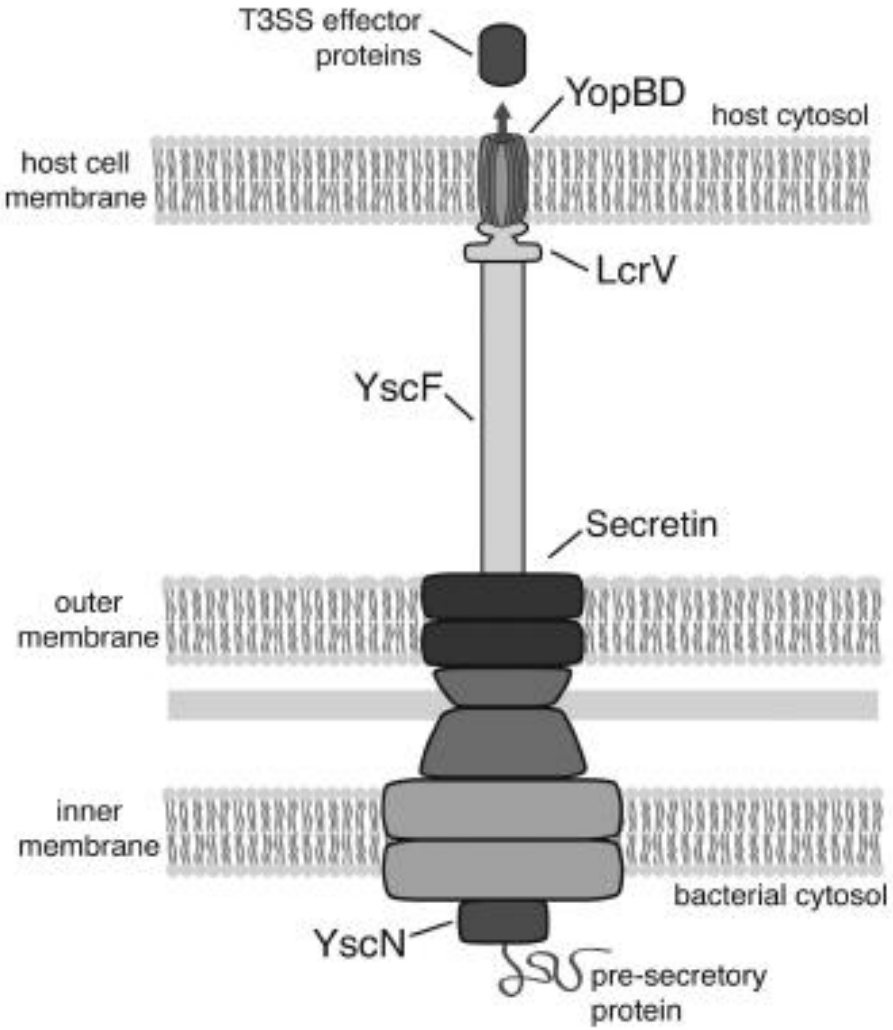
Abstract: Antibiotic resistance has prompted the search for new agents that can inhibit bacterial growth. Moreover, colonization of abiotic surfaces by microorganisms and the formation of biofilms is a major cause of infections associated with medical implants, resulting in prolonged hospitalization periods and patient mortality. In this study we describe a water-based synthesis of yttrium fluoride (YF_3) nanoparticles (NPs) using sonochemistry. The sonochemical irradiation of an aqueous solution of yttrium (III) acetate tetrahydrate [$Y(Ac)_3 \cdot (H_2O)_4$], containing acidic HF as the fluorine ion source, yielded nanocrystalline needle-shaped YF_3 particles. The obtained NPs were characterized by scanning electron microscopy and X-ray elemental analysis. NP crystallinity was confirmed by electron and powder X-ray diffractions. YF_3 NPs showed antibacterial properties against two common bacterial pathogens (*Escherichia coli* and *Staphylococcus aureus*) at a μg/mL range. We were also able to demonstrate that antimicrobial activity was dependent on NP size. In addition, catheters were surface modified with YF_3 NPs using a one-step synthesis and coating process. The coating procedure yielded a homogeneous YF_3 NP layer on the catheter, as analyzed by scanning electron microscopy and energy dispersive spectroscopy. These YF_3 NP-modified catheters were investigated for their ability to restrict bacterial biofilm formation. The YF_3 NP-coated catheters were able to significantly reduce bacterial colonization compared to the uncoated surface. Taken together, our results highlight the potential to further develop the concept of utilizing these metal fluoride NPs as novel antimicrobial and antibiofilm agents, taking advantage of their low solubility and providing extended protection.

Keywords: yttrium fluoride, nanoparticles, biofilms, antibacterial, catheter, sterile surfaces

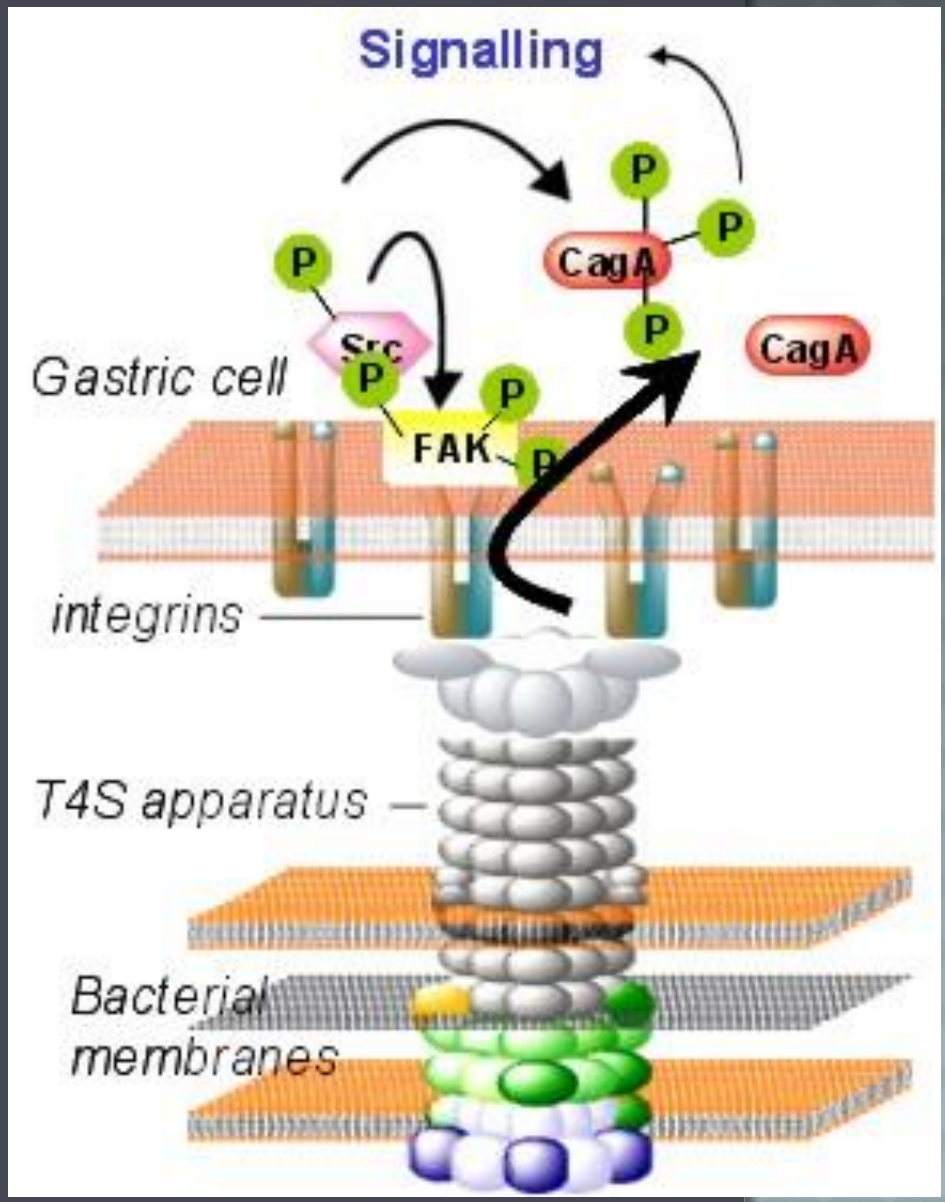
BLOQUEANTES DE FACTORES DE VIRULENCIA

- Sistemas de secreción especializados. Traslocan factores de virulencia a través de la membrana:
  - T2SS: responsable de el ensamblaje de los pili en la suoerficie bacteriana
  - T3SS. Utilizado por patógenos para causar enfermedad, inyecta proteínas efectoras dentro de la célula del huésped evitando la respuesta inmune y causando enfermedad
  - T4SS, trasloca también información genética

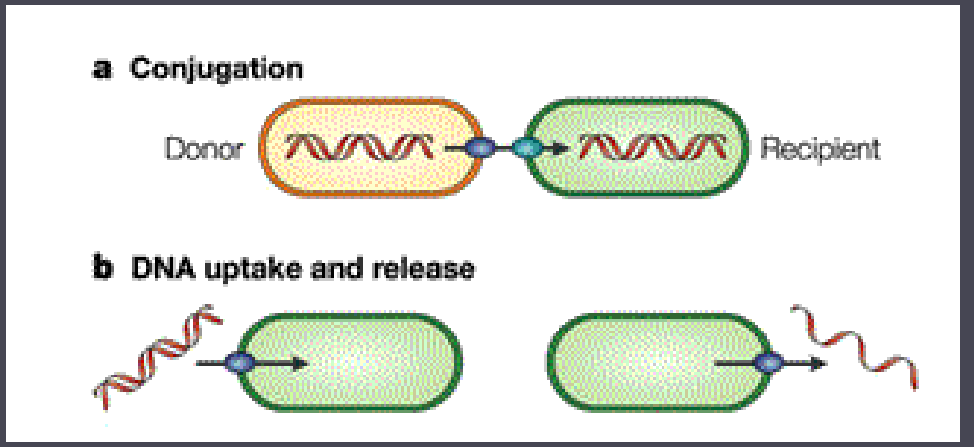
T3SS

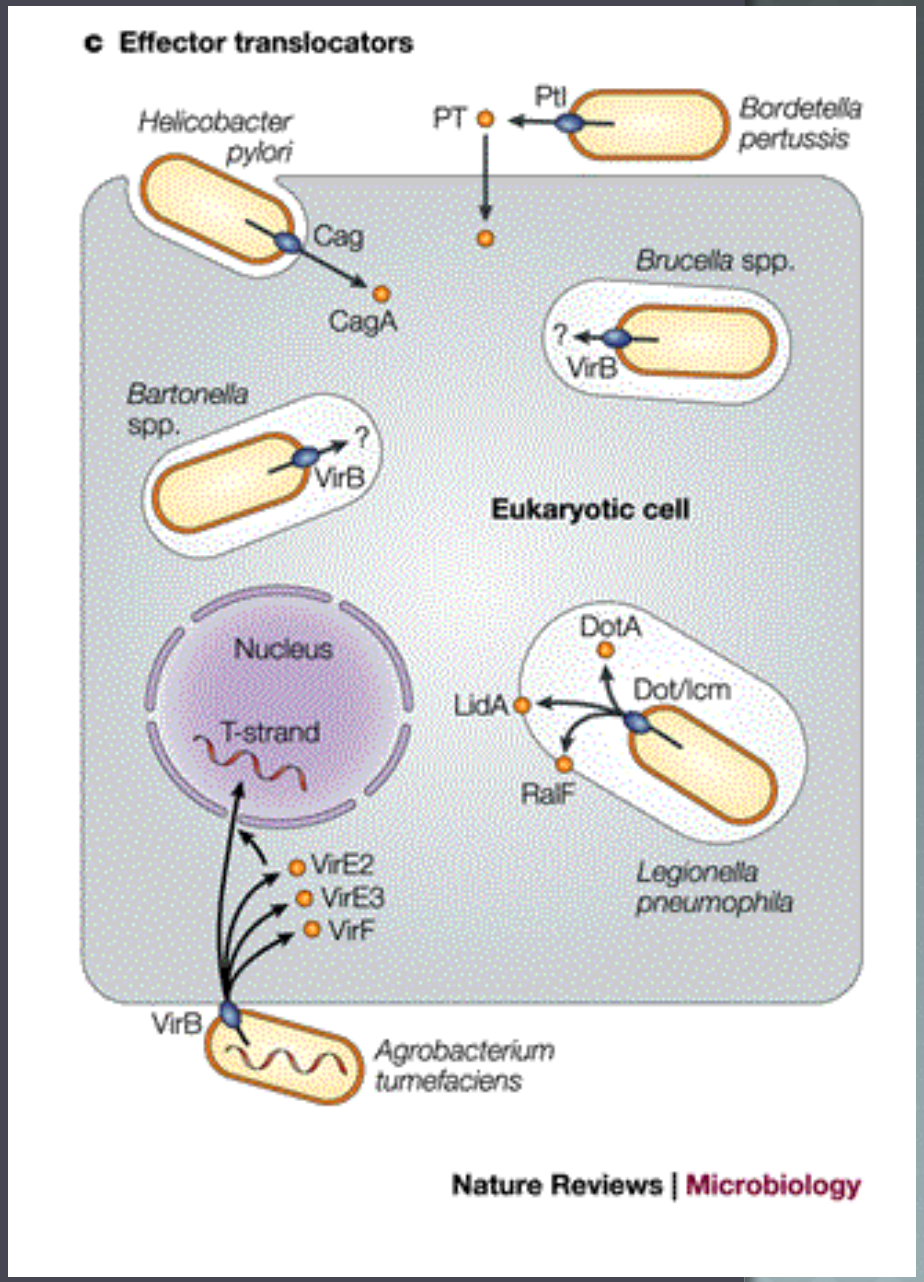

T3SS effector proteins
YopBD
host cytosol
host cell membrane
LcrV
YscF
Secretin
outer membrane
inner membrane
bacterial cytosol
YscN
pre-secretory protein

T4SS


Signalling
P
CagA
Src
Gastric cell
FAK
integrins
T4S apparatus
Bacterial membranes

SISTEMAS SECRECIÓN TIPO IV





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MINIREVIEW

Chemical Inhibitors of the Type Three Secretion System: Disarming Bacterial Pathogens

Miles C. Duncan,[a] Roger G. Linington,[b] and Victoria Auerbuch[a]

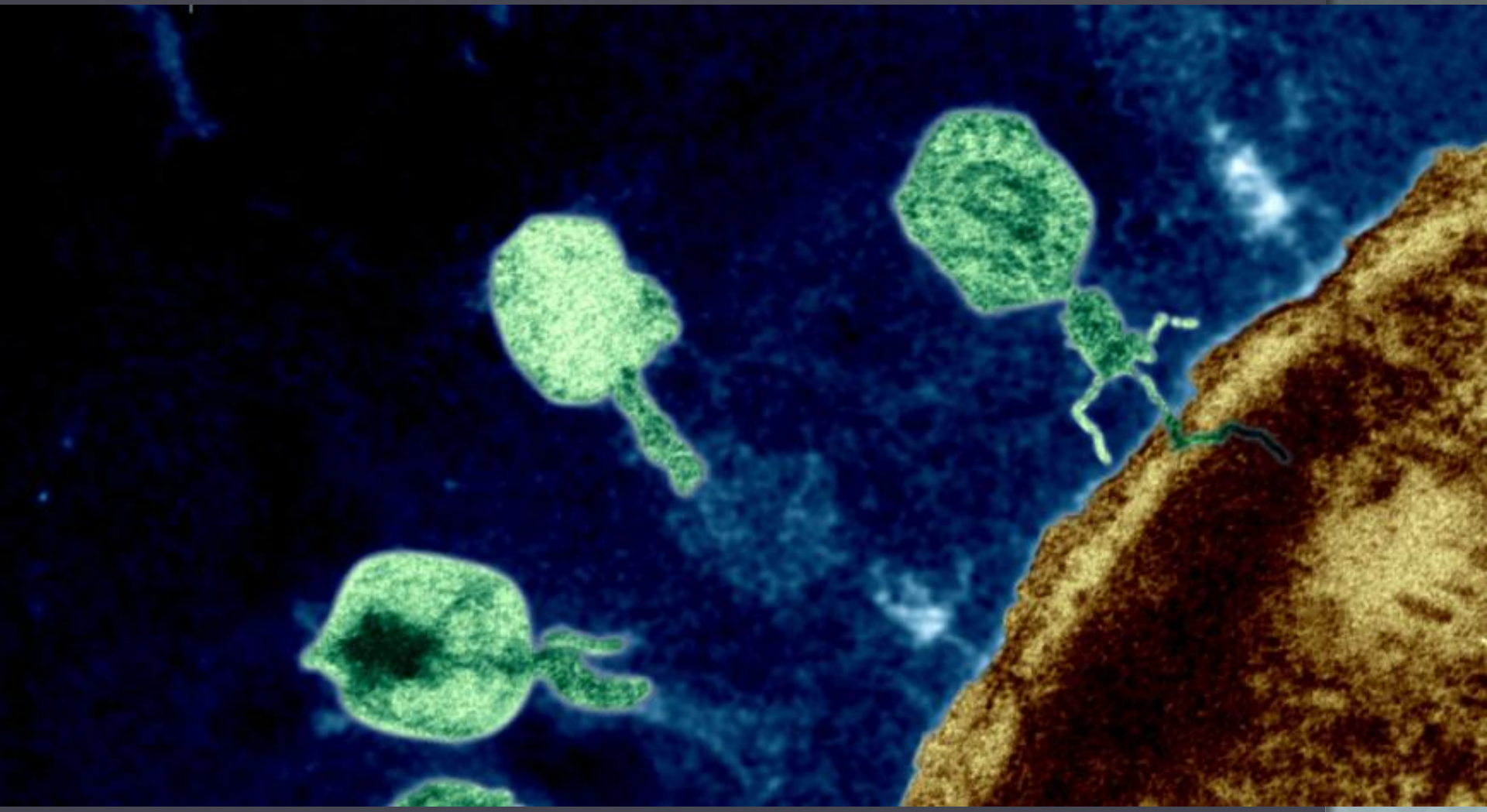
Department of Microbiology and Environmental Toxicology,[a] and Department of Chemistry and Biochemistry,[b] University of California, Santa Cruz, Santa Cruz, California, USA

The recent and dramatic rise of antibiotic resistance among bacterial pathogens underlies the fear that standard treatments for infectious disease will soon be largely ineffective. Resistance has evolved against nearly every clinically used antibiotic, and in the near future, we may be hard-pressed to treat bacterial infections previously conquered by "magic bullet" drugs. While traditional antibiotics kill or slow bacterial growth, an important emerging strategy to combat pathogens seeks to block the ability of bacteria to harm the host by inhibiting bacterial virulence factors. One such virulence factor, the type three secretion system (T3SS), is found in over two dozen Gram-negative pathogens and functions by injecting effector proteins directly into the cytosol of host cells. Without T3SSs, many pathogenic bacteria are unable to cause disease, making the T3SS an attractive target for novel antimicrobial drugs. Interdisciplinary efforts between chemists and microbiologists have yielded several T3SS inhibitors, including the relatively well-studied salicylidene acylhydrazides. This review highlights the discovery and characterization of T3SS inhibitors in the primary literature over the past 10 years and discusses the future of these drugs as both research tools and a new class of therapeutic agents.

TABLE 1 Published type three secretion system inhibitors

Compound name(s)/class(es) (compound no. in this study)	Yr	Reference	Molecular target	Source	Effective against:
Caminoside A (5)	2002	Linington et al. (44)	Unknown	Marine sponge	*E. coli*
Salicylidene acylhydrazide (1)	2003	Kauppi et al. (33)	Unknown; possibly WrbA, Tpx, and FolX	Synthetic compound library	*Yersinia*, *Chlamydia*, *Pseudomonas*, *E. coli*, *Salmonella*, *Shigella*
Clioxanide (2), 2-arylsulfonylamino-benzanilide (3)	2003	Kauppi et al. (33)	Unknown	Synthetic compound library	*Yersinia*
Salicylideneanilide (4)	2005	Gauthier et al. (24)	Unknown	Natural compound library	*E. coli*, *Pseudomonas*
Dipropionate (7), compounds 1 and 4 (6, 8)	2007	Pan et al. (56)	Unknown	Natural/synthetic compound library	*Yersinia*
Guadinomines A-D (9–13), guadinomic acid (14)	2008	Iwatsuki et al. (30)	Unknown	Microbial extracts from soil samples	*E. coli*
Thiazolidinone (15)	2008	Felise et al. (21)	Unknown; possibly secretin	Natural/synthetic compound library	*Yersinia*, *Salmonella*, *Francisella*, *Pseudomonas*
N-Hydroxybenzimidazole (30–65)	2009	Kim et al. (38)	LcrF (transcriptional activator)	Synthetic compound library	*Yersinia*
Compounds 1–8 (16–23)	2010	Harmon et al. (26)	Unknown; possibly a T3SS-host membrane interaction	Natural/synthetic compound library	*Yersinia*
Compounds 1–5 (24–28)	2010	Aiello et al. (2)	Unknown	Natural/synthetic compound library	*Yersinia*, *Pseudomonas*, *Chlamydia*
Aurodox (29)	2011	Kimura et al. (39)	Unknown	Natural compound library	*E. coli*, *Citrobacter rodentium*
7086, 7832, 7812 (66–68)	2011	Swietnicki et al. (75)	YscN (ATPase)	Synthetic compound library	*Yersinia*, *E. coli*

TERAPIA CON FAGOS



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Review article

Bacteriophage: Time to Re-Evaluate the Potential of Phage Therapy as a Promising Agent to Control Multidrug-Resistant Bacteria

*[1]Masoud Sabouri Ghannad, [1]Avid Mohammadi

Abstract

Nowadays the most difficult problem in treatment of bacterial infections is the appearance of resistant bacteria to the antimicrobial agents so that the attention is being drawn to other potential targets. In view of the positive findings of phage therapy, many advantages have been mentioned which utilizes phage therapy over chemotherapy and it seems to be a promising agent to replace the antibiotics. This review focuses on an understanding of phages for the treatment of bacterial infectious diseases as a new alternative treatment of infections caused by multiple antibiotic resistant bacteria. Therefore, utilizing bacteriophage may be accounted as an alternative therapy. It is appropriate time to re-evaluate the potential of phage therapy as an effective bactericidal and a promising agent to control multidrug-resistant bacteria.

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PLOS ONE

Synergistic Action of Gentamicin and Bacteriophage in a Continuous Culture Population of *Staphylococcus aureus*

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Biology Department, Emory University, Atlanta, Georgia, United State of America

Abstract

With the increasing frequency of antibiotic resistance and the decreasing frequency of new antibiotics entering the market, interest has returned to developing bacteriophage as a therapeutic agent. Acceptance of phage therapy, however, is limited by the unknown pharmacodynamics of a replicating agent, as well as the potential for the evolution of resistant bacteria. One way to overcome some of these limitations is to incorporate phage and antibiotics into a dual therapy regimen; however, this increases the complexity of the pharmacodynamics. The aim of this study is to develop an experimental system to evaluate the pharmacodynamics of dual phage-drug therapy. A continuous culture system for *Staphylococcus aureus* is used to simulate the pharmacokinetics of periodic antibiotic dosing alone and in combination with lytic phage. A computer model representation of the system allows further evaluation of the conditions governing the observed pharmacodynamics. The results of this experimental/modeling approach suggest that dual therapy can be more efficacious than single therapies, particularly if there is an overlap in the physiological pathways targeted by the individual agents. In this case, treatment with gentamicin induces a population of cells with a strong aggregation phenotype. These aggregators also have an increased ability to form biofilm, which is a well-known, non-genetic mechanism of drug resistance. However, the aggregators are also more susceptible than the parental strain to the action of the phage. Thus, dual treatment with gentamicin and phage resulted in lower final cell densities than either treatment alone. Unlike in the phage-only treatment, phage-resistant isolates were not detected in the dual treatment.

INMUNOTERAPIA

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Journal of Antimicrobial Chemotherapy

Magic bullets for the 21st century: the reemergence of immunotherapy for multi- and pan-resistant microbes

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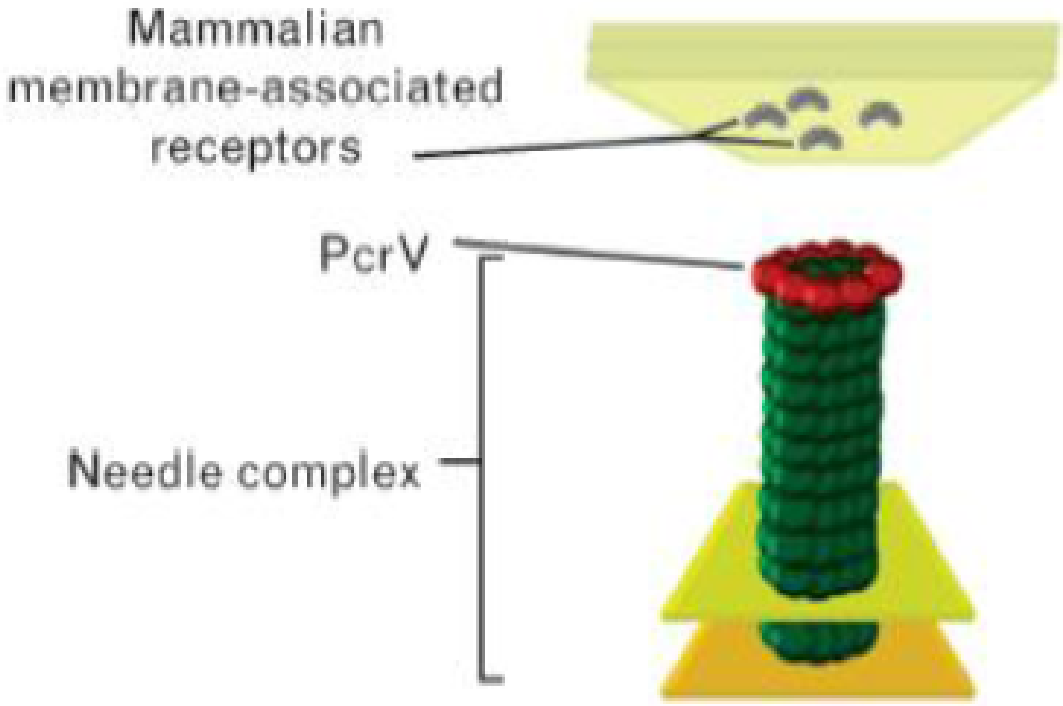
In our current world, antibiotic resistance among pathogenic microbes keeps getting worse with few new antibiotics being pursued by pharmaceutical companies. Modern-day immunotherapies, reminiscent of the serootherapy approaches used in the early days of antimicrobial treatments, are a potential counter-measure, but are usually limited by the narrow spectrum against target antigens. Surprisingly, many multidrug-resistant (MDR) bacteria share a common surface polysaccharide, poly-β-1,6-*N*-acetylglucosamine (PNAG). Natural antibodies to PNAG are present in normal human sera, but are not protective. However, human monoclonal antibodies (MAbs) or polyclonal antisera raised to a deacetylated glycoform of PNAG mediate opsonic killing and protect mice against infections due to all PNAG-positive MDR pathogens tested. An MAb is currently in Phase II clinical trials. These discoveries could lead to utilization of antibodies to PNAG for either therapeutic use in patients infected by PNAG-producing MDR bacteria or prophylactic use in patients at risk of developing MDR infections.

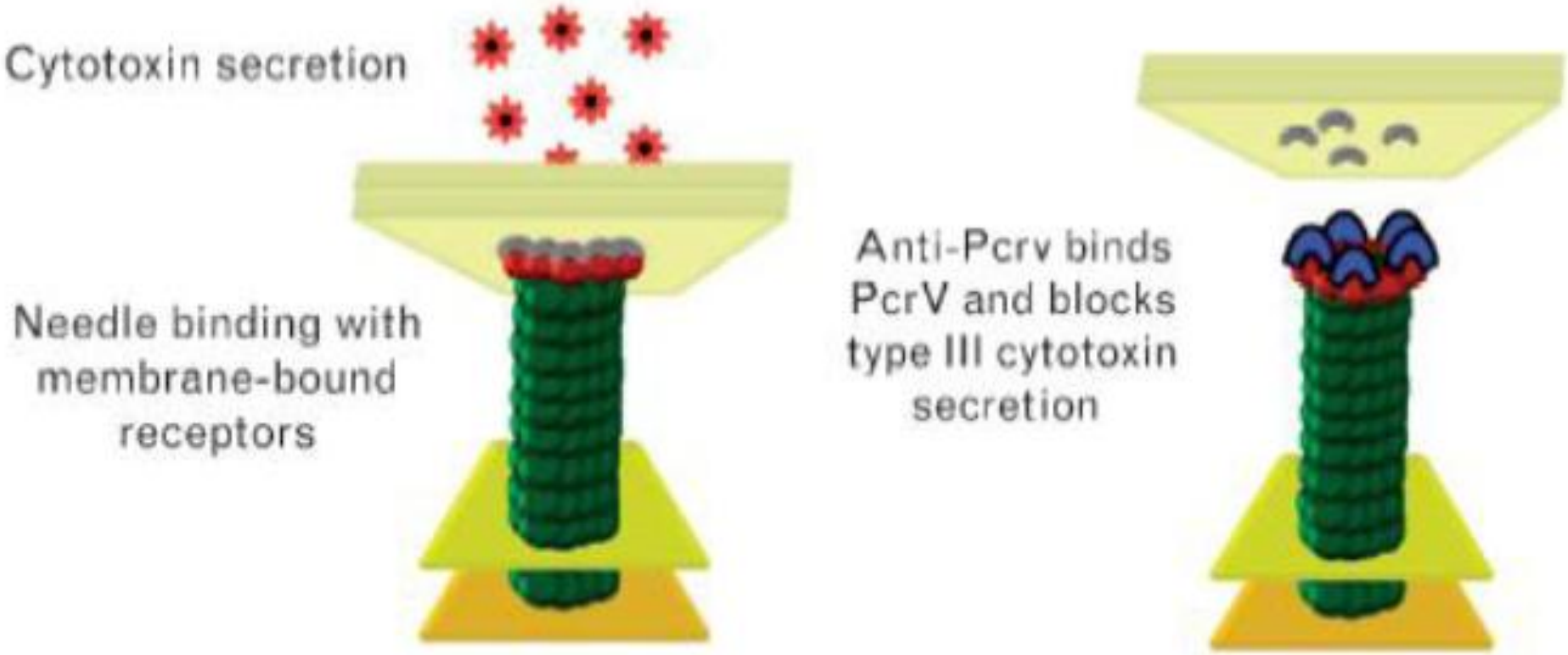
KB001: ANTICUERPO ANTI-PCRV DE *P. AERUGINOSA* (KALOBIOS)

- The type III secretion system involves a needle-like complex that traverses the bacterial bi-layer, crowned by PcrV proteins at the distal tip.

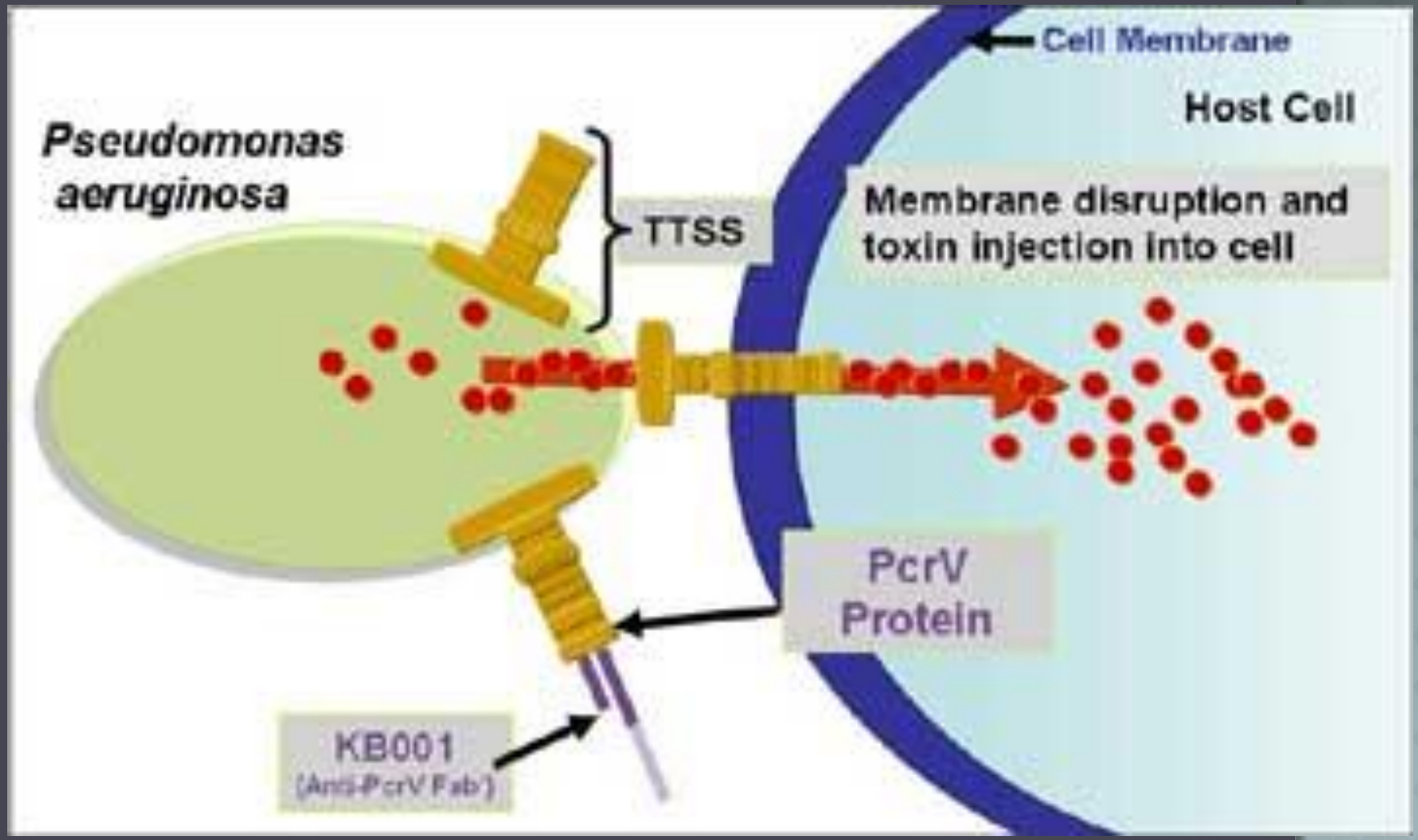
Kubori et al. Science 1998



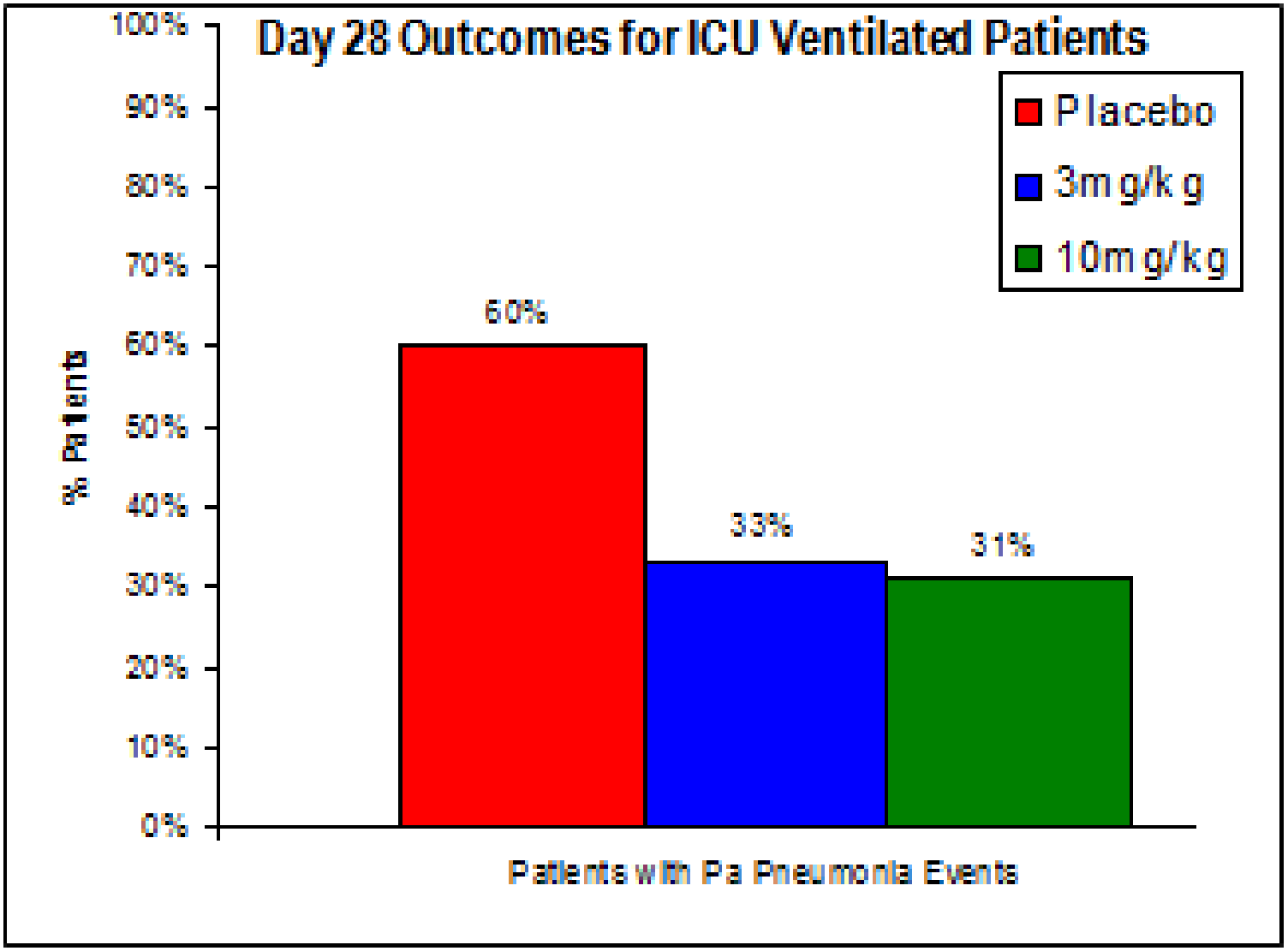
KB001: Anticuerpo anti-PcrV de *P. aeruginosa* (KaloBios)



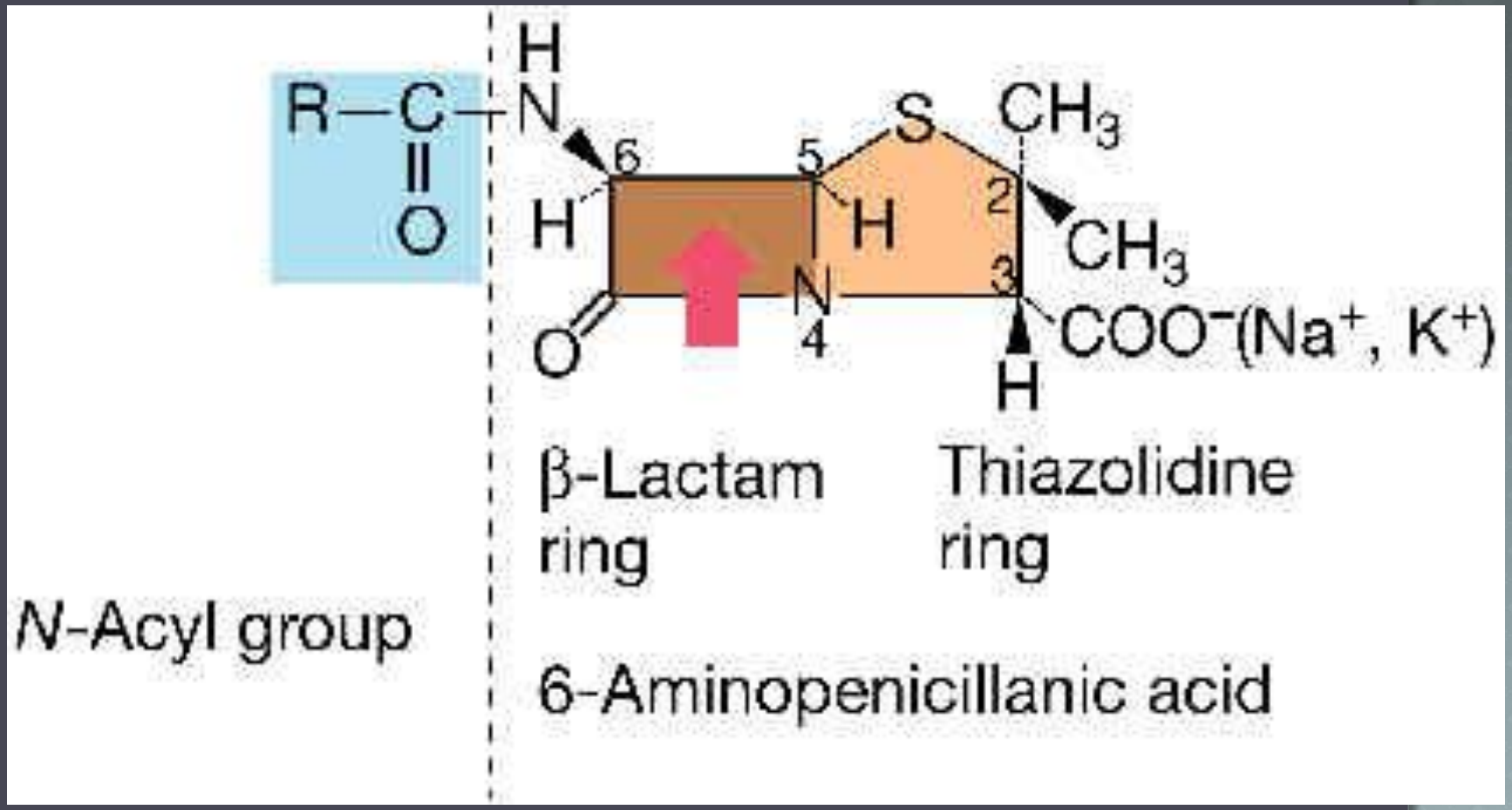
KB001: ANTICUERPO ANTI-PCRV DE *P. AERUGINOSA* (KALOBIOS)

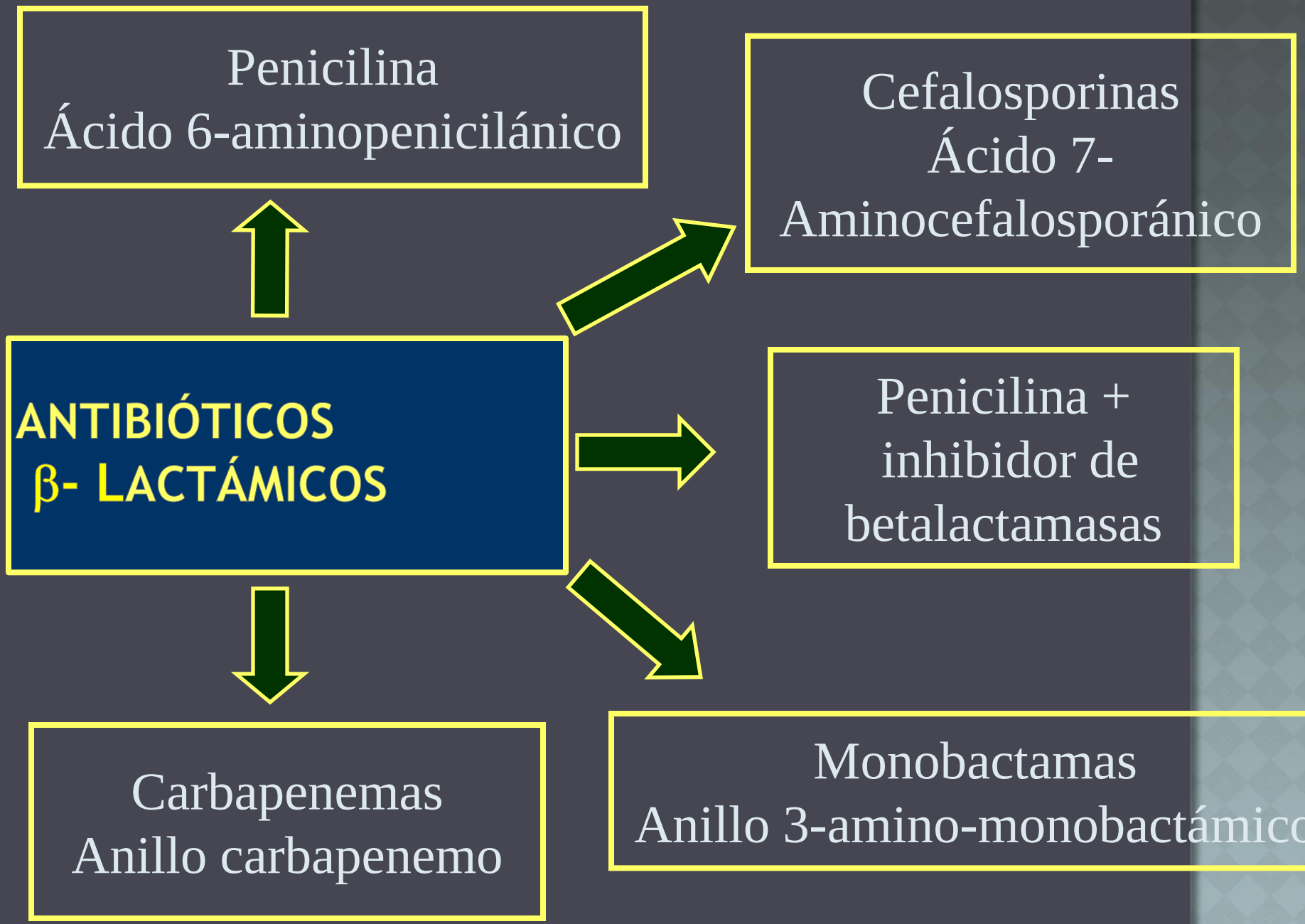


KB001 Reduced *Pa* Pneumonia Events in ICU Ventilated Patients

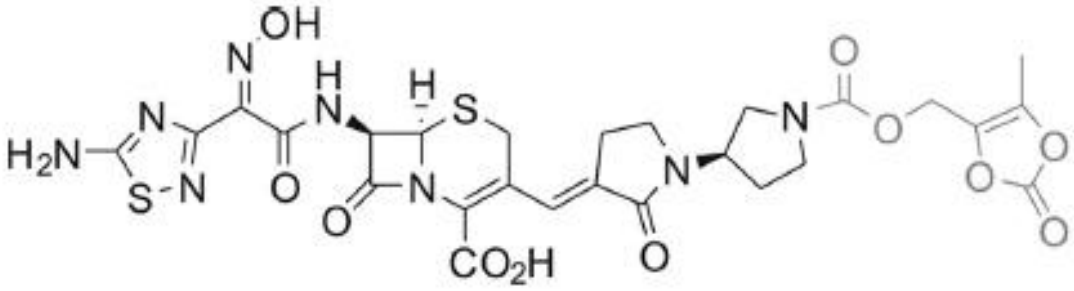


DESARROLLO EN β-LACTÁMICOS

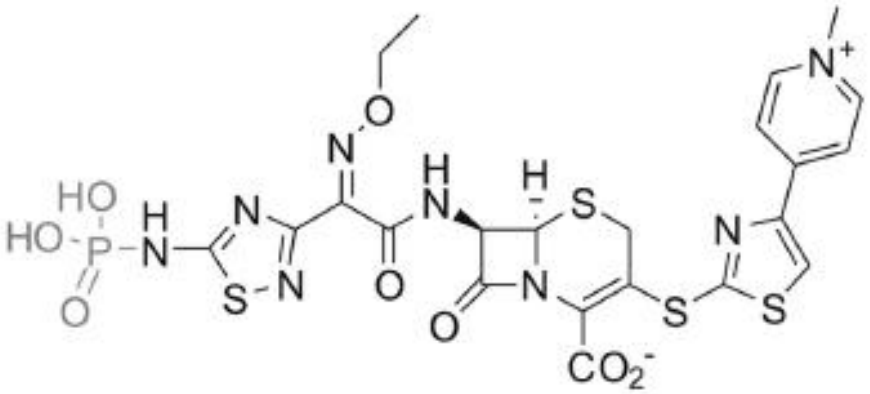



Penicilina
Ácido 6-aminopenicilánico
Cefalosporinas
Ácido 7-
Aminocefalosporánico
ANTIBIÓTICOS
β- LACTÁMICOS
Penicilina +
inhibidor de
betalactamasas
Carbapenemas
Anillo carbapenemo
Monobactamas
Anillo 3-amino-monobactámico

CEFALOSPORINAS ACTIVAS FRENTE A MRSA: CEFALOSPORINAS DE 5ª GENERACIÓN



Ceftobiprole medocaril

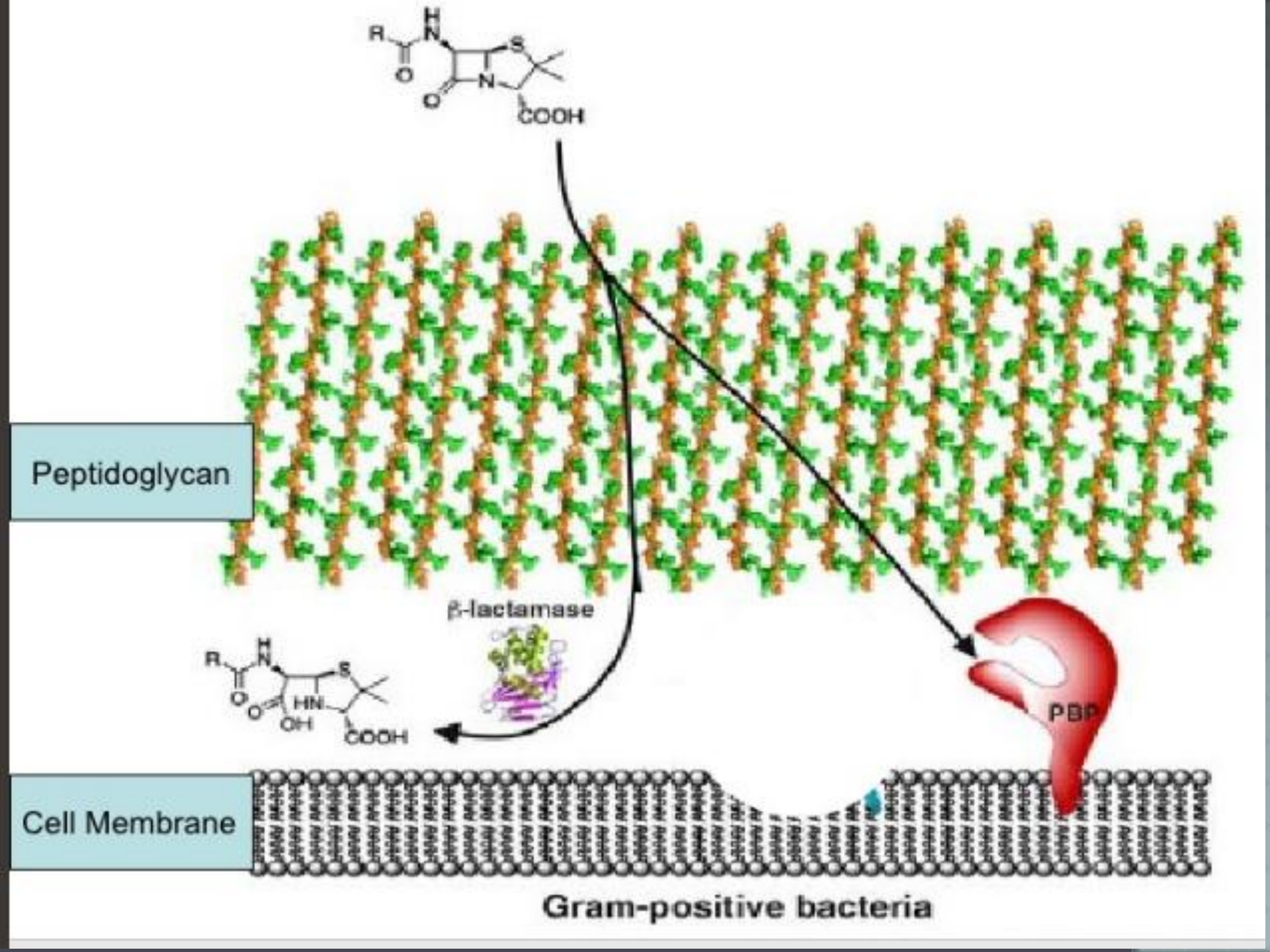


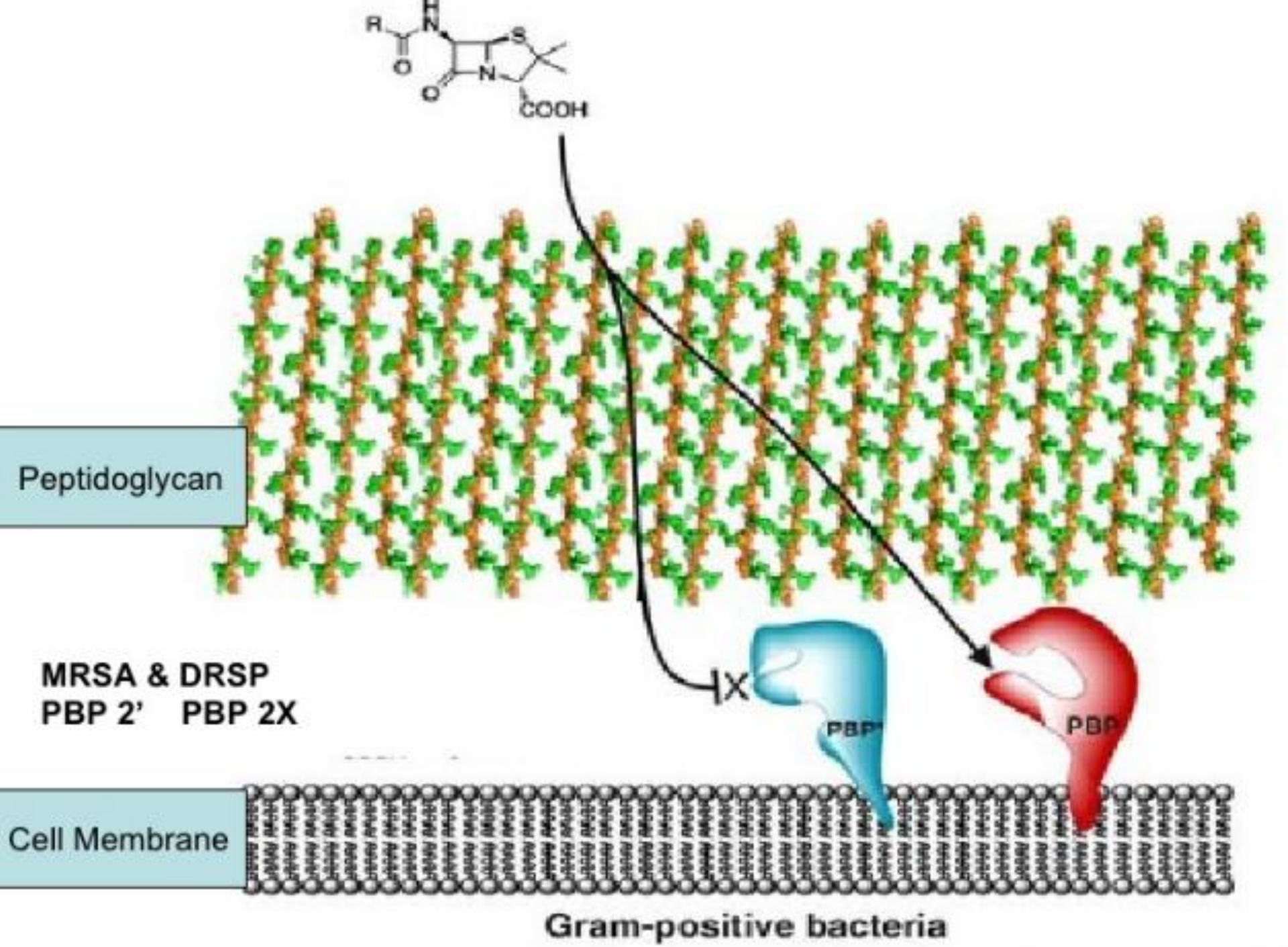
Ceftaroline fosamil

GENERACIONES DE CEFALOSPORINAS

	1ª	2ª	3ª	3ª	4ª	5ª
	Cefazolina	Cefamandol	Ceftriax	Ceftaz	Cefepima	Ceftobiprol
MSSA	+++	+++	+++	+	+++	+++
MRSA	0	0	SD	0	0	+++
MRCoNS	0	0	0	0	0	+++
Strept. spp.	+++	+++	+++	+++	+++	+++
PRSP	SD	SD	++	+	++±	+++
E. cloacae	0	+	SD	+	++±	++±
E. coli	++	++	+++	+++	+++	+++
P. vulgaris	0	+++	SD	+++	+++	+++
P. aeruginosa	0	0	0	++	+++	+++
Serratia spp.	0	++	0	+++	+++	+++
H. influenzae	+	++	+++	+++	+++	+++

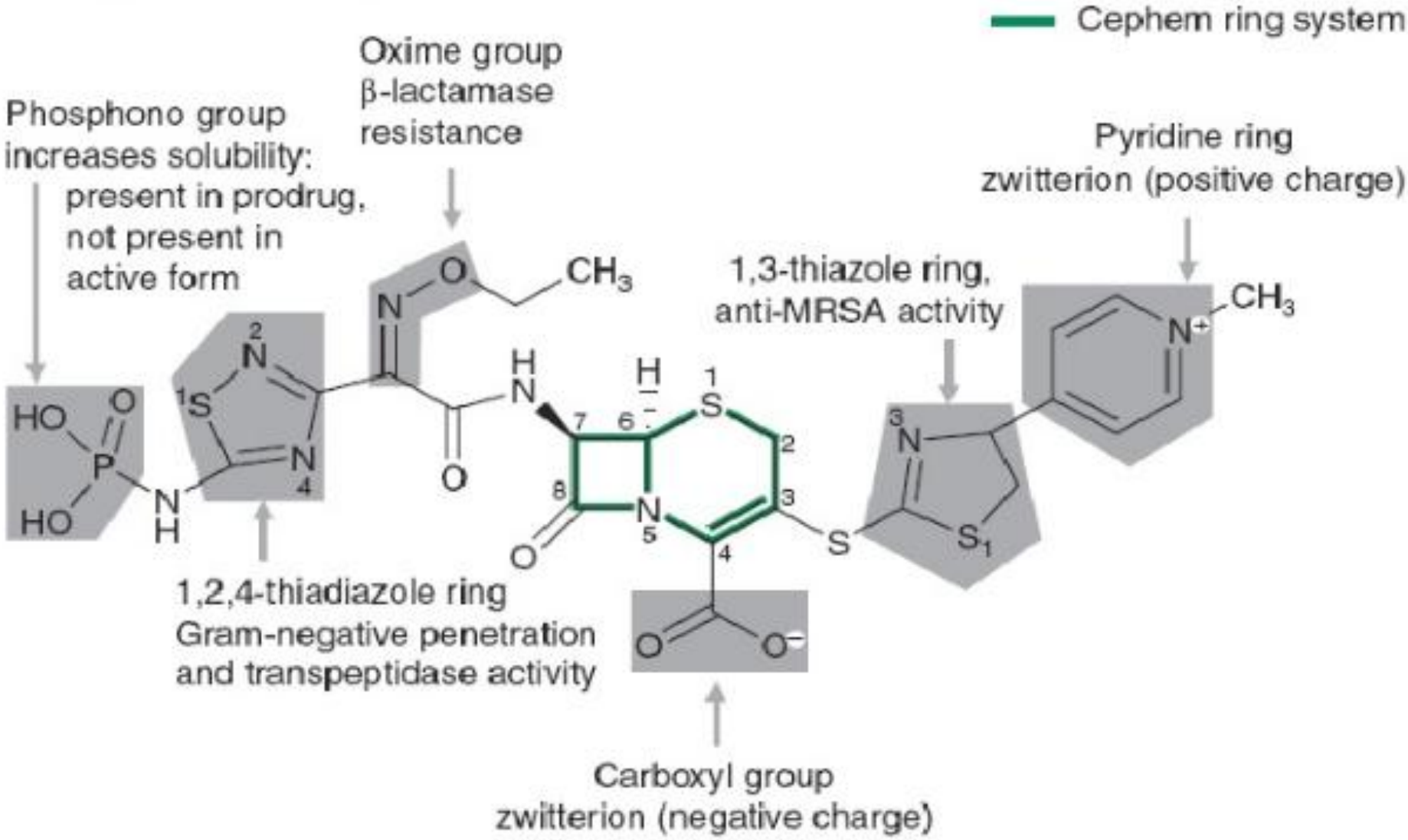
SD = Sin datos. Deresinski, Diagn Microbiol Infect Dis 2008


Peptidoglycan
β-lactamase
PBP
Cell Membrane
Gram-positive bacteria


R
H
N
O
S
N
O
COOH
Peptidoglycan
MRSA & DRSP
PBP 2' PBP 2X
X
PBP
PBP
Cell Membrane
Gram-positive bacteria

SAR of Ceftaroline

Starting point: cefozopran



MICROBIOLOGY

Prodrug	fosamil
PBP 2a IC50	1 μg/ml
MRSA MIC90	2 μg/ml
MSSA MIC90	0.25 μg/ml
Beta-lactamase susceptibility profile	ESBLs, carbapenemases, ampC

Zhanel, et al. Drugs 2009; 69: 809; Vidaillac & Rybak, Pharmcother. 2009;29:511

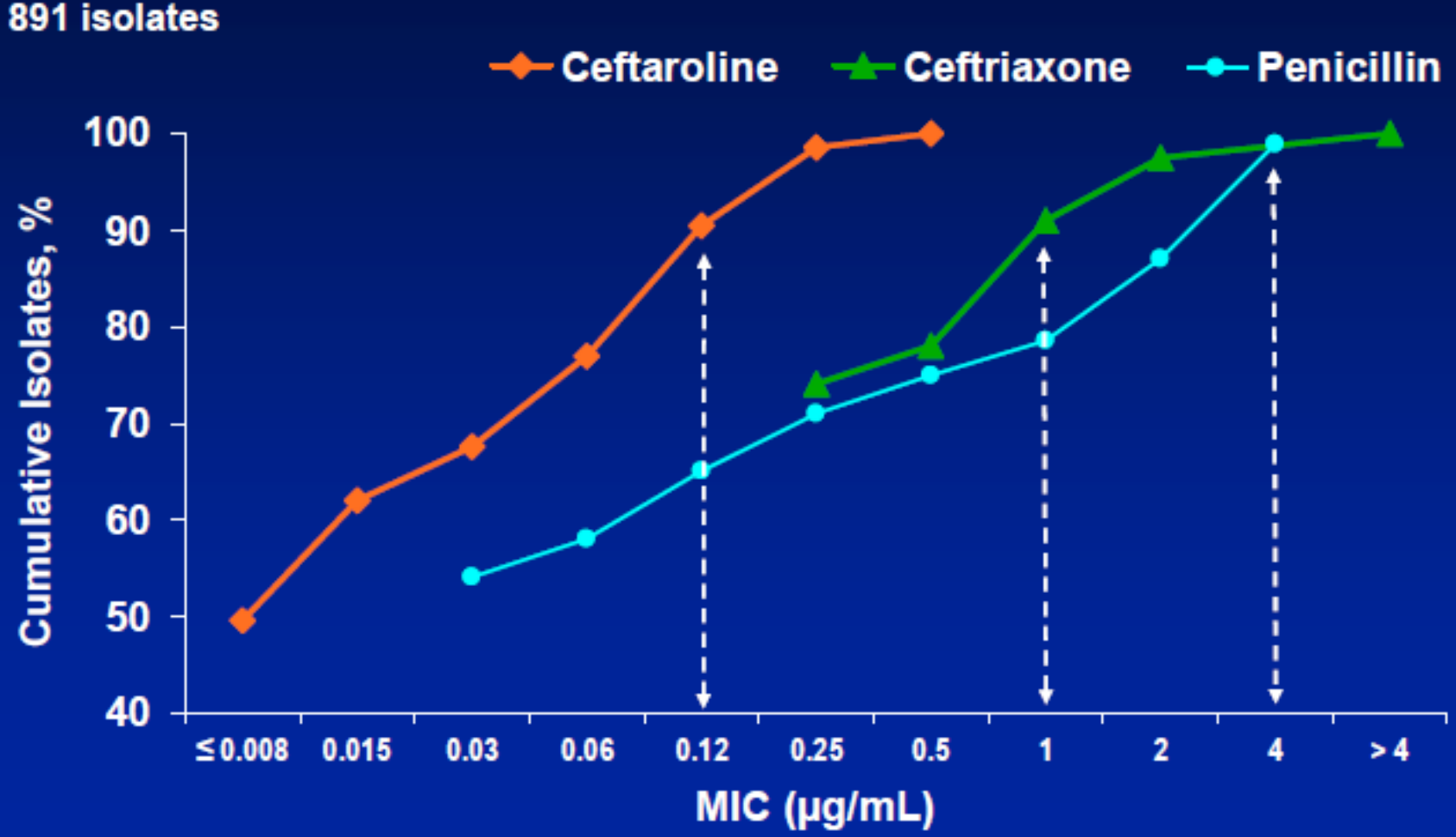
TYPICAL MICS (MG/ML) FOR GRAM-NEGATIVES

	MIC50	MIC90
H. influenzae	<0.02	<0.06
E. coli	0.06	0.12
E. coli (ESBL+)	>32	>32
E. cloacae	0.12	32
E. cloacae (ampC↑)	>32	>32
Ps. aeruginosa	16	>32
Acineto. baumannii	16	>32

Zhanel, et al. Drugs 2009; 69: 809; Vidaillac & Rybak. Pharmcother. 2009;29:51; Sader, et al. AAC 2005;49:3501

Lower MICs than Comparators Against *S. pneumoniae*

US Surveillance Isolates from 2008



Arrows indicate MIC_{90} values for each agent

Jacobs RM et al. *Antimicrob Agents Chemother* 2010 54(6):2716-9.

PHARMACOLOGY

Normal Dose	600 mg q12h
Cmax	20 μg/ml
Protein binding	<20%
Vd	28 L/kg
T1/2	2.6 h
Clearance	49% renal
Renal dose	400 mg q12h

Zhanel, et al. Drugs 2009; 69: 809; Vidaillac & Rybak, Pharmcother. 2009;29:511

Proposed Indications

- Ceftaroline is indicated for patients with cSSSI caused by susceptible isolates of gram-positive and gram-negative microorganisms
  - *S. aureus* (including MSSA and MRSA)
  - *S. pyogenes*, *S. agalactiae*, *S. dysgalactiae*, *S. anginosus* group
  - *E. coli* (ceftazidime-susceptible)
  - *K. pneumoniae*, *K. oxytoca* (ceftazidime-susceptible)
  - *M. morganii* (ceftazidime-susceptible)
- Proposed dose
  - 600 mg q12h IV over 1 hour
  - 400 mg q12h IV over 1 hour for subjects with moderate to severe renal impairment (CrCl < 50mL/min)

Proposed Indications

- Ceftaroline is indicated for patients with CABP caused by susceptible isolates of gram-positive and gram-negative microorganisms:
  - *S. pneumoniae* (including MDRSP and cases with concurrent bacteremia)
  - *S. aureus* (MSSA)
  - *H. influenzae*
  - *H. parainfluenzae*
  - *K. pneumoniae (ceftazidime susceptible)*
  - *E. coli (ceftazidime susceptible)*
- Proposed dose
  - 600 mg q12h IV over 1 hour
  - 400 mg q12h IV over 1 hour for subjects with moderate to severe renal impairment (CrCl < 50 mL/min)

Conclusions

- Ceftaroline is a fifth generation cephalosporin with excellent activity against GPCs including MRSA & DRSP
- Affinity for all PBPs including PBP 2' and PBP 2X
- Not ESBL stable, Not active against Non fermentors
- Administer prodrug as slow IV infusion 600 mg IV BID
- Ceftaroline fosamil acetate (water solubility 100 mg/ml) rapidly converts to active ceftaroline *in vivo*
- Well tolerated, predictable PK
- T > MIC predicts for clinical efficacy, concentration independent or time dependent killing
- Indicated for:
  - Complicated skin & soft tissue infections
  - Community acquired pneumonia

INHIBIDORES DE BL "DE 2ª GENERACIÓN"

CLINICAL MICROBIOLOGY REVIEWS, Jan. 2010, p. 160–201 Vol. 23, No. 1
0893-8512/10/$12.00 doi:10.1128/CMR.00037-09

Three Decades of β-Lactamase Inhibitors

Sarah M. Drawz[1] and Robert A. Bonomo[2,3,4,5]*

Departments of Pathology,[1] Medicine,[2] Pharmacology,[3] and Molecular Biology and Microbiology,[4] Case Western Reserve University School of Medicine, Cleveland, Ohio, and Research Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio[5]

Ac. Clavulánico
+
Amoxicilina

Tazobactam
+
Piperacilina

Sulbactam
+
Ampicilina

INHIBIDORES DE BL "DE 2ª GENERACIÓN"

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Sarah M. Drawz[1] and Robert A. Bonomo[2,3,4,5]*

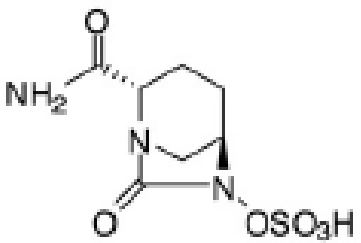
Departments of Pathology,[1] Medicine,[2] Pharmacology,[3] and Molecular Biology and Microbiology,[4] Case Western Reserve University School of Medicine, Cleveland, Ohio, and Research Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio[5]

INHIBIDORES DE β-LACTAMASAS

		Clase β-lactamasa			
		A	B	C	D
BL	BLI-489	+	?	+	+
	BAL 30376	?	+	?	?
No BL	N avibactam	+	?	+	+
	ME1071	?	+	?	?

INHIBIDORES DE BETA-LACTAMASAS NO BETALACTÁMICOS

- NXL104 (=AVE1330A).
  - Inhibidor no B-lactámico
  - Diazabiciclo (3.2.1) octanona
  - Inhibe a BL clase A, C y D.
  - Combinado con:
    - Ceftazidima
    - Ceftarolina



26 NXL104

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Activity of Ceftaroline-Avibactam Tested against Gram-Negative Organism Populations, including Strains Expressing One or More β-Lactamases and Methicillin-Resistant *Staphylococcus aureus* Carrying Various Staphylococcal Cassette Chromosome *mec* Types

Mariana Castanheira,[a] Helio S. Sader,[a] David J. Farrell,[a]* Rodrigo E. Mendes,[a] and Ronald N. Jones[a,b]

JMI Laboratories, North Liberty, Iowa, USA,[a] and Tufts University School of Medicine, Boston, Massachusetts, USA[b]

TABLE 1 Frequency distributions for ceftaroline-avibactam tested against β-lactamase-producing *Enterobacteriaceae* grouped by enzyme type, nonfermentative Gram-negative bacilli, and *S. aureus* strains, including MRSA with defined SCC*mec* types

Organism and type of enzyme or SCC*mec* (no. of strains tested)	No. of strains (cumulative % inhibited) inhibited at a ceftaroline-avibactam[a] MIC (μg/ml) of:											
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥32
Enterobacteriaceae (272)												
ESBL (33)	1 (3.0)	3 (12.1)	11 (45.4)	11 (79.8)	4 (90.9)	0 (90.9)	3 (100.0)					
Plasmid-mediated AmpC (36)		4 (11.1)	8 (33.3)	14 (72.2)	8 (94.4)	2 (100.0)						
Ceftazidime-resistant AmpC-producing species (27)			3 (11.1)	13 (59.3)	7 (85.2)	3 (96.3)	1 (100.0)					
Serine-carbapenemase (32)			1 (3.1)	3 (12.5)	3 (21.9)	15 (68.7)	6 (87.5)	2 (93.7)	2 (100.0)			
Serine-carbapenemase in AmpC-producing species (37)			1 (2.7)	2 (5.4)	6 (24.3)	8 (45.9)	13 (81.1)	6 (97.3)	1 (100.0)			
Metallo-β-lactamase (8)												8 (100.0)
Multiple β-lactamases (57)	1 (1.7)	1 (3.5)	24 (45.6)	12 (66.7)	12 (87.7)	3 (98.2)	1 (100.0)					
Multiple β-lactamases including KPC (15)					3 (20.0)	7 (66.7)	3 (86.7)	1 (93.3)	1 (100.0)			
Multiple β-lactamases in AmpC-producing species (27)				4 (14.8)	6 (37.0)	5 (55.6)	5 (74.1)	6 (96.3)	1 (100.0)			
P. aeruginosa (25)								3 (12.0)	3 (24.0)	1 (28.0)	7 (56.0)	11 (100.0)
Acinetobacter spp. (24)						1 (4.2)	1 (8.3)	2 (16.7)	3 (29.2)	0 (29.2)	4 (45.8)	13 (100.0)
S. aureus (110)					10 (9.1)	28 (34.5)	45 (75.4)	26 (99.1)	1 (100)		-	
SCC*mec* type I (19)							1 (5.3)	17 (94.7)	1 (100.0)			
SCC*mec* type II (20)						2 (10.0)	15 (85.0)	3 (100.0)				
SCC*mec* type III (20)						2 (10.0)	12 (70.0)	6 (100.0)				
SCC*mec* type IV (41)						24 (58.5)	17 (100.0)					

[a] Ceftaroline combined with avibactam at a fixed concentration of 4 μg/ml.

Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America

Helen W. Boucher,[1] George H. Talbot,[2] John S. Bradley,[3,4] John E. Edwards, Jr,[5,6,7] David Gilbert,[8] Louis
Michael Scheld,[11] Brad Spellberg,[5,6,7] and John Bartlett[12]

Clinical Infectious Diseases 2009; 48:1–1

E *Enterococcus faecium*

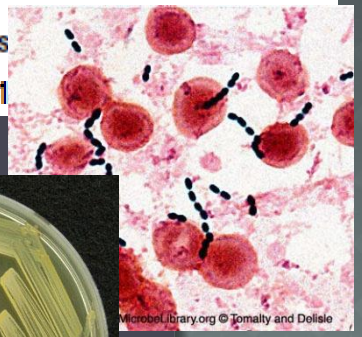
S *Staphylococcus aureus*

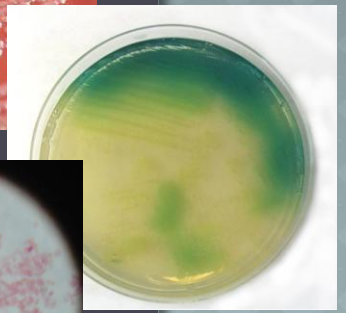
K *Klebsiella pneumoniae*

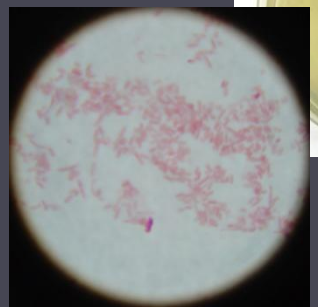
A *Acinetobacter baumannii*

P *Pseudomonas aeruginosa*

E *Enterobacter spp.*







E

S

Nuevos:

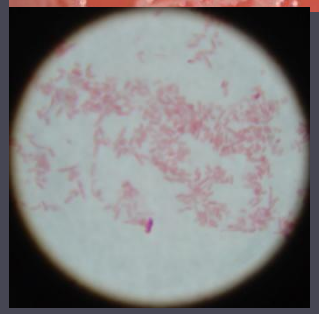
- Glicopéptidos
- Cefalosporinas
- Carbapenémicos

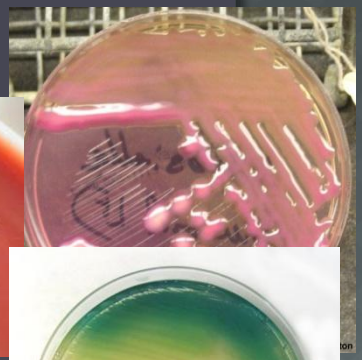
K

A

P

E





Nuevos:

- Fluorquinolonas
- Aminometil tetraciclinas
- Penémicos y carbapenémicos
- Inhibidores de BL: 2ª generación

EUROPEAN ANTIBIOTIC AWARENESS DAY

A European Health Initiative

Tratamiento antibiótico dirigido