Novel antibiotics - Multiresistant organisms

Joost Wiersinga, MD PhD

Academic Medical Center, Amsterdam

Infectious Diseases, Center Experimental Molecular Medicine

ISICEM2018, Brussels, March 21, 2018

Disclosures

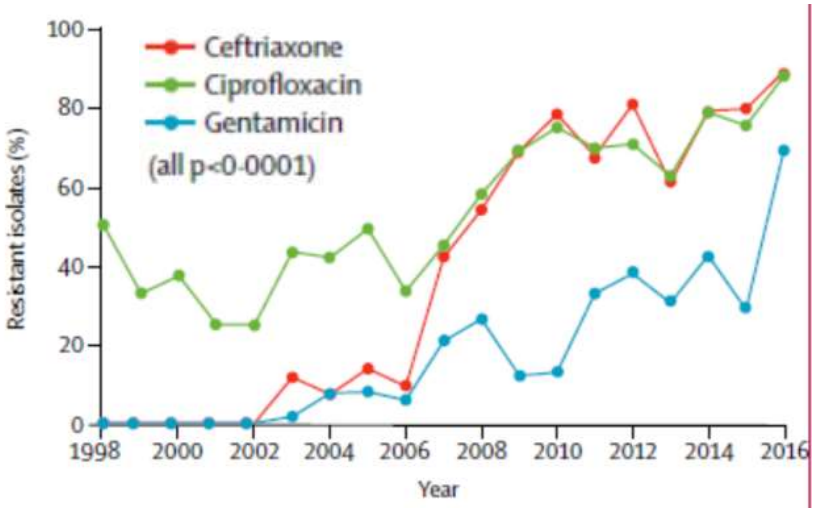
- Received funding from:
    - Netherlands Organisation for Scientific Research (NWO)
    - Netherlands Organisation for Health Research and Development (ZonMW)
    - Academic Medical Center, Amsterdam
    - European Union H2020 programme

Trends in antimicrobial resistance in bloodstream infection isolates at a large urban hospital in Malawi (1998–2016): a surveillance study

Patrick Musicha, Jennifer E Cornick, Naor Bar-Zeev, Neil French, Clemens Masesa, Brigitte Denis, Neil Kennedy, Jane Mallewa, Melita A Gordon, Chisomo L Msefula, Robert S Heyderman, Dean B Everett, Nicholas A Feasey

- 1998-2016: 30000 pathogens isolated from 195000 blood cultures
- ESBL resistance rose to 30% in *E. coli* and 90% in *Klebsiella* spp
- Resistance to ciprofloxacin rose to 31% in *E. coli* and to 70% in *Klebsiella* spp
- By contrast, more than 92% of common Gram-positive pathogens remain susceptible to either penicillin or chloramphenicol.
- MRSA represented 18% of *S. aureus* isolates
- These results highlight the growing challenge of bloodstream infections that are effectively impossible to treat in this resource-limited setting.

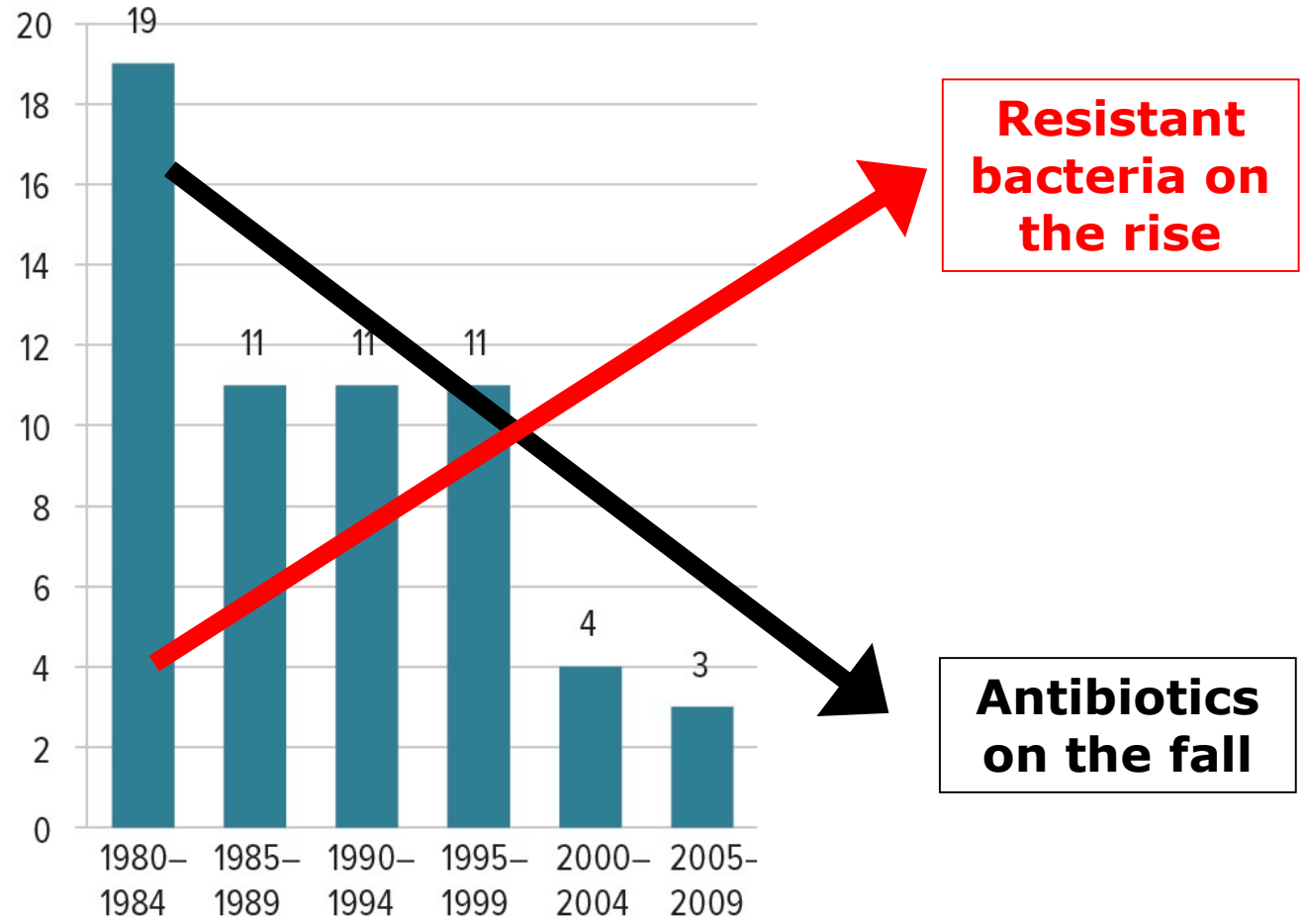
K. pneumoniae



Musicha, Lancet Infect Dis, 2017

A perfect storm…

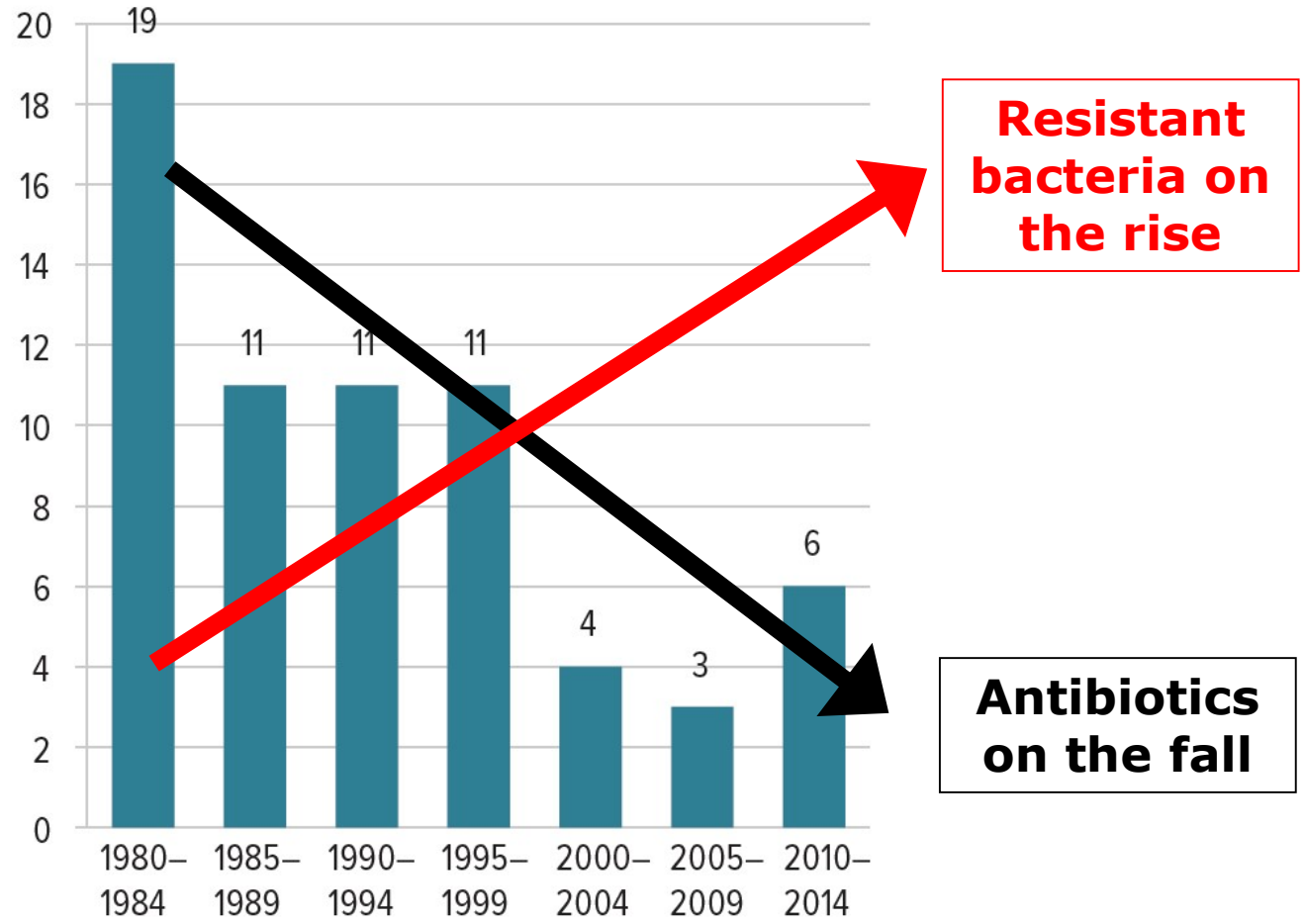
Figure 3 Number of Antibacterial New Drug Application Approvals Versus Year Intervals



Kuehn, JAMA, 2011; Ventola; P&T, 2015; Till, Trends Microbiol, 2014

A perfect storm…

Figure 3 Number of Antibacterial New Drug Application Approvals Versus Year Intervals



Kuehn, JAMA, 2011; Ventola; P&T, 2015; Till, Trends Microbiol, 2014

Agenda

- Novel antibiotics for Gram-positive infections
- Novel antibiotics for Gram-negative infections
- Future perspective: novel approaches for antibiotic development

Novel antibiotics for Gram-positive infections

Novel antibiotics for Gram-positive infections

- Oxazolidinonen
  - Tedizolid (“similar to linezolid”)

  Inhibits synthesis of proteins (binds to ribosome)

- Lipoglycopeptiden
  - Oritavancine (“similar to vancomycin”)
  - Dalbavancine (“similar to teicoplanin”)

  Inhibitis synthesis of peptidoglycan

Crotty, J Clin Microbiol, 2016

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

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

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.

ORIGINAL ARTICLE

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

G. Ralph Corey, M.D., Heidi Kabler, M.D., Purvi Mehra, M.D., Sandeep Gupta, M.D.,

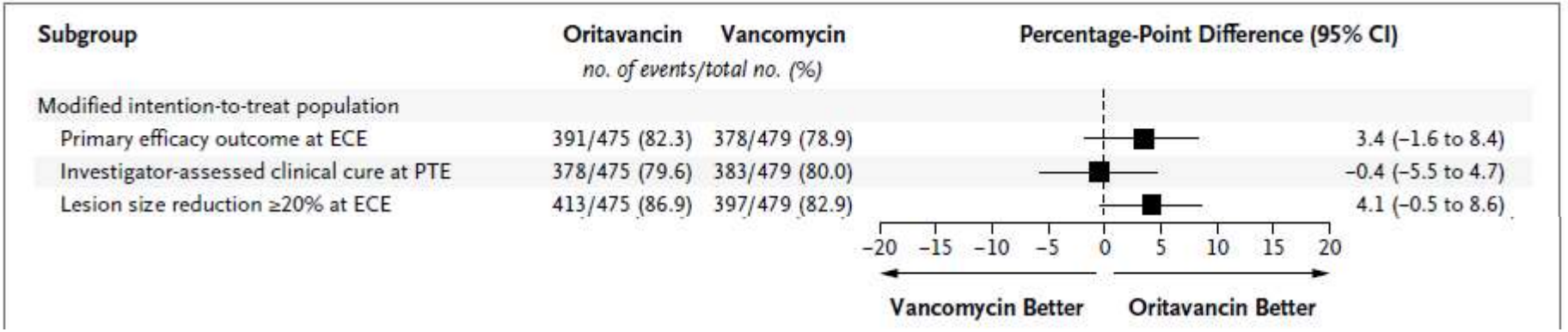
Moran, Lancet Infect Dis, 2014; Boucher, NEJM, 2014; Corey, NEJM, 2014

ORIGINAL ARTICLE

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

G. Ralph Corey, M.D., Heidi Kabler, M.D., Purvi Mehra, M.D., Sandeep Gupta, M.D.,

- 2011-2012, 954 patients mostly from US and India
- Patients with cellulitis, abscesses, wound infections. 63% admitted to hospital
- Intervention: Oritavancin 1x i.v. vs vancomycin 2dd1 i.v. for 7-10 days
- Primary endpoint (composite): early clinical response (decrease skin lesion, no fever, no rescue antibiotics needed) after 48 to 72 hrs.



New antibiotics for Gram-positive infections (MRSA, VRE): what will be its use in clinical practice?

	Dose	Adjustment kidney	Indication	Costs per dose
Tedizolid	oral and i.v. once daily 6 days	No	ABSSSI	$ 250
Dalbavancin	i.v. once weekly 2 weeks	Yes	ABSSI	$ 1788
Oritavancin	i.v. once	No	(ABSSI)	follows
Vancomycin	oral en i.v. 2-3 x per day	Yes	ABSSI, endocarditis, pneumonia, osteomyelitis,..	$ 3,80
Linezolid	oral en i.v. twice daily	No	ABSSI, bacteriemia, pneumonia, osteomyelitis,..	$ 86
Daptomycin	i.v. Once daily 1-6 weeks	Yes	ABSSI, bacteriemia, osteomyelitis,..	$ 404
Ceftaroline	i.v. twice daily	No	ABSSI, pneumonia,..	$ 75

Novel antibiotics for Gram-negative infections

New β-Lactamase Inhibitors: a Therapeutic Renaissance in an MDR World

Sarah M. Drawz,[a] Krisztina M. Papp-Wallace,[b,c] Robert A. Bonomo[b,c,d,e]

TABLE 1 MICs of β-lactam and β-lactam-avibactam combinations against select pathogens[a]

Pathogen	MIC (μg/ml)[b]					
	CAZ	CAZ-AVI	CPT	CPT-AVI	ATM	ATM-AVI
K. pneumoniae with OXA-48	256/512	0.25/0.5				
K. pneumoniae with CTX-M-15	8/64	0.06/0.25				
K. pneumoniae with KPC-2	≥512/≥512	0.25/1			≥512/≥512	≤0.06/≤0.06
E. coli with ESBL	16/64	0.12/0.25				
E. coli with AmpC	16/64	0.12/0.5				
E. coli with OXA-48	4	<0.008				
E. coli with IMP-1	256	64				
Enterobacteriaceae with multiple β-lactamases, including KPC-2			>64/>64	0.5/2		
Enterobacteriaceae with multiple β-lactamases, including AmpC			256/>256	0.5/2		
Enterobacteriaceae with VIM	64–512	64–512			0.25–256	0.12–0.5
P. aeruginosa	8/64	4/8	>64/>64	16/>32	16/32	8/32
P. aeruginosa with ESBL PER-1	128/128	4/16				
A. baumannii			>64/>64	32/>32		
A. baumannii with PER-1, OXA-51, and OXA-58	128/≥512	32/256				
S. aureus			1/2	1/2		

[a] Data were adapted from references 15, 16, 19, 20, 21, and 24. Avibactam was added at 4 μg/ml. Abbreviations: CAZ, ceftazidime; AVI, avibactam; CPT, ceftaroline; ATM, aztreonam.

- Active against ESBL, KPC, OXA-48, but not against all Enterobacteriaceae and Acinetobacters.

Drawz, Antimicrob Agents Chemother, 2014

LANCET

Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

Antoni Torres, Nanshan Zhong, Jan Pachl, Jean-François Timsit, Marin Kollef, Zhangjing Chen, Jie Song, Dianna Taylor, Peter J Laud, Gregory G Stone, Joseph W Chow

LANCET

Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI)

Florian M Wagenlehner, Obiamiwe Umeh, Judith Steenbergen, Guojun Yuan, Rabih O Darouiche

JAMA

new

Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection

The TANGO I Randomized Clinical Trial

Keith S. Kaye, MD, MPH; Tanaya Bhowmick, MD; Symeon Metallidis, MD; Susan C. Bleasdale, MD; Olexiy S. Sagan, MD; Viktor Stus, MD, PhD; Jose Vazquez, MD; Valerii Zaitsev, PhD; Mohamed Bidair, MD; Erik Chorvat, MD; Petru Octavian Dragoescu, MD; Elena Fedosiuk, MD; Juan P. Horcajada, MD, PhD; Claudia Murta, MD; Yaroslav Sarychev, MD; Ventsislav Stoev, MD; Elizabeth Morgan, BS; Karen Fusaro, BS; David Griffith, BS; Olga Lomovskaya, PhD; Elizabeth L. Alexander, MD; Jeffery Loutit, MBChB; Michael N. Dudley, PharmD; Evangelos J. Giamarellos-Bourboulis, MD, PhD

Torres, Lancet Infect Dis, 2017; Wagenlehner, Lancet, 2015; Kaye, JAMA, 2018

Novel antibiotics: phase II/III

• Relebactam/Primaxin	Carbapenem + BLI	
RPX7009	Carbapenem + BLI	
S-649266	Cefalosporine	
• Plazomicin	Aminoglycoside	cUTI
• Delafloxacin	Fluorochinolon	CAP
• Eravacycline	Tetracycline	cIAI, cUTI
Omadacycline	Tetracycline	CAP
• Solithromycin	Macrolide	CAP

Novel approaches: 5 examples

ARTICLE

doi:10.1038/nature14098

A new antibiotic kills pathogens without detectable resistance

Losee L. Ling[1]*, Tanja Schneider[2,3]*, Aaron J. Peoples[1], Amy L. Spoering[1], Ina Engels[2,3], Brian P. Conlon[4], Anna Mueller[2,3], Till F. Schäberle[3,5], Dallas E. Hughes[1], Slava Epstein[6], Michael Jones[7], Linos Lazarides[7], Victoria A. Steadman[7], Douglas R. Cohen[1], Cintia R. Felix[1], K. Ashley Fetterman[1], William P. Millett[1], Anthony G. Nitti[1], Ashley M. Zullo[1], Chao Chen[4] & Kim Lewis[4]

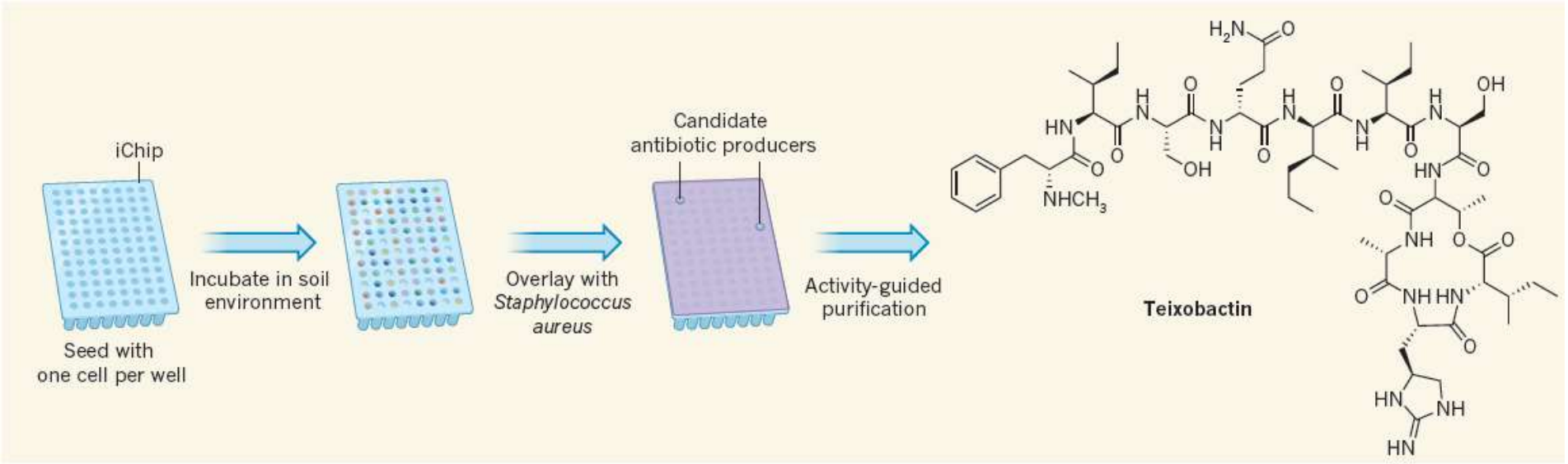
- Teixobactin: a novel antibiotic that solves the antibiotic crisis?

- Classic approach: Most antibiotics are released by soil bacteria in order to keep competitors at a distance. Since the 1950s soil bacteria are screened for these mediators.

- Problem: Only 1% of soil bacteria are culturable.. Lack of discovery of new compounds..

Ling, Nature, 2015

- New method to culture bacteria with the iChip



- Teixobactin inhibits cell wall synthesis by binding to two highly conserved motifs of lipid II (precursor peptidoglycan) + lipid III (precursor cell wall teichoic acid).

- Superior efficacy compared to vancomycin in MRSA mouse model.
  No mutants of *S. aureus* or *M. tuberculosis* resistant to teixobactin obtained.

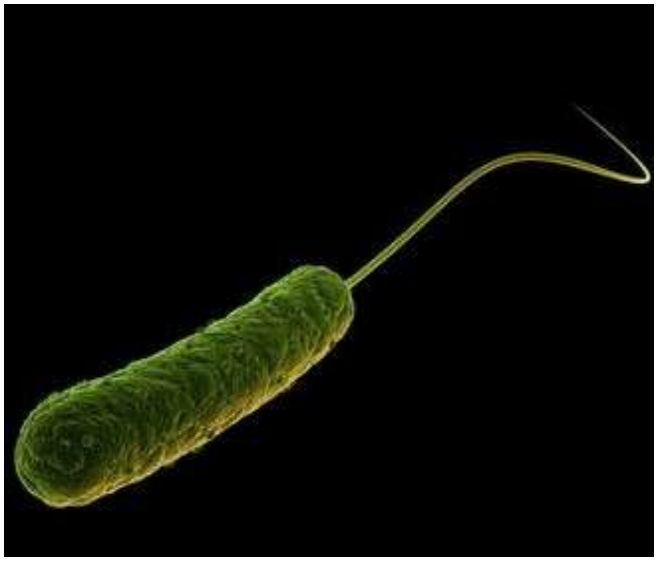
- Future: first studies in man scheduled for 2018?

Ling, Nature, 2015

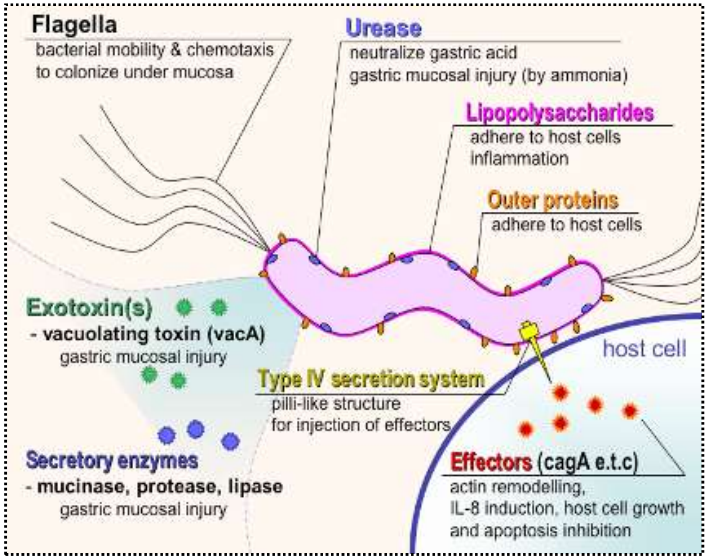
Targeting specific virulence factors

Assessment of panobacumab as adjunctive immunotherapy for the treatment of nosocomial *Pseudomonas aeruginosa* pneumonia

Y.-A. Que · H. Lazar · M. Wolff · B. François · P.-F. Laterre · E. Mercier · J. Garbino · J.-L. Pagani · J.-P. Revelly · E. Mus · A. Perez · M. Tamm · J.-J. Rouby · Q. Lu · J. Chastre · P. Eggimann

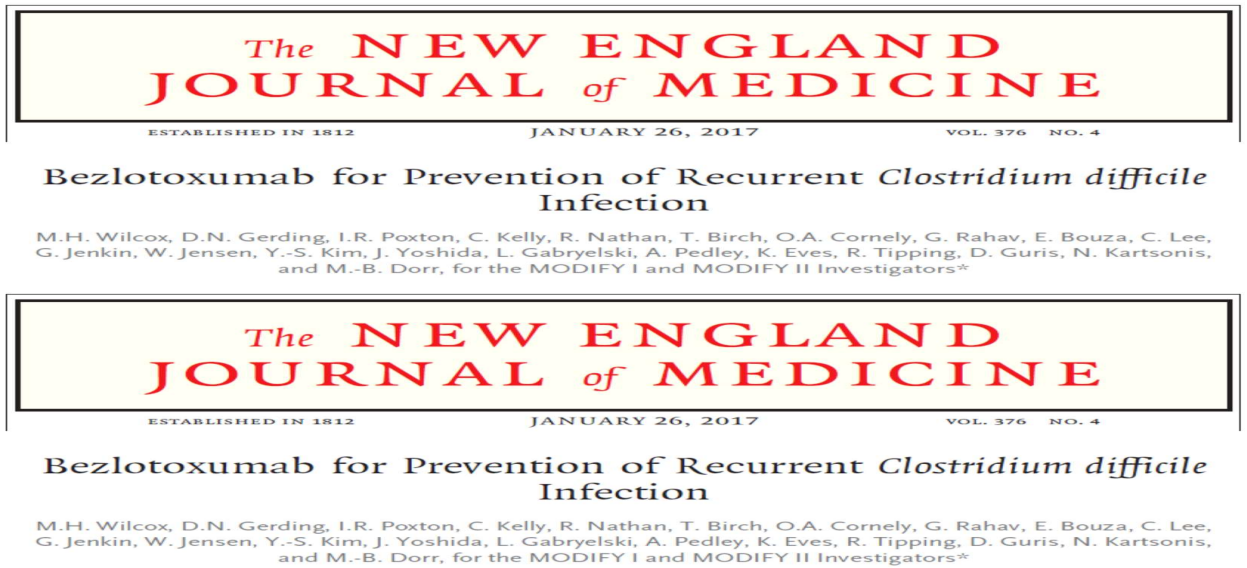


Panobacumab: monoclonal anti-LPS *P. aeruginosa* (ST O11)



Lu, J Antimicrob Chemother, 2011; Que, Eur J Clin Microbiol Infect Dis, 2014

Human monoclonal antibodies against bacterial toxins



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 26, 2017 VOL. 376 NO. 4

Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection

M.H. Wilcox, D.N. Gerding, I.R. Poxton, C. Kelly, R. Nathan, T. Birch, O.A. Cornely, G. Rahav, E. Bouza, C. Lee, G. Jenkin, W. Jensen, Y.-S. Kim, J. Yoshida, L. Gabryelski, A. Pedley, K. Eves, R. Tipping, D. Guris, N. Kartsonis, and M.-B. Dorr, for the MODIFY I and MODIFY II Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 26, 2017 VOL. 376 NO. 4

Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection

M.H. Wilcox, D.N. Gerding, I.R. Poxton, C. Kelly, R. Nathan, T. Birch, O.A. Cornely, G. Rahav, E. Bouza, C. Lee, G. Jenkin, W. Jensen, Y.-S. Kim, J. Yoshida, L. Gabryelski, A. Pedley, K. Eves, R. Tipping, D. Guris, N. Kartsonis, and M.-B. Dorr, for the MODIFY I and MODIFY II Investigators*

- Actoxumab and bezlotoxumab: antibodies against *C. difficile* toxins A and B, respectively
  - 2655 adults receiving standard antibiotics for primary or recurrent *C. difficile*
  - Primary end point: recurrent infection (new episode after cure) within 12 wks
  - Bezlotoxumab: lower rate of recurrent infection than placebo with a safety profile similar to placebo (17% vs 28%). No additional effect of actoxumab

- Other antibodies against bacterial toxins in development:
  - Alpha-toxin of *S. aureus*
  - *P. aeruginosa* (e.g. targeting PsI, surface exopolysaccharide)

Wilcox, New Engl J Med, 2017

Vaccines

Safety, immunogenicity, and preliminary clinical efficacy of a vaccine against extraintestinal pathogenic *Escherichia coli* in women with a history of recurrent urinary tract infection: a randomised, single-blind, placebo-controlled phase 1b trial

Angela Huttner, Christoph Hatz, Germie van den Dobbelsteen, Darren Abbanat, Alena Hornacek, Rahel Frölich, Anita M Dreyer, Patricia Martin, Todd Davies, Kellen Fae, Ingrid van den Nieuwenhof, Stefan Thoelen, Serge de Vallière, Anette Kuhn, Enos Bernasconi, Volker Viereck, Tilemachos Kavvadias, Kerstin Kling, Gloria Ryu, Tanja Hülder, Sabine Gröger, David Scheiner, Cristina Alaimo, Stephan Harbarth, Jan Poolman, Veronica Gambillara Fonck

- Phase I: bioconjugate vaccine containing O-antigens of four *E. coli* serotypes
  - 188 healthy adult women with recurrent UTIs
  - Fewer UTIs caused by *E. coli* of any serotype in vaccine group

- Other vaccin examples in development:
  - against *P. aeruginosa:* Phase II/III: tested in ventilated ICU patients at high risk of Pseudomonas infection
  - against *C. difficile:* Phase II: induces strong immune response to toxin A/B

Huttner, Lancet Infect Dis, 2017

Focus on the microbiome

ARTICLE

doi:10.1038/nature18634

Human commensals producing a novel antibiotic impair pathogen colonization

Alexander Zipperer[1,2]*, Martin C. Konnerth[3]*, Claudia Laux[1,2], Anne Berscheid[4], Daniela Janek[1,2]†, Christopher Weidenmaier[2,5], Marc Burian[6], Nadine A. Schilling[3,7], Christoph Slavetinsky[1,2], Matthias Marschal[5], Matthias Willmann[2,5], Hubert Kalbacher[7], Birgit Schittek[6], Heike Brötz-Oesterhelt[2,4], Stephanie Grond[3], Andreas Peschel[1,2] & Bernhard Krismer[1,2]

- *S. aureus* is found in the noses of around 30% of the population… how is it that the other 70% resist colonisation?

- Analysis of 90 *Staphylococcus* strains from the nasal microbiome showed that one strain, *Staphylococcus lugdunensis,* produced **lugdunin** which has potent anti *S. aureus* potential

Table 1 | Lugdunin spectrum of activity

Species and strain	Resistance	Lugdunin MIC ($\mu g\,ml^{-1}$)
Staphylococcus aureus USA300 (LAC)	MRSA	1.5
+ 50% human serum		1.5
Staphylococcus aureus USA300 (NRS384)	MRSA	1.5
Staphylococcus aureus Mu50	GISA	3
Staphylococcus aureus SA113		3
Staphylococcus aureus RN4220		3
Enterococcus faecium BK463	VRE	3
Enterococcus faecalis VRE366	VRE	12
Listeria monocytogenes ATCC19118		6
Streptococcus pneumoniae ATCC49619		1.5
Bacillus subtilis 168 (*trpC2*)		4
Pseudomonas aeruginosa PAO1		>50
Escherichia coli DH5α		>50

Zipperer, Nature, 2016

Take home message: novel antibiotics

- Pipeline of novel antibiotics is growing but strong stewardship policies essential to safeguard old antibiotics
- Multiple new agents for Gram-positive infections: tedizolid, oritavancine and dalbavancine
- Gram-negative infections: focus on new beta-lactam inhibitors
- Examples of novel approaches:
  - Advances in antibiotic discovery technology (teixobactin)
  - Targeting specific virulence factors (*Pae* LPS)
  - Human monoclonal antibodies against bacterial toxins (bezlotoxumab)
  - Use of vaccins in high-risk populations (E. coli in recUTI)
  - Microbiome as new reservoir for antibiotic discovery (lugdunin)