Developing new strategies in bacterial infections

New antibiotics & alternatives to antibiotic therapy

Angela Huttner MD
Infection Control Program &
Division of Infectious Diseases
Geneva University Hospitals
Geneva, Switzerland

angela.huttner@hcuge.ch

No conflicts of interest

Supported by:

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The three questions

1. Ceftobiprole is approved for treatment of ventilator-associated pneumonia.
   - Yes
   - No

2. Dalbavancin can be used against carbapenem-resistant Klebsiella spp.
   - Yes
   - No

3. It is likely that at least one phage therapy will be FDA-approved within the next 5 to 10 years.
   - Yes
   - No

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New antibiotics & alternatives to antibiotic therapy

BACKGROUND	NEW ANTIBIOTICS	VACCINES	PHAGE THERAPY	NEW INITIATIVES

- Current landscape
- New and coming antibacterials
- Vaccines for bacterial infections
- Phage therapy for bacterial infections
- Initiatives to spur development

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A fine mess

Antibacterial resistance Us! Antibiotic pipeline

Antibacterial resistance

"It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them...there is the danger that the ignorant man may easily under-dose himself and, by ex- posing his microbes to nonlethal quantities of the drug, make them resistant." —Alexander Fleming

Nobel Prize Lecture, December 11, 1945.
http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming.pdf

Antibacterial resistance

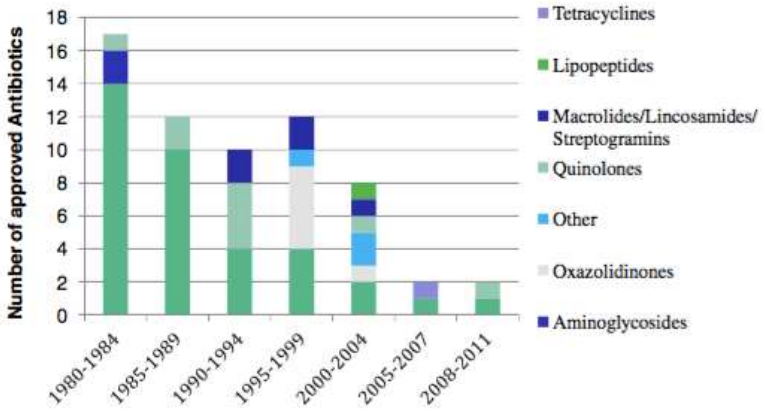
- Which are the "problem" bacteria now?
  - MRSA
  - EXTENDED-BETA-LACTAMASE (ESBL)-PRODUCING BACTERIA
  - CARBAPENEM-RESISTANT BACTERIA
  - COLISTIN-RESISTANT BACTERIA

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu, BS*, Yang Wang, PhD†, Prof Timothy R Walsh, DSc, Ling-Xian Yi, BS, Rong Zhang, PhD, James Spencer, PhD, Yohei Doi, MD, Guobao Tian, PhD, Baolei Dong, BS, Xianhui Huang, PhD, Lin-Feng Yu, BS, Danxia Gu, PhD, Hongwei Ren, BS, Xiaojie Chen, MS, Luchao Lv, MS, Dandan He, MS, Hongwei Zhou, PhD, Prof Zisen Liang, MS, Prof Jian-Hua Liu, PhD, Prof Jianzhong Shen, PhD

Lancet Infectious Diseases, 2016: 16 (2): 161–168

A dry pipeline



No successful discoveries of new classes of antibiotics since 1987

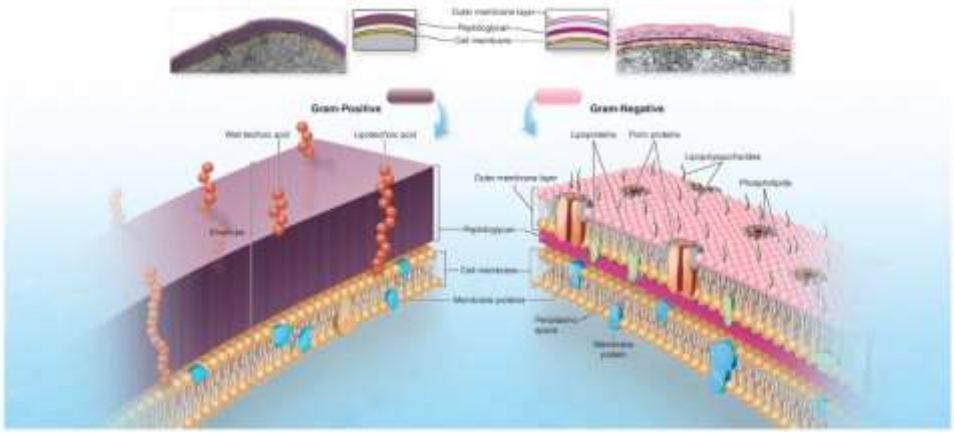
Bassetti et al. *Annals of Clinical Microbiology and Antimicrobials* 2013, 12:22

Late-stage pipeline: antibiotics recently approved, in registration or in phase III development

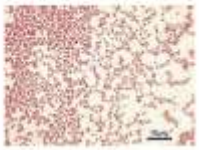
	Drug (brand name) - Company	Antibiotic	Activity spectrum/resistant	Phase and indication[1]	Regulatory status		
New BLI	Ceftazidime+ avibactam [40] (AvycazTM) – AstraZeneca/ Actavis	Cephalosporin + new BLI	Gram–, including MDR P. aeruginosa, ESBL-producing strains and KPC	Approved February 2015 for cIAI in combination with metronidazole, and for cUTI in patients who have limited or no alternative treatment options, in phase III for HAP/VAP and cIAI	Approved February 2015	Not submitted yet	Not submitted yet
	Ceftolozane+ tazobactam [41] (ZerbaxaTM) – Cubist Pharmaceuticals / Merck Sharp & Dohme	Cephalosporin + BLI	Gram–, including carbapenem, piperacillin+tazobactam and ceftazidime-resistant Pseudomonas aeruginosa. ESBL-producing strains	Approved for cUTI and cIAI, in phase III for VAP and phase I for paediatric use	Approved December 2014	Under review since August 2014	Under review since September 2014[2]
	Ceftobiprole medocaril [45] (Zevtera®/Mabelio®) – Basilea Pharmaceutica/Quintiles	Cephalosporin	Gram+ and –, including MRSA, VRSA, penicillin- and ceftriaxone-resistant Streptococcus pneumoniae, Enterobacteriaceae, P. aeruginosa	Approved for CABP and HAP, excluding VAP	Not submitted (additional phase III data required	Approved October 2013	Approved December 2014
Gram +	Oritavancin [42] (OrbactivTM) – The Medicines Company	Glycopeptide	Gram+, including MRSA	Approved for ABSSSI, in phase I for paediatric use	Approved August 2014	Approved May 2015	Under review[2]
Gram +	Tedizolid phosphate [43] (SivextroTM) – Cubist Pharmaceuticals / Merck Sharp & Dohme	Oxazolidinone	Gram+, including MRSA and linezolid-resistant MRSA	Approved for ABSSSI, in phase III for HAP/VAP and for ABSSSI in adolescents	Approved June 2014	Approved March 2015	Under review since second quarter 2014[2]
Gram +	Dalbavancin [42] (DalvanceTM/ XydalbaTM) – Actavis / Durata Therapeutics	Glycopeptide	Gram+, including MRSA	Approved for ABSSSI, in phase III for CABP and phase I and III for paediatric use	Approved May 2014	Approved March 2015	Unknown
New BLI	Meropenem+RPX7009 [54, 55] (CarbavanceTM) – The Medicines Company	Carbapenem + new class of BLI	Gram–, including CRE and particularly KPC	Phase III for cUTI and infections caused by CRE[3]	NA	NA	NA
	Eravacycline [56] – Tetraphase Pharmaceuticals	Tetracycline	Gram+ and –, including CRE, ESBL-producing strains, MDR Acinetobacter baumanii, VRE, MRSA	Phase III for cUTI and cIAI[3]	NA	NA	NA
	Plazomicin [57] – Achaogen	Aminoglycoside	Gram–, including CRE	Phase III for bloodstream infection and nosocomial pneumonia caused by CRE[3]	NA	NA	NA
	Delafloxacin [51] – Melinta Therapeutics	Fluoroquinolone	Gram+ and –, including MRSA	Phase III for ABSSSI	NA	NA	NA
	Solithromycin [52] – Cempra	Macrolide	Gram+, including macrolide-t strains	Phase III for CABP and uncomplicated gonorrhoea, in phase I for paediatric use	NA	NA	NA

Bettiol et al. Swiss Med Wkly 2015;145:w14167

Gram-positive & Gram-negative organisms



Gram-positive & Gram-negative organisms

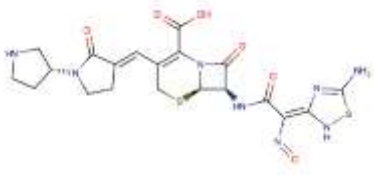
Characteristics	Gram Positive	Gram Negative
Gram Reaction	 Retain crystal violet dye and stain blue or purple	 Can be decolorized to accept counterstain (safranin) and stain pink or red
Cell Wall	Cell Wall is 20-30 nm thick.	Cell Wall is 8-12 nm thick.
Cell Wall	The wall is Smooth.	The wall is wavy.
Peptidoglycan Layer	Thick (multilayered)	Thin (single-layered)
Teichoic Acids	Present in many	Absent
Periplasmic Space	Absent	Present
Outer Membrane	Absent	Present
Porins	Absent	Occurs in Outer Membrane
Lipopolysaccharide (LPS) Content	Virtually None	High

New antibiotics for Gram-positive bacteria
(with overlap!)

ANTIBIOTIC	FAMILY	MECHANISM OF ACTION
CEFTOBIPROLE	CEPHALOSPORIN	BINDS TO PENICILLIN-BINDING PROTEINS
DALBAVANCIN	GLYCOPEPTIDES	BIND TO ACYL-D-ALANYL-D-ALANINE IN PEPTIDOGLYCAN
ORITAVANCIN		
TEDIZOLID	OXAZOLIDINONE	BINDS TO 50S SUBUNIT OF rRNA

Ceftobiprole

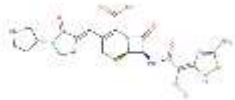
- Mechanism: binds strongly to PBP2A (Staphylococci)
- Pharmacokinetics:
  - Renally cleared
  - Half-life 3 – 3.5h
  - Volume of distribution 18 – 20 L
  - Protein binding: 16%
  - i.v. only (poor oral absorption)



- Pharmacodynamics:
  - Time-dependent killing
  - May have some post-antibiotic effect (*in vitro*!)

Leonard SN et al. *Antimicrob Agents Chemother*. 2008;52(8):2974–2976
Rossollini et al. *J Antimicrob Chemother*. 2011;66(1):151–159

Ceftobiprole



- Approved in Europe for community-acquired & hospital-associated pneumonia (2013)
- In the US…

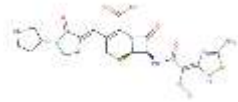
Ceftobiprole antibiotic to fight tougher bacterial infections fails to win approval in US

FDA: *Data from Studies BAP00154 and BAP00414 cannot be relied upon because inspections and audits of* ***approximately one-third of the clinical trial sites for these studies found the data from a large proportion of these sites to be unreliable or unverifiable…***

- $$$$:
  In Germany, a 7-day treatment course costs € 1392,37

Noel et al. Clin Infect Dis 2008; 46 (5): 647-655. doi: 10.1086/52
Noel et al. Antimicrob Agents Chemother 2008; 52(1):37-44

Ceftobiprole



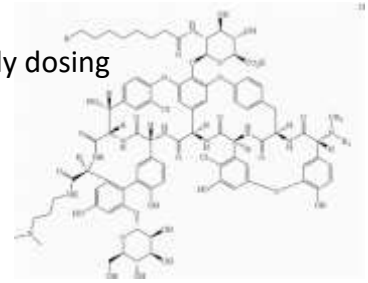
- Wide spectrum of *in vitro* activity
  - Has *in vitro* activity against MRSA resistant to vancomycin & linezolid…
  - **but is hydrolyzed by ESBL and AmpC beta-lactamases** → vulnerable to common resistance mechanisms in Enterobacteriaceae
  - Still, for non-ESBL, non-AmpC producers, may do better against Gram-negative organisms than Gram-positives
- Clinical:
  - Not approved for ventilator-associated pneumonia (VAP)
    - Cure rates for VAP 23% vs 37% (ceftaz+linezolid), microbiologic eradication 30 vs 50%
  - Weak against Pseudomonas-associated VAP
  - Side effects: **nausea/vomiting**, diarrhea, hyponatremia, LFT ↑

Theuretzbacher 2015: http://cddep.org/blog/posts/recent_fda_antibiotic_approvals_good_news_and_bad_news#

Rossollini et al. *J Antimicrob Chemother*. 2011;66(1):151–159
Awad et al. Clin Infect Dis. 2014 Jul 1;59(1):51-61

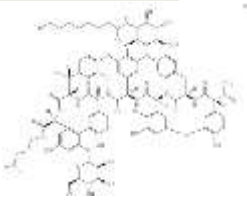
Dalbavancin

- Mechanism: binds to acyl-d-alanyl-d-alanine (peptidoglycan)
- Pharmacokinetics:
  - Dual elimination - urine & feces
  - **Half-life 150 - 250h** (!) → once weekly dosing
  - Volume of distribution 15.7 L
  - Protein binding: 98% (!)
  - i.v. only (poor oral absortion)
- Pharmacodynamics:
  - Concentration-dependent killing (+ area under the curve)



Billeter et al. Clin Infect Dis 2008:46 577-83
Juul et al. Therapeut Clin Risk Management 2016:12 225–232

Dalbavancin



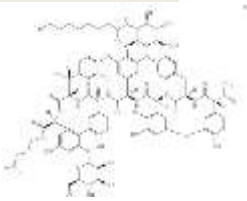
- Not really new!
  - 1987: described by researchers at Lepetit Research Center
    → Biosearch Italy → Vicuron → acquired by Pfizer…
    - clinical development not successful, no approval!
  - 2009: rights won by Durata, which repeated ph3 trials
    → 2014: acquired by **Actavis**
- Approved in USA in 2014, Europe in 2015
- $$$$
  - $1100 – 1500 per 500 mg vial → full treatment = $3300 - 4500

Theuretzbacher 2015: http://cddep.org/blog/posts/recent_fda_antibiotic_approvals_good_news_and_bad_news#

Juul et al. Therapeut Clin Risk Management 2016:12 225–232

BACKGROUND NEW ANTIBIOTICS VACCINES PHAGE THERAPY NEW INITIATIVES

Dalbavancin

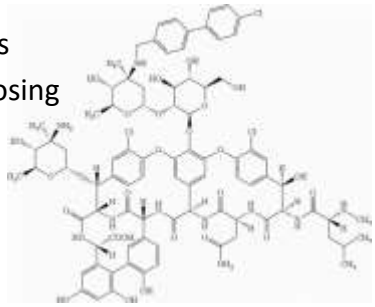


- Spectrum of activity:
  - Gram-positive only
  - Not active against vancomycin-resistant *S. aureus*
  - *In vitro* activity against vancomycin-resistant Enterococci with *vanB* & *vanC* resistance genes, but not *vanA* (the most common!)
- Clinical:
  - Approved for acute bacterial skin & skin structure infections
    - Trials ongoing for CA pneumonia (MRSA) & pediatric osteomyelitis
  - Side effects: ??? / headache, fever
  - THINK CAREFULLY (half-life, resistance, MRSA in decline…)

Juul et al. Therapeut Clin Risk Management 2016:12 225–232
Ramdeen et al. Expert Opin Pharmacother. 2015;16(13):2073-81

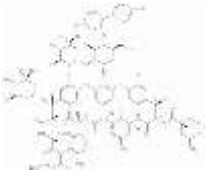
Oritavancin

- Mechanism: binds to acyl-d-alanyl-d-alanine (peptidoglycan)
- Pharmacokinetics:
  - Excreted unchanged in urine & feces
  - **Half-life 393h (!)** → once weekly dosing
  - Volume of distribution 100 L
  - Protein binding: 90% (!)
  - i.v. only (poor oral absorption)
- Pharmacodynamics:
  - Concentration-dependent killing



Tice. *Clin Infect Dis* 2012;54(S3):S239–43
Bassetti et al. *Ann Clin Microbiol Antimicrob* 2013, 12:22

Oritavancin



- Not really new!
  - vancomycin derivate originally discovered and developed by Eli Lilly, where first development was discontinued

    → acquired by Targanta:

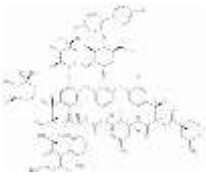
    completed Phase 3 trials but failed to achieve approval

    → acquired by the Medicine Company:

    successfully repeated ph3 trials
- Approved in USA in 2014, Europe in 2015
- $$$$

Theuretzbacher 2015: http://cddep.org/blog/posts/recent_fda_antibiotic_approvals_good_news_and_bad_news#

Oritavancin



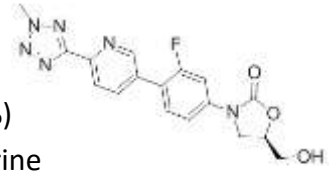
- Spectrum of activity:
  - Gram-positive only!
  - MICs for vancomycin-I and -R *S. aureus* lower than for vancomycin but still above the preliminary PK/PD breakpoint

- Clinical:
  - Approved for acute bacterial skin & skin structure infections
    - Trials ongoing for pediatric use
  - Side effects: ??? / headache, fever
  - Little justification for its use in MSSA

Theuretzbacher 2015: http://cddep.org/blog/posts/recent_fda_antibiotic_approvals_good_news_and_bad_news#
Tice. *Clin Infect Dis* 2012;54(S3):S239–43
Bassetti et al. *Ann Clin Microbiol Antimicrob* 2013, 12:22

Tedizolid

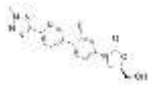
- Mechanism: binds to peptidyl transferase A-site of ribosomal ribonucleic acid (rRNA, 50S subunit) →inhibits protein synthesis



- Pharmacokinetics:
  - High **oral** bioavailability (86 – 100%)
  - Elimination: 80 – 90% feces, rest urine
  - Half-life: 12h
  - Volume of distribution: 70 L
  - Protein binding: 75-80%
- Pharmacodynamics:
  - concentration-dependent killing

Rybak et al. *Infect Dis Ther* 2015; 4:1–14
Ong et al. *Drug Metab Dispos* 2014; 4:1275-84

Tedizolid



- Approved in USA in 2014, in Europe in 2015
- Spectrum of activity:
  - Gram-positive only!
  - *In vitro* potency 2-8x higher than linezolid
    - But protein binding *in vivo* may offset its activity
- Clinical:
  - Approved for acute bacterial skin & skin structure infections (ABSSSI)
  - Ph3 trials ongoing for HAP & VAP
  - Side effects: **Nausea/vomiting**, diarrhea; ?? thrombocytopenia
- $$$$: 6 days of tedizolid p.o. = $2,212 (i.v. = $1,692)

Rybak et al. *Infect Dis Ther* (2015) 4:1–14

New antibiotics for Gram-negative bacteria
(with overlap!)

ANTIBIOTIC	FAMILY	MECHANISM OF ACTION
MEROPENEM + **RPX7009**	CARBAPENEM + **BLI**	SERINE CARBAPENEMASE INHIBITOR
ERAVACYCLINE	TETRACYCLINE	BINDS TO 30S RIBOSOMAL SUBUNIT
PLAZOMYCIN	AMINOGLYGOSIDE	BINDS TO 16S PORTION OF 30S RIBOSOMAL SUBUNIT

Meropenem + RPX7009 (Carbavance™)

- Mechanism of RPX7009: beta-lactamase inhibitor (anti-serine carbapenemase)

Antimicrob Agents Chemother. 2015 Aug;59(8):4856-60. doi: 10.1128/AAC.00843-15. Epub 2015 Jun 1.

Activity of Meropenem Combined with RPX7009, a Novel β-Lactamase Inhibitor, against Gram-Negative Clinical Isolates in New York City.

Lapuebla A[1], Abdallah M[1], Olafisoye O[1], Cortes C[2], Urban C[2], Quale J[1], Landman D[3].

Author information

Abstract

Multidrug-resistant Klebsiella pneumoniae carbapenemase (KPC)-producing Enterobacteriaceae are endemic to hospitals in New York City and other regions. RPX7009 is a novel β-lactamase inhibitor with activity against serine carbapenemases. We tested the activity of meropenem plus RPX7009 against 4,500 recent Gram-negative clinical isolates from 11 New York City hospitals. The meropenem-RPX7009 combination was found to have excellent in vitro activity against Escherichia coli, K. pneumoniae, and Enterobacter spp., including multidrug-resistant (MDR) KPC-producing strains. Overall, 131/133 (98.5%) KPC-producing Enterobacteriaceae strains were inhibited by meropenem (≤1 μg/ml) plus RPX7009 (8 μg/ml). In a limited number of strains, the combination appeared to have reduced activity against KPC-producing K. pneumoniae isolates with diminished ompK35 and ompK36 expression. The addition of RPX7009 did not affect the activity of meropenem against Acinetobacter baumannii and Pseudomonas aeruginosa. The meropenem-RPX7009 combination shows promise as a novel agent against KPC-producing Enterobacteriaceae and deserves further study. Other approaches will be needed to address multidrug-resistant A. baumannii and P. aeruginosa, which typically possess different mechanisms of carbapenem resistance.

BACKGROUND NEW ANTIBIOTICS VACCINES PHAGE THERAPY NEW INITIATIVES

Meropenem + RPX7009 (Carbavance™)

- Current status:
  - in phase 3 development for complicated urinary tract infection and infections with carbapenem-resistant Enterobacteriaceae (CRE)
  - Results in 2016…

Bettiol et al. Swiss Med Wkly 2015;145:w14167

Eravacycline

- Mechanism: binds to 30S ribosomal subunit

Antimicrob Agents Chemother. 2015 Dec 14;60(3):1888-91. doi: 10.1128/AAC.02403-15.

Activity of Eravacycline against Escherichia coli Clinical Isolates Collected from U.S. Veterans in 2011 in Relation to Coresistance Phenotype and Sequence Type 131 Genotype.

Johnson JR[1], Porter SB[2], Johnston BD[3], Thuras P[3].

Author information

Abstract

Eravacycline is a novel broad-spectrum fluorocycline with potent Gram-negative activity, including for multidrug-resistant strains. Among 472 *Escherichia coli* clinical isolates from 24 Veterans Affairs medical centers (in 2011), divided equally as susceptible versus resistant to fluoroquinolones, broth microdilution eravacycline MICs were distributed unimodally, ranging from 0.03 to 1.0 μg/ml (MIC50 of 0.125 μg/ml, MIC90 of 0.25 μg/ml). Eravacycline MICs were ~2-fold higher among fluoroquinolone-resistant, gentamicin-resistant, multidrug-resistant, and sequence type 131 (ST131) isolates ($P < 0.01$ for each comparison).

BACKGROUND NEW ANTIBIOTICS VACCINES PHAGE THERAPY NEW INITIATIVES

Eravacycline

- Current status:
  - In phase 3 development for cUTI and complicated intra-abdominal infections (cIAI)
  - cIAI OK
  - cUTI:

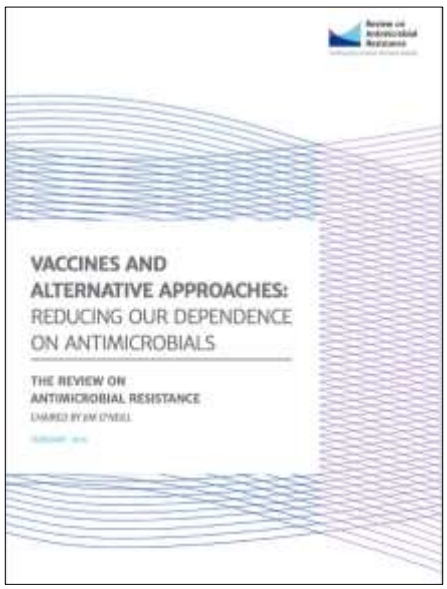
  8 Sept. 2015: *Tetraphase today announced that the IGNITE2 phase 3 clinical trial of eravacycline…did not achieve its primary endpoint of statistical non-inferiority compared to levofloxacin.*
    - Poor dose selection?

http://ir.tphase.com/releasedetail.cfm?releaseid=930613
Bettiol et al. Swiss Med Wkly 2015;145:w14167

Plazomycin

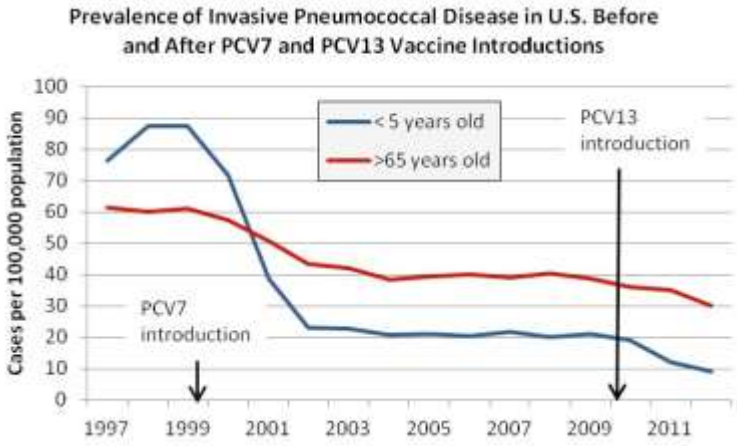
- Mechanism: binds to 16S portion of 30S ribosomal subunit
- Cross-resistance with other aminoglycosides
- Current status:
  - In phase 3 development for bloodstream infection and nosocomial pneumonia caused by CRE (end date 2018)
  - Ph3 for cUTI recently added

Bettiol et al. Swiss Med Wkly 2015;145:w14167
https://www.clinicaltrials.gov/ct2/show/NCT01970371



http://amr-review.org/sites/default/files/Vaccines%20and%20alternatives_v4_LR.pdf

Pneumococcal conjugate vaccine: a success story



http://www.cdc.gov/abcs/reports-findings/surv-reports.html

And vaccines for hospital-associated infections?

- None licensed
- Great interest & advocation…
  - At *in vitro* level

Vaccination with *Klebsiella pneumoniae*-derived extracellular vesicles protects against bacteria-induced lethality via both humoral and cellular immunity

Won-Hee Lee[1], Hyun-Il Choi[1], Sung-Wook Hong[1], Kwang-sun Kim[2], Yong Song Gho[3] and Seong Gyu Jeon[3]

Alternatives to antibiotics—a pipeline portfolio review

Lloyd Czaplewski, Richard Bax, Martha Clokie, Mike Dawson, Heather Fairhead, Vincent A Fischetti, Simon Foster, Brendan F Gilmore, Robert E W Hancock, David Harper, Ian R Henderson, Kai Hilpert, Brian V Jones, Aras Kadioglu, David Knowles, Sigríður Ólafsdóttir, David Payne, Steve Projan, Sunil Shaunak, Jared Silverman, Christopher M Thomas, Trevor J Trust, Peter Warn, John H Rex

- Only prophylactic

Lee et al., Experiment & Molec Med 2015; 47 e183
Czaplewski et al. Lancet Infect Dis 2016 16: 239–51

And vaccines for hospital-associated infections?

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"
Search for studies:
Advanced Search | Help | Studies by Topic | Glos

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home › Find Studies › Study Record Detail

Vaccine Against Escherichia Coli Infection

This study has been completed.

Sponsor:
GlycoVaxyn AG

Information provided by (Responsible Party):
GlycoVaxyn AG

ClinicalTrials.gov Identifier:
NCT02289794

First received: November 3, 2014
Last updated: February 10, 2016
Last verified: February 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

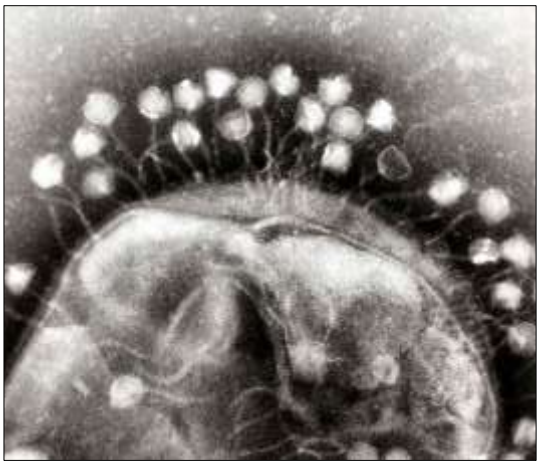
Purpose

This Phase I multi-center placebo controlled study is conducted in healthy women with a history of recurrent urinary tract infections (UTI) aged between 18 and 70 years.

Condition	Intervention	Phase
E.Coli Infections	Biological: E.coli bioconjugate vaccine Biological: Placebo	Phase 1

Manuscript in preparation

Phage therapy



www.wikipedia.org

Phage therapy

- What is a bacteriophage?
  - Bacterial virus that invades bacterial cells
  - Lytic phages disrupt bacterial metabolism, causing lysis

- A long history…
  - 1896: Ernest Hankin
  - 1898: Gamaleya
  - 1916: Frederick Twort
  - 1917: Felix d'Herelle "officially discovers" bacteriophages

Sulakvelidze et al. Antimcrob Ag Chemother 2001; 45:649–659

BACKGROUND NEW ANTIBIOTICS VACCINES PHAGE THERAPY NEW INITIATIVES

Phage therapy: history

- First clinical use:
  - 1919: D'Herelle, his boss & other staff self-test for safety
  - Administered to a boy with dysentery → clinical cure
  - Several uncontrolled studies confirmed clinical cure
- Commercialization by D'Herelle:
  - Bacté-coli-phage
  - Bacté-rhino-phage
  - Bacté-intesti-phage → Marketed by L'Oreal (France)
  - Bacté-pyo-phage
  - Bacté-staphy-phage
- 1940s: Phages developed in the USA (Eli Lily)

Sulakvelidze et al. Antimcrob Ag Chemother 2001; 45:649–659
Summers. Felix d'Herelle and the origins of molecular biology. 1999, Yale University Press

Phage therapy: what happened next…

- In the West, ANTIBIOTICS
- In Eastern Europe, continued use & research – and a record in Russian, Georgian and Polish
  - None published in English
  - None randomized
  - Most uncontrolled

Sulakvelidze et al. Antimcrob Ag Chemother 2001; 45:649–659

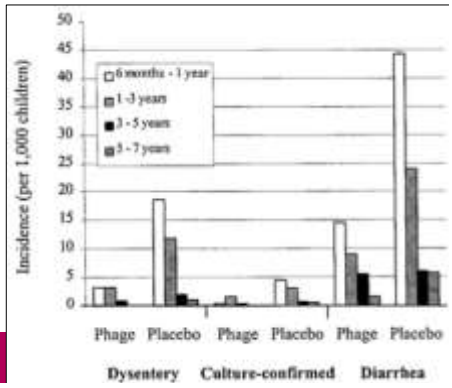
Phage therapy: clinical studies

Reference(s)	Infection(s)	Etiologic agent(s)	Comments
Babalova et al. (7)	Bacterial dysentery	*Shigella*	*Shigella* phages were successfully used for prophylaxis of bacterial dysentery.
Bogovazova et al. (11)	Infections of skin and nasal mucosa	*K. ozaenae*, *K. rhinoscleromatis*, and *K. pneumoniae*	Adapted phages were reported to be effective in treating *Klebsiella* infections in all of the 109 patients.
Ciślo et al. (17)	Suppurative skin infections	*Pseudomonas*, *Staphylococcus*, *Klebsiella*, *Proteus*, and *E. coli*	Thirty-one patients having chronically infected skin ulcers were treated orally and locally with phages. The success rate was 74%.
Ioseliani et al. (22)	Lung and pleural infections	*Staphylococcus*, *Streptococcus*, *E. coli*, and *Proteus*	Phages were successfully used together with antibiotics to treat lung and pleural infections in 45 patients.
Kochetkova et al. (25)	Postoperative wound infections in cancer patients	*Staphylococcus* and *Pseudomonas*	A total of 131 cancer patients having postsurgical wound infections participated in the study. Of these, 65 patients received phages and the rest received antibiotics. Phage treatment was successful in 82% of the cases, and antibiotic treatment was successful in 61% of the cases.
Kucharewicz-Krukowska and Slopek (27)	Various infections	*Staphylococcus*, *Klebsiella*, *E. coli*, *Pseudomonas*, and *Proteus*	Immunogenicity of therapeutic phages was analyzed in 57 patients. The authors concluded that the phages' immunogenicity did not impede therapy.
Kwarciński et al. (29)	Recurrent subphrenic abscess	*E. coli*	Recurrent subphrenic abscess (after stomach resection) caused by an antibiotic-resistant strain of *E. coli* was successfully treated with phages.
Litvinova et al. (32)	Intestinal dysbacteriosis	*E. coli* and *Proteus*	Phages were successfully used together with bifidobacteria to treat antibiotic-associated dysbacteriosis in 500 low-birth-weight infants.
Meladze et al. (33)	Lung and pleural infections	*Staphylococcus*	Phages were used to treat 223 patients having lung and pleural infections, and the results were compared to 117 cases where antibiotics were used. Full recovery was observed in 82% of the patients in the phage-treated group, as opposed to 64% of the patients in the antibiotic-treated group.
Miliutina and Voroshylova (35)	Bacterial dysentery and salmonellosis	*Shigella* and *Salmonella*	The effectiveness of treating salmonellosis using phages and a combination of phages and antibiotics was examined. The combination of phages and antibiotics was reported to be effective in treating cases where antibiotics alone were ineffective.

Sulakvelidze et al. Antimcrob Ag Chemother 2001; 45:649–659

Phage therapy: clinical studies

- The Georgian/Soviet study of 1963
- 30,769 children included:
  - Children on one side of a street got Shigella phages (n=17,044)
  - Children on the other got placebo (n=13,725)
- Outcome:
  - Clinical cure



Sulakvelidze et al. Antimcrob Ag Chemother 2001; 45:649–659
Babalova et al. Zh. Mikrobiol. Epidemiol. Immunobiol 1968; **2**:143

Phage therapy: advantages over antibiotics

Bacteriophages	Antibiotics	Comments
Very specific (i.e., usually affect only the targeted bacterial species); therefore, dysbiosis and chances of developing secondary infections are avoided (15).	Antibiotics target both pathogenic microorganisms and normal microflora. This affects the microbial balance in the patient, which may lead to serious secondary infections.	High specificity may be considered to be a disadvantage of phages because the disease-causing bacterium must be identified before phage therapy can be successfully initiated. Antibiotics have a higher probability of being effective than phages when the identity of the etiologic agent has not been determined.
Replicate at the site of infection and are thus available where they are most needed (59).	They are metabolized and eliminated from the body and do not necessarily concentrate at the site of infection.	The "exponential growth" of phages at the site of infection may require less frequent phage administration in order to achieve the optimal therapeutic effect.
No serious side effects have been described. ?	Multiple side effects, including intestinal disorders, allergies, and secondary infections (e.g., yeast infections) have been reported (76).	A few minor side effects reported (17, 58) for therapeutic phages may have been due to the liberation of endotoxins from bacteria lysed in vivo by the phages. Such effects also may be observed when antibiotics are used (42).
Phage-resistant bacteria remain susceptible to other phages having a similar target range.	Resistance to antibiotics is not limited to targeted bacteria.	Because of their more broad-spectrum activity, antibiotics select for many resistant bacterial species, not just for resistant mutants of the targeted bacteria (47).
Selecting new phages (e.g., against phage-resistant bacteria) is a relatively rapid process that can frequently be accomplished in days or weeks.	Developing a new antibiotic (e.g., against antibiotic-resistant bacteria) is a time-consuming process and may take several years (16, 51).	Evolutionary arguments support the idea that active phages can be selected against every antibiotic-resistant or phage-resistant bacterium by the ever-ongoing process of natural selection.

Sulakvelidze et al. Antimcrob Ag Chemother 2001; 45:649–659

Phage therapy: problems

- OPAQUE
  - No toxicology studies!
  - Very few reports on pharmacokinetics
  - Very few reports on pharmacodynamics
    - T4 phage sequenced: LYSIS IS A COMPLICATED PROCESS
  - Proof of efficacy not established
    - 1934: Council on Pharmacy and Chemistry of the American Medical Association requests full review of all papers

    →Conclusion: not in favor of phage therapy

Sulakvelidze et al. Antimcrob Ag Chemother 2001; 45:649–659
Kutter et al. *In* Molecular biology of bacteriophage T4 (1994). American Society for Microbiology

BACKGROUND NEW ANTIBIOTICS VACCINES PHAGE THERAPY NEW INITIATIVES

Phage therapy: problems

Problem	Comments	Solution and/or required approach
Narrow host range of phages	Because of the high specificity of phages, many negative results may have been obtained because of the failure to select phages lytic for the targeted bacterial species (19).	Determine the phage susceptibility of the etiologic agent before using phages therapeutically (40, 77); use polyvalent phage cocktails which lyse the majority of strains of the etiologic agent (15, 45, 58, 59).
Insufficient purity of phage preparations	Early therapeutic phages were in crude lysates of host bacteria, and they contained numerous contaminants (including endotoxins) that may have counteracted the effect of phages.	Ion-exchange chromatography, high-speed centrifugation, and other modern purification techniques should be used to obtain phage preparations of high purity (11).
Poor stability and/or viability of phage preparations	Some commercial phage preparations were supplemented with mercurials or oxidizing agents or were heat treated to ensure bacterial sterility (14). Many of these treatments also may have inactivated the phages, resulting in ineffective phage preparations.	Advanced purification techniques can be used to purify phages and to ensure that they are bacterium free. The viability and titer of phages should be determined before using them therapeutically.
Lack of understanding of the heterogeneity and mode of action of phages (i.e., lytic vs lysogenic phages)	Failure to differentiate between lytic and lysogenic phages may have resulted in some investigators using lysogenic phages, which are much less effective than lytic phages.	Carefully select for lytic phages. This is also critical for avoiding the possible horizontal transfer of bacterial toxin, antibiotic resistance, etc., genes by lysogenic phages (3) (Fig. 2).
Exaggerated claims of effectiveness of commercial phage preparations	One example of this would be the preparation called *Enterophagos*, which was marketed as being effective against herpes infections, urticaria, and eczema (8)—conditions against which phages could not possibly be effective.	Phage preparations should be accompanied by specific, scientifically supported information about their efficacy against specific bacterial pathogens, their possible side-effects, etc.
Failure to establish scientific proof of efficacy of phage treatment	Most clinical studies using therapeutic phages were conducted without placebo controls; also, when placebo controls were used, data were evaluated in a subjective manner questioned by many peers (20, 26).	Carefully controlled, double-blinded placebo studies with highly purified, lytic phages should be conducted, and results must be evaluated based on both clinical observations and scrupulous laboratory analysis.

Sulakvelidze et al. Antimcrob Ag Chemother 2001; 45:649–659

Phage therapy: where are we now?

- Hugely increased interest (specificity, abundance)
- BUT 

  - Phages for Gram-positive, spore-forming bacteria (Clostridia, Bacillus spp.):

    "Currently much of the available literature focuses on their **primary isolation and characterization** rather than the development of practical applications"
  - Phages for Gram-negatives:

    Substantial experimentation has taken place clinically prior to the development of robust experimental animal disease models and also **outside of what today would be considered to be desirable** practices for clinical trials"

Nakonieczna et al. J Appl Microbiol 2015: 119, 620—631
Abedon. Bacteriophage 2015: 5:1, e1020260

BACKGROUND NEW ANTIBIOTICS VACCINES PHAGE THERAPY NEW INITIATIVES

Phage therapy: where are we now?

SUMMARY OF THE PIPELINE OF ALTERNATIVE THERAPIES

	Brief description	Current pipeline	Likelihood of 1 registration by 2025	Considerations
WILD-TYPE AND ENGINEERED BACTERIOPHAGES	Natural or engineered viruses that attack and kill bacteria	THREE PRODUCTS: *C. difficile* (1); *Pseudomonas aeruginosa* (2)	9 PERCENT (earliest could be 2023: *C. difficile* and *Pseudomonas*)	Very specific, regulatory complexity (multiple phages per treatment, phages change in patient), not suitable for acute infections (requires patient specific testing), hyper-local manufacturing, dosing considerations

http://amr-review.org/sites/default/files/Vaccines%20and%20alternatives_v4_LR.pdf

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New initiatives

(European Commission, 7th Framework: old antibiotics)

(Innovative Medicines Initiative [EC + EFPIA]: new antibiotics)

"Global Antibiotic Research & Development Partnership": old & new antibiotics

BACKGROUND NEW ANTIBIOTICS VACCINES PHAGE THERAPY NEW INITIATIVES

New initiatives

COMBACTE

Combatting Bacterial Resistance in Europe

Summary

Antimicrobial resistance (AMR) is a growing problem worldwide, and with few new drugs making it to the market, there is an urgent need for new medicines to treat resistant infections. Enter the IMI-funded COMBACTE project, which aims to give antibiotic drug development a much-needed boost by pioneering new ways of designing and implementing efficient clinical trials for novel antibiotics. COMBACTE forms part of the New Drugs for Bad Bugs (ND4BB) initiative, IMI's wider programme to tackle AMR.

more

Facts & Figures

Start Date	01/01/2013
End Date	31/12/2019
Contributions	**€**
IMI funding	109 433 010
EFPIA in kind	133 912 392
Other	7 131 466
Total cost	250 476 868

The three questions again

1. Ceftobiprole is approved for treatment of ventilator-associated pneumonia.
   - Yes
   - No

2. Dalbavancin can be used against carbapenem-resistant Klebsiella spp.
   - Yes
   - No

3. It is likely that at least one phage therapy will be FDA-approved within the next 5 to 10 years.
   - Yes
   - No

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Thank you!

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