Klinik Uygulamamızı Değiştiren Yayınlar

Dr. Murat Akova

Hacettepe Üniversitesi Tıp Fakültesi,
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı

- Halen yaklaşık 29.100.000 yayın mevcut
- Her yıl ortalama 500.000 yeni yayın eklenmekte
- 1665 yılından bu yana 55 milyon makale yayınlandığı tahmin ediliyor

Sanders Auditoryumu-Harvard

Home (Improbable Blog)

What is Improbable Research?

Ig Nobel Prizes
- About the Igs
- 2018 Ceremony
- The Winners
- 24/7
- Archive

Publications
- Magazine (Annals of Improbable Research)
- Newsletter (mini-AIR)
- Newspaper column
- Classics

Podcast & videos
- Podcast
- Improbable TV

Events Schedule
- Upcoming Events
- Past Events

Press Clips

Luxuriant Hair Clubs for Scientists

Store

Info / Contact Us

Improbable Research Podcast

What Is Improbable Research?

Improbable research is research that makes people **laugh** and then **think**.

We collect improbable research. Real research, about anything and everything, from everywhere. Research that's maybe good or bad, important or trivial, valuable or worthless.

Things We Do

We do many things, all related:

- The Ig Nobel Prizes
- The magazine, *Annals of Improbable Research*, and its newsletter, *mini-AIR*
- The blog
- Events
- Improbable Research Talks
- Books and Videos
- —Some things we did: the newspaper column (in *The Guardian*), and the podcast (with CBS)

Why We Do It

Our goal is to make people LAUGH, then THINK. We also hope to **spur people's curiosity**, and to raise the question: **How do you decide what's important and what's not, and what's real and what's not** — in science and everywhere else?

> "The most exciting phrase to hear in science, the one that heralds new discoveries, is not 'Eureka!' but, 'That's funny...'" —*Isaac Asimov*

> "Once you eliminate the impossible, whatever remains, no matter how improbable, must be the truth." —*Sherlock Holmes*

The Magazine

The *Annals of Improbable Research* (*AIR*) is a six-issues-a-year magazine, spotlighting genuine, improbable research culled from the entire world. We also publish original improbable research.

The Ig Nobel Prizes

The Ig Nobel Prizes honor achievements that make people laugh, and then make them think. The winners come to a gala ceremony at Harvard University's Sanders Theatre, and then give public lectures at MIT.

Events

We produce the annual Ig Nobel Prize ceremony, the annual Ig Nobel EuroTours, and other events—See our Events Calendar.

Ig Nobel Prize Winner Dr. Elena Bodnar demonstrates her invention (a brassiere that can quickly convert into a pair of protective face masks) assisted by Nobel laureates Wolfgang Ketterle (left), Orhan Pamuk, and Paul Krugman (right). Photo credit: Alexey Eliseev, 2009 Ig Nobel Ceremony

Ig Nobel (‘*Ignoble*’) 2018 Tıp Ödülü

ORIGINAL CONTRIBUTION

Validation of a Functional Pyelocalyceal Renal Model for the Evaluation of Renal Calculi Passage While Riding a Roller Coaster

Marc A. Mitchell, DO
David D. Wartinger, DO, JD

From the Doctors Clinic in Poulsbo, Washington (Dr Mitchell), and the Department of Osteopathic Surgical Specialties at the Michigan State University College of Osteopathic Medicine in East Lansing (Dr Wartinger).

Financial Disclosures:

Context: The identification and evaluation of activities capable of dislodging calyceal renal calculi require a patient surrogate or validated functional pyelocalyceal renal model.

Objective: To evaluate roller coaster facilitation of calyceal renal calculi passage using a functional pyelocalyceal renal model.

Methods: A previously described adult ureteroscopy and renoscopy simulator (Ideal Anatomic) was modified and remolded to function as a patient surrogate. Three renal calculi of different sizes from the patient who provided the original computed tomo-

The Journal of the American Osteopathic Association 2016;116:647

Stripes and tails against flies

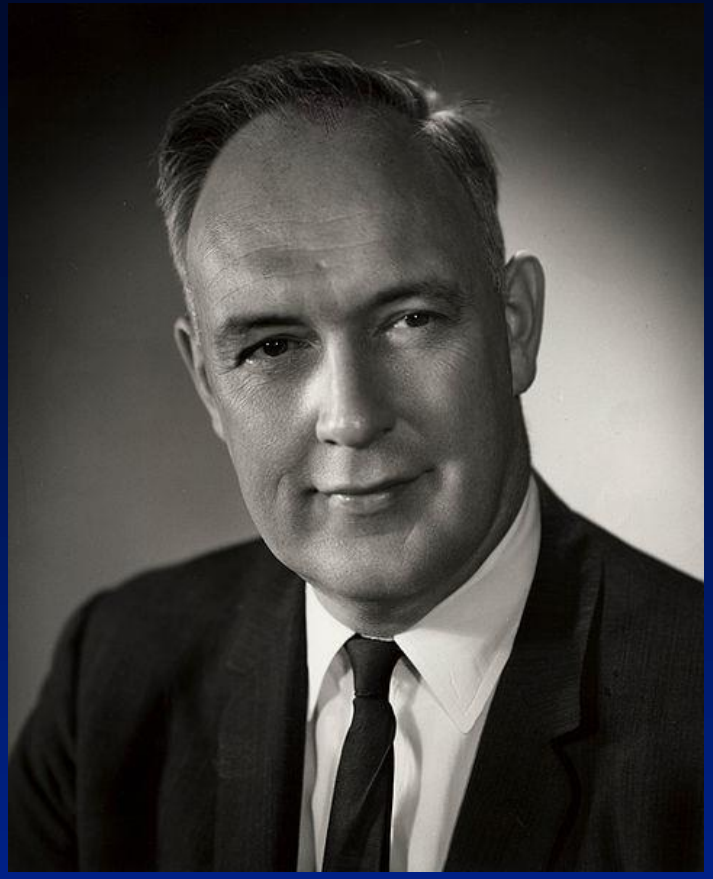
February 20th, 2019

"The Surprising Reason Zebras Have Stripes," Ed Yong's essay in *The Atlantic*, celebrates the most recently published research about how some large mammals manage to protect themselves against flies. Tim Caro and colleagues experimented with striped blankets, publishing their story in the research journal *PLoS ONE*.

Ig Nobel Prize winners Gábor Horváth, Susanne Äkesson, and colleagues published a paper about the attractiveness or repulsiveness of zebra stripes to flies, in 2012 in *The Journal of Experimental Biology*. This year they published a paper in Royal Society Open Science about the effect, on flies, of stripes painted on humans.

Last year, Ig Nobel Prize winner David Hu and colleagues published a paper, in the *Journal of Experimental Biology*, about how zebras and other animals use their tails to repel flies. Co-author Marguerite Matherne presented this


DEU
DOKUZ EYLUL ÜNİVERSİTESİ
MANAV
DEU
MANAV



Dr. William H. Stewart (1921-2008)

ABD Sağlık Bakanı

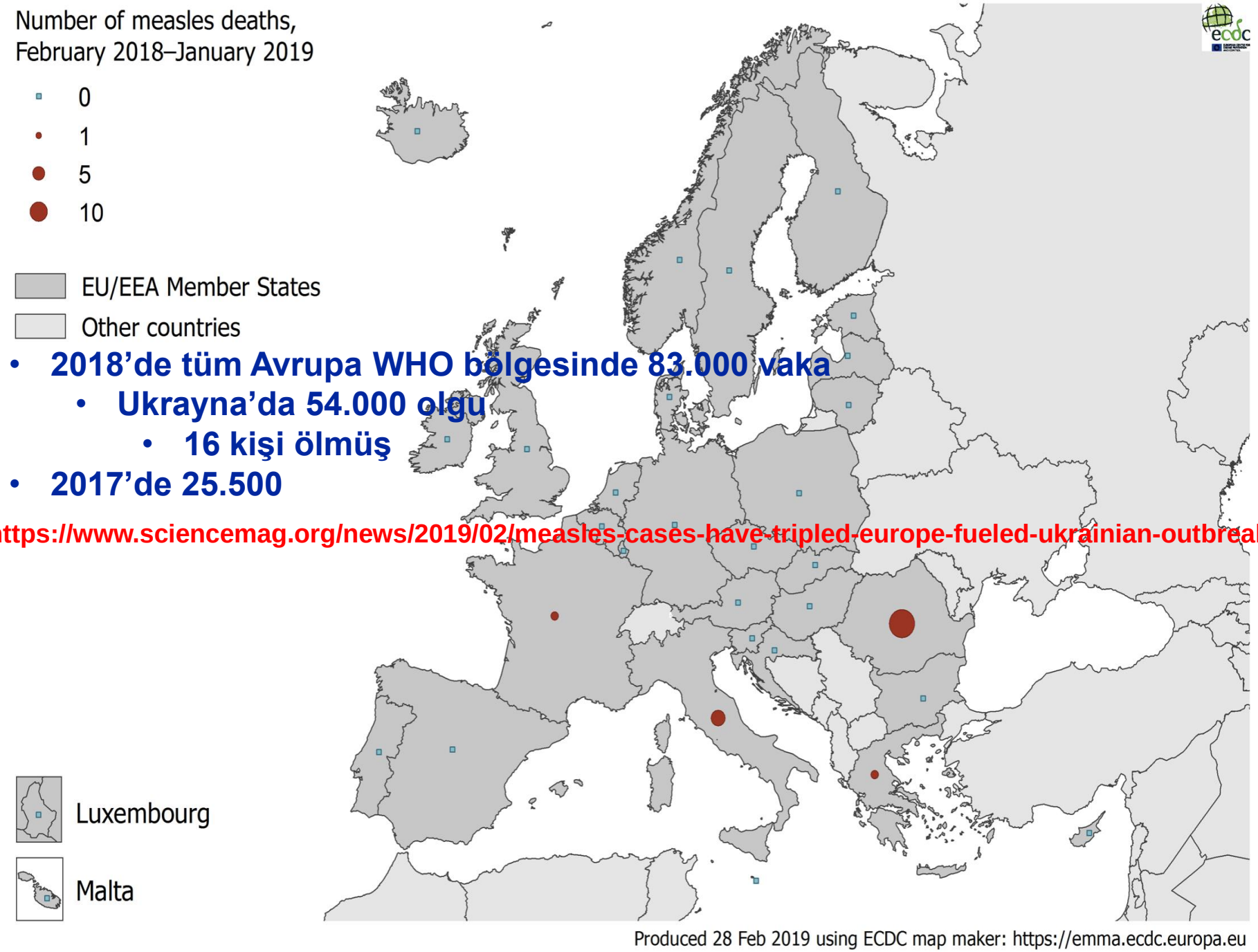
"Artık infeksiyon hastalıkları ile ilgili konuyu kapatmak gerek. Mikroplara karşı kazandığımız zaferi ilan ediyoruz."

1967

Dünya Sağlığı İçin 10 Tehdit WHO-2019

- Hava kirliliği ve iklim değişikliği
- Bulaşıcı olmayan hastalıklar
- Global influenza pandemisi
- Kuraklık ve savaş
- Antibiyotik direnci
- Ebola vd yüksek riskli patojenler
- Kötü 1. basamak tedavi
- Aşı karşıtlığı
- Dengue
- HIV

https://www.who.int/emergencies/ten-threats-to-global-health-in-2019



- **2018'de tüm Avrupa WHO bölgesinde 83.000 vaka**
  - **Ukrayna'da 54.000 olgu**
    - **16 kişi ölmüş**
- **2017'de 25.500**

https://www.sciencemag.org/news/2019/02/measles-cases-have-tripled-europe-fueled-ukrainian-outbreak

Clinical Infectious Diseases

IDSA Infectious Diseases Society of America

hivma hiv medicine association

Vaccines and Autism: A Tale of Shifting Hypotheses FREE

Stanley Plotkin ✉, Jeffrey S. Gerber, Paul A. Offit

Clinical Infectious Diseases, Volume 48, Issue 4, 15 February 2009, Pages 456–461, https://doi.org/10.1086/596476

Published: 15 February 2009 **Article history** ▼

Abstract

Although child vaccination rates remain high, some parental concern persists that vaccines might cause autism. Three specific hypotheses have been proposed: (1) the combination measles-mumps-rubella vaccine causes autism by damaging the intestinal lining, which allows the entrance of encephalopathic proteins; (2) thimerosal, an ethylmercury-containing preservative in some vaccines, is toxic to the central nervous system; and (3) the simultaneous administration of multiple vaccines overwhelms or weakens the immune system. We will discuss the genesis of each of these theories and review the relevant epidemiological evidence.

MMR Aşısı ve Otizm Arasında İlişkinin Gösterilemediği Çalışmalar

Source	Study design	Study location
Taylor et al., 1999 [5]	Ecological	United Kingdom
Farrington et al., 2001 [6]	Ecological	United Kingdom
Kaye et al., 2001 [7]	Ecological	United Kingdom
Dales et al., 2001 [8]	Ecological	United States
Fombonne et al., 2006 [9]	Ecological	Canada
Fombonne and Chakrabarti, 2001 [10]	Ecological	United Kingdom
Taylor et al., 2002 [11]	Ecological	United Kingdom
DeWilde et al., 2001 [12]	Case-control	United Kingdom
Makela et al., 2002 [13]	Retrospective cohort	Finland
Madsen et al., 2002 [14]	Retrospective cohort	Denmark
DeStefano et al., 2004 [15]	Case-control	United States
Peltola et al., 1998 [16]	Prospective cohort	Finland
Patja et al., 2000 [17]	Prospective cohort	Finland

Plotkin S, et al. Clin Infect Dis 2009;48: 456

Aşılar İçindeki Thimerosal ile Otizm Arasında İlişkinin Gösterilemediği Çalışmalar

Source	Study design	Location
Stehr-Green et al., 2003 [22]	Ecological	Sweden and Denmark
Madsen et al., 2003 [23]	Ecological	Denmark
Fombonne et al., 2006 [9]	Ecological	Canada
Hviid et al., 2003 [24]	Retrospective cohort	Denmark
Verstraeten et al., 2003 [25]	Retrospective cohort	United States
Heron and Golding, 2004 [26]	Prospective cohort	United Kingdom
Andrews et al., 2004 [27]	Retrospective cohort	United Kingdom

Plotkin S, et al. Clin Infect Dis 2009;48: 456

Analysis of the clinical antibacterial and antituberculosis pipeline

Ursula Theuretzbacher, Simon Gottwalt, Peter Beyer, Mark Butler, Lloyd Czaplewski, Christian Lienhardt, Lorenzo Moja, Mical Paul, Sarah Paulin, John H Rex, Lynn L Silver, Melvin Spigelman, Guy E Thwaites, Jean-Pierre Paccaud, Stephan Harbarth

This analysis of the global clinical antibacterial pipeline was done in support of the Global Action Plan on Antimicrobial Resistance. The study analysed to what extent antibacterial and antimycobacterial drugs for systemic human use as well as oral non-systemic antibacterial drugs for *Clostridium difficile* infections were active against pathogens included in the WHO priority pathogen list and their innovativeness measured by their absence of cross-resistance (new class, target, mode of action). As of July 1, 2018, 30 new chemical entity (NCE) antibacterial drugs, ten biologics, ten NCEs against *Mycobacterium tuberculosis*, and four NCEs against *C difficile* were identified. Of the 30 NCEs, 11 are expected to have some activity against at least one critical priority pathogen expressing carbapenem resistance. The clinical pipeline is dominated by derivatives of established classes and most development candidates display limited innovation. New antibacterial drugs without pre-existing cross-resistance are under-represented and are urgently needed, especially for geographical regions with high resistance rates among Gram-negative bacteria and *M tuberculosis*.

Lancet Infect Dis 2019; 19: e40–50

Published Online October 15, 2018 http://dx.doi.org/10.1016/S1473-3099(18)30513-9

Center for Anti-Infective Agents, Vienna, Austria (U Theuretzbacher PhD); Biovision Foundation for Ecological Development, Zurich, Switzerland (S Gottwalt); Essential Medicines and Health

Yeni Beta-laktamaz İnhibitörlerinin *in vitro* Aktiviteleri

	Avibactam	Vaborbactam	Relebactam	Clavulanate	Sulbactam	Tazobactam
Class A						
TEM	+	+	+	+	+	+
SHV	+	+	+	+	+	+
CTX-M	+	+	+	+	+	+
KPC	+	+	+	-	-	-
Class B						
MBL	-	-	-	-	-	-
Class C						
AmpC	+	+	+	-	-	±
Class D						
OXA	±	-	±	-	-	-

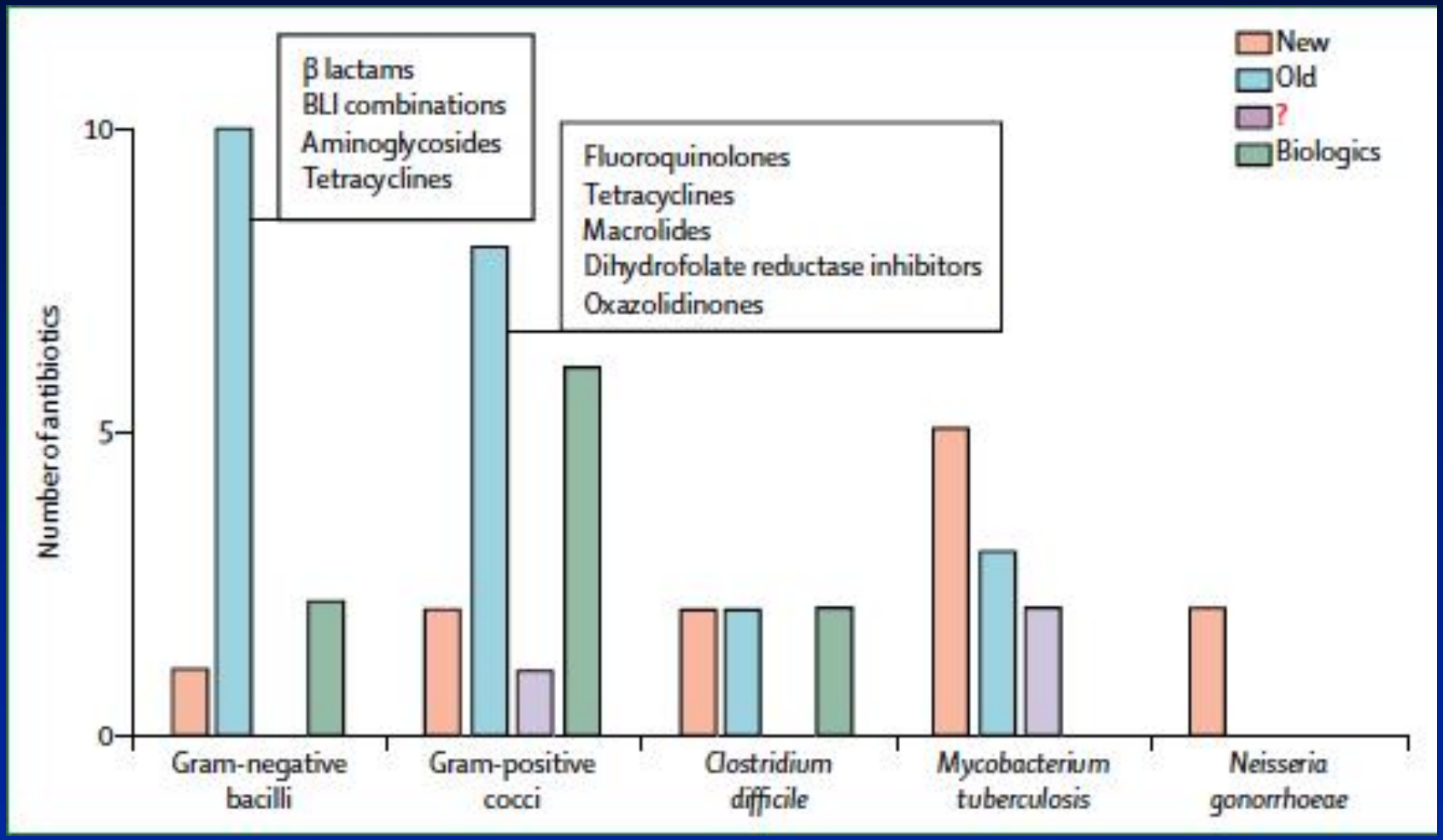
Modified from Zhanel GG, et al. Drugs 2018;78:65

Geliştirilmekte Olan İnhibitör Kombinasyonları

Combination	Phase	Route	CRAB	CRPA	CRE
Avibactam + aztreonam	3	iv	±	±	+
AAI101 + Cefepime	3	iv	-	-	-
ETX2514 + sulbactam	2	iv	+	-	-
Zidebactam + Cefepime	1	iv	-	±	+
VNRX-5133 + cefepime	1	iv	±	±	+
ETX0282 + cefpodoxime	1	po	-	-	+
AIC-499 + unknown BLI	1	iv	±	±	±

Theuretzbacher U, et al. Lancet Infect Dis 2018; October 15

Number of Antibiotics in Clinical Development

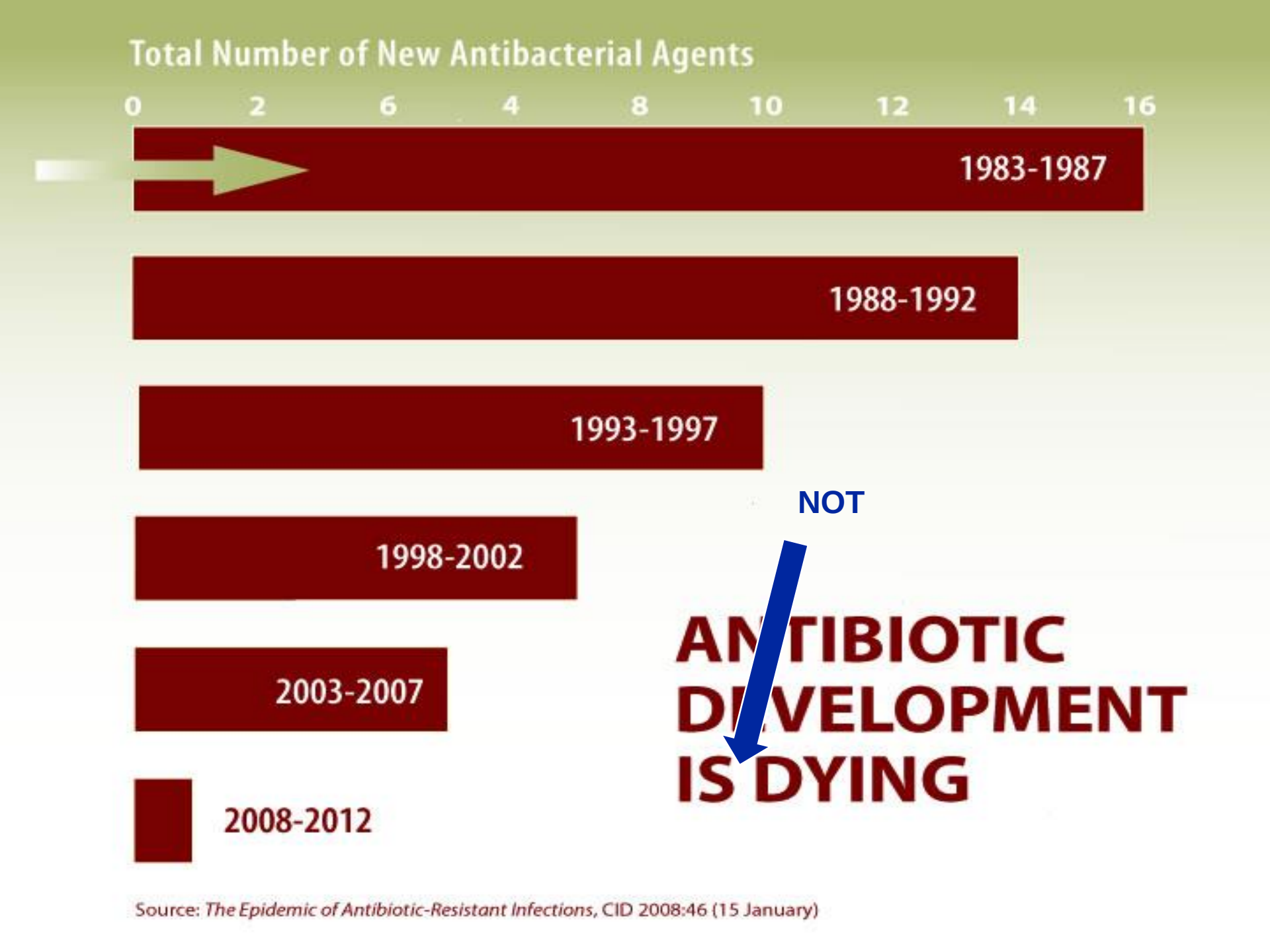


Theuretzbacher U, et al. Lancet Infcet Dis 2019;19:e40

Antivirulence Strategies
Approved Drugs

Compound name	Subtype or chemistry	Molecular targets	Furthest developmental stage
Clostridium botulinum			
BabyBIG	Human, mostly IgG, plasma-derived immune globulin	BoNT serotypes A and B	FDA approved
BAT	Equine, Fab and $F(ab')_2$; plasma-derived immunoglobulin	BoNT serotypes A–G	FDA approved (NCT00360737)
Bacillus anthracis			
Raxibacumab	Human, mAb IgG1	Protective antigen of anthrax toxin	FDA approved
Obiltoxaximab	Human, mAb IgG1	Protective antigen of anthrax toxin	FDA approved
Clostridium difficile			
Bezlotoxumab (also known as MDX-1388)	Human, mAb IgG	TcdB	FDA approved (NCT01241552, NCT01513239)

Dickey SW, et al. Nature Rev Drug Discover 2017;16:457


Total Number of New Antibacterial Agents
0
2
6
4
8
10
12
14
16
1983-1987
1988-1992
1993-1997
1998-2002
2003-2007
2008-2012
NOT
ANTIBIOTIC
DEVELOPMENT
IS DYING
Source: The Epidemic of Antibiotic-Resistant Infections, CID 2008:46 (15 January)

Clinical Microbiology and Infection 24 (2018) 684–686

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Hot topic

Microbiota transplantation and/or CRISPR/Cas in the battle against antimicrobial resistance

Study design	No. of patients	Bacteria targeted	Intervention used	% of success	Length of follow-up	Study
Case report	1	ESBL-producing *Escherichia coli*	FMT by nasoduodenal tube	ESBL-*E. coli* negative in stool after 2 weeks	1, 2, 4 and 12 weeks	[9]
Case report	1	Several MDROs	FMT by colonoscopy	Success	25 months	[10]
Case report	1	VRE	FMT by nasoduodenal tube	Relative abundance of VRE (84%) before FMT (24%) after 3 weeks (0.2%) after 7 months	1 and 3 weeks, and 7 months	[11]
Case report	1	OXA-48–producing *Klebsiella pneumoniae*	FMT by nasoduodenal tube	Success	7 and 14 days	[12]
Case report	1	VIM-1– producing *K. pneumoniae*	Colonoscopy	Success	1 and 6 weeks, and 6 months	[13]
Case report	1	ESBL-producing *E. coli*	FMT by nasoduodenal tube	No success	1 week to 3 months	[14]
Prospective single-centre study[a]	11	VRE	FMT via enema	72.7%	7, 30 and 60 days, and 6 months	[15]
Pilot prospective multicentre study	8	CRE and VRE	FMT by nasoduodenal tube	25% (first month) 37.5% (third month)	1 and 3 months	[16]
Prospective single-centre study	20	Several MDROs	FMT by nasoduodenal tube	75% (1 month) 93% (6 month)	1 and 6 months	[17]

CRE, carbapenem-resistant *Enterobacteriaceae*; ESBL, extended-spectrum β-lactamase; FMT, faecal microbiota transplantation; MDRO, multidrug-resistant organism; VRE, vancomycin-resistant enterococci.

[a] Stool VRE clearance in *post hoc* analysis of phase 2 PUNCH CD study assessing a microbiota-based drug for recurrent *Clostridium difficile* infection.

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

EXPERIMENTAL THERAPEUTICS

Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant *Acinetobacter baumannii* Infection

Robert T. Schooley,[a] Biswajit Biswas,[b,c] Jason J. Gill,[d,e] Adriana Hernandez-Morales,[f] Jacob Lancaster,[e] Lauren Lessor,[e] Jeremy J. Barr,[g,o] Sharon L. Reed,[a,h] Forest Rohwer,[g] Sean Benler,[g] Anca M. Segall,[g] Randy Taplitz,[a] Davey M. Smith,[a] Kim Kerr,[a] Monika Kumaraswamy,[a] Victor Nizet,[i,j] Leo Lin,[i] Melanie D. McCauley,[a] Steffanie A. Strathdee,[a] Constance A. Benson,[a] Robert K. Pope,[k] Brian M. Leroux,[k] Andrew C. Picel,[l] Alfred J. Mateczun,[b] Katherine E. Cilwa,[n] James M. Regelmbal,[b] Luis A. Estrella,[b] David M. Wolfe,[b] Matthew S. Henry,[b,c] Javier Quinones,[b,c] Scott Salka,[m] Kimberly A. Bishop-Lilly,[b,c] Ry Young,[e,f] Theron Hamilton[b]

Department of Medicine, University of California, San Diego, La Jolla, California, USA[a]; Biological Defense Research Directorate, Naval Medical Research Center, Frederick, Maryland, USA[b]; Henry M. Jackson Foundation, Bethesda, Maryland, USA[c]; Department of Animal Science, Texas A&M University, College Station, Texas, USA[d]; Center for Phage Technology, Texas A&M AgriLife Research and Texas A&M University, College Station, Texas, USA[e]; Department of Biochemistry and Biophysics, Texas A&M University, College Station, Texas, USA[f]; Department of Biology, San Diego State University, San Diego, California, USA[g]; Department of Pathology, University of California, San Diego, La Jolla, California, USA[h]; Department of Pediatrics, University of California, San Diego, La Jolla, California, USA[i]; Skaggs School of Pharmacy & Pharmaceutical Sciences, University of California, San Diego, La Jolla, California, USA[j]; National Biodefense Analysis and Countermeasures Center, Frederick, Maryland, USA[k]; Department of Radiology, University of California, San Diego, La Jolla, California, USA[l]; AmpliPhi Biosciences, San Diego, California, USA[m]; Advanced Surgical Imaging Program, Department of Regenerative Medicine, Naval Medical Research Center, Silver Spring, Maryland, USA[n]; Monash University, School of Biological Sciences, Melbourne, Australia[o]

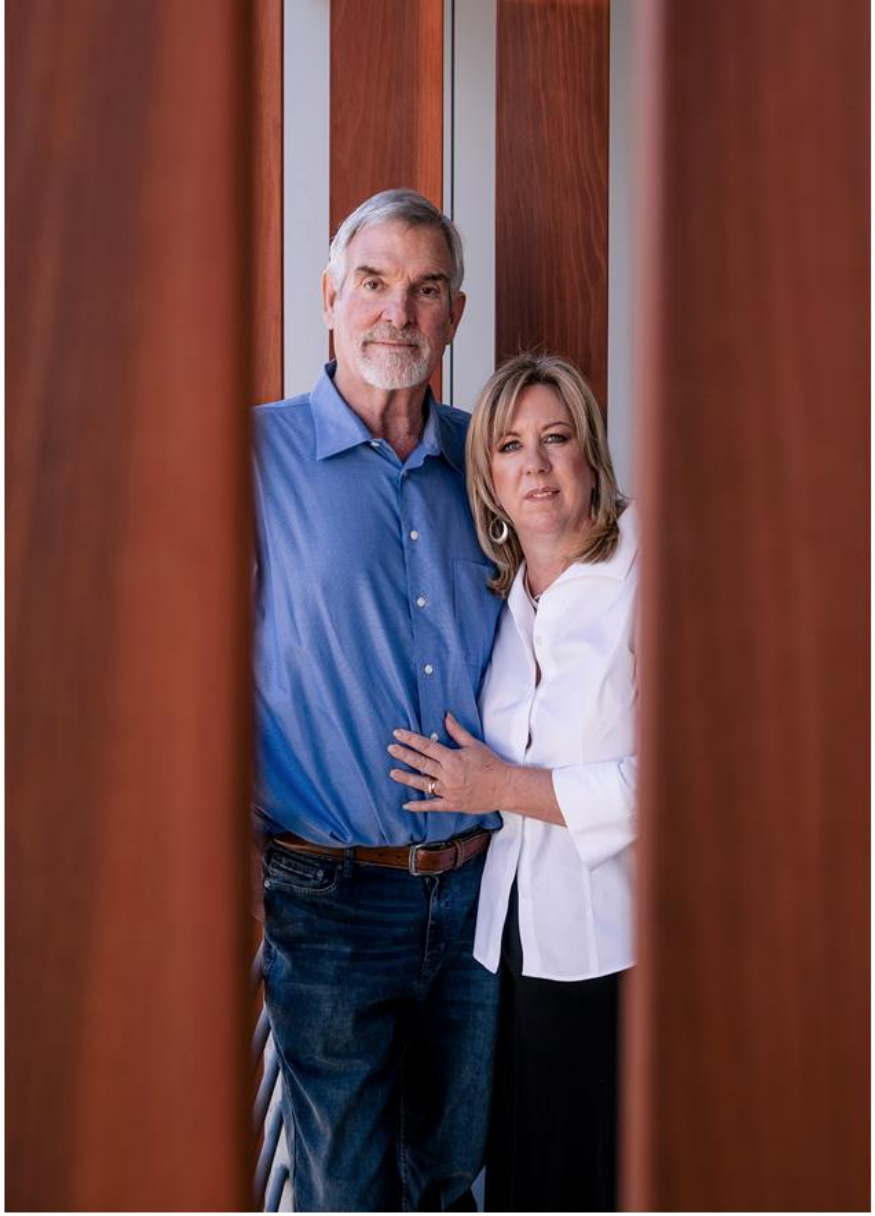
ABSTRACT Widespread antibiotic use in clinical medicine and the livestock industry has contributed to the global spread of multidrug-resistant (MDR) bacterial pathogens, including *Acinetobacter baumannii*. We report on a method used to produce a personalized bacteriophage-based therapeutic treatment for a 68-year-old diabetic patient with necrotizing pancreatitis complicated by an MDR *A. baumannii* infection. Despite multiple antibiotic courses and efforts at percutaneous drainage of a pancreatic pseudocyst, the patient deteriorated over a 4-month period. In the absence of effective antibiotics, two laboratories identified nine different bacteriophages with lytic activity for an *A. baumannii* isolate from the patient. Administration of these bacteriophages intravenously and percutaneously into the abscess cavities was associated with reversal of the patient's downward clinical trajectory, clearance of the *A. baumannii* infection, and a return to health. The outcome of this case suggests that the methods described here for the production of bacteriophage therapeutics could be applied to similar cases and that more concerted efforts to investigate the use of therapeutic bacteriophages for MDR bacterial infections are warranted.

KEYWORDS *Acinetobacter*, bacteriophage therapy, multidrug resistance

Received 18 May 2017 **Returned for modification** 28 June 2017 **Accepted** 2 August 2017

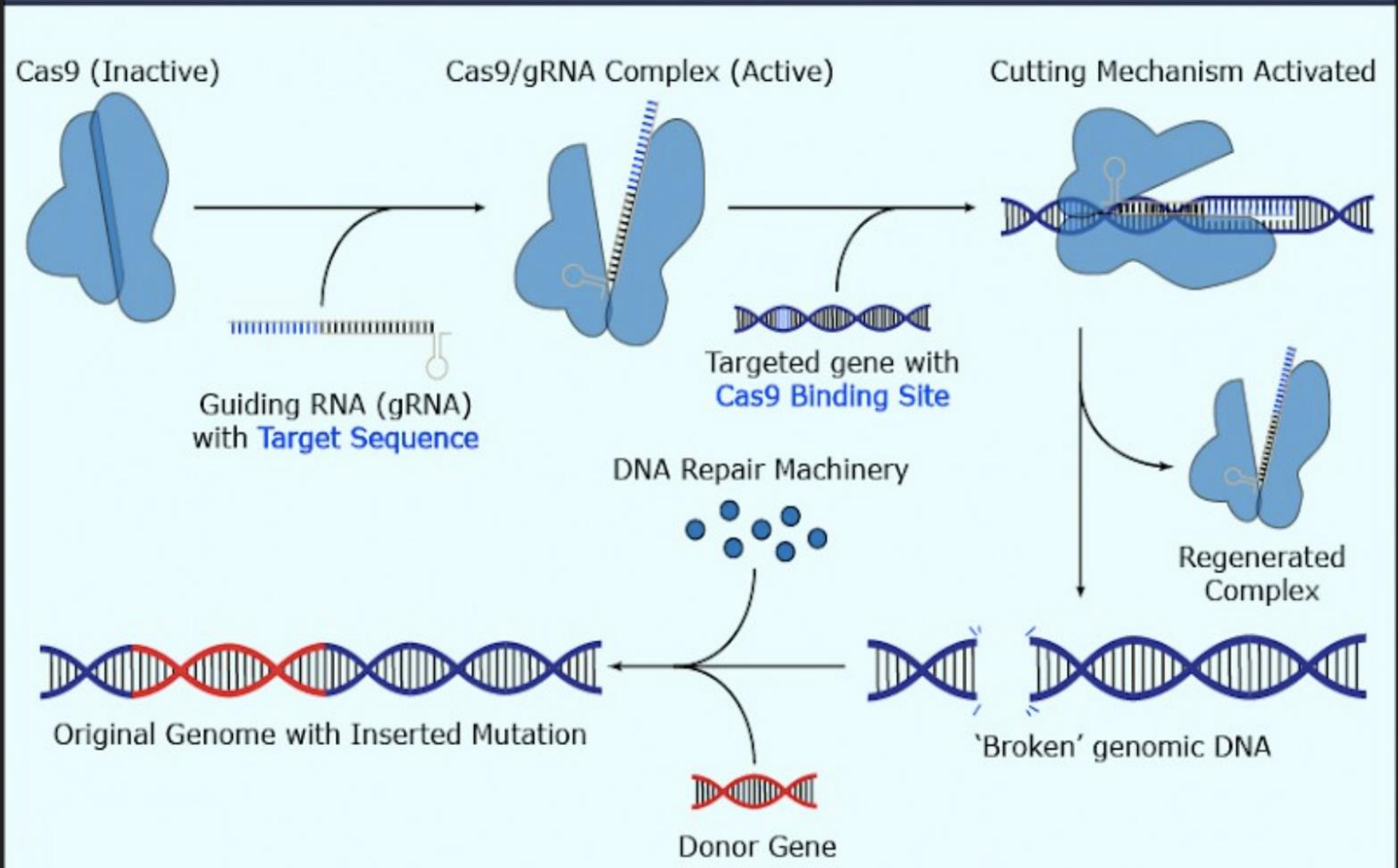
Accepted manuscript posted online 14 August 2017

Citation Schooley RT, Biswas B, Gill JJ, Hernandez-Morales A, Lancaster J, Lessor L, Barr JJ, Reed SL, Rohwer F, Benler S, Segall AM, Taplitz R, Smith DM, Kerr K, Kumaraswamy M, Nizet V, Lin L, McCauley MD, Strathdee SA, Benson CA, Pope RK, Leroux BM, Picel AC, Mateczun AJ, Cilwa KE, Regelmbal JM, Estrella LA, Wolfe DM, Henry MS, Quinones J, Salka S, Bishop-Lilly KA, Young R, Hamilton T. 2017. Development and use of personalized bacteriophage-based therapeutic cocktails to treat a patient with a disseminated resistant *Acinetobacter baumannii* infection. Antimicrob Agents Chemother 61:e00954-17. https://doi.org/10.1128/AAC.00954-17.



Tom Patterson and Steffanie Strathdee

CRISPR/Cas9 Technology - A Cure for Genetic Disease?



MENU

nature
International journal of science

Letter | Published: 05 March 2019

HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation

Ravindra K Gupta ✉, Sultan Abdul-jawad, Laura E McCoy, Hoi Ping Mok, Dimitra Peppa, Maria Salgado, Javier Martinez-Picado, Monique Nijhuis, Annemarie M. J. Wensing, Helen Lee, Paul Grant, Eleni Nastouli, Jonathan Lambert, Matthew Pace, Fanny Salasc, Christopher Monit, Andrew Innes, Luke Muir, Laura Waters, John Frater, Andrew M. L. Lever, S. G. Edwards, Ian H. Gabriel & Eduardo Olavarria

Nature (2019) | Download Citation ⬇

UKD Universitätsklinikum Düsseldorf

CROI 4-7 March 2019, Seattle

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

ANALYTIC TREATMENT INTERRUPTION (ATI) AFTER ALLOGENEIC CCR5-D32 HSCT FOR AML IN 2013

Björn-Erik O. Jensen[1], Elena Knops[3], Nadine Lübke[4], Annemarie Wensing[5], Javier Martinez-Picado[6], Rolf Kaiser[3], Monique Nijhuis[5], Maria Salgado[6], Thomas Harrer[7], Eva Heger[3], Johanna M. Eberhard[8], Ilona Hauber[9], Jacob D. Estes[10], Carsten Münk[1], Dieter Häussinger[1], Guido Kobbe[2]

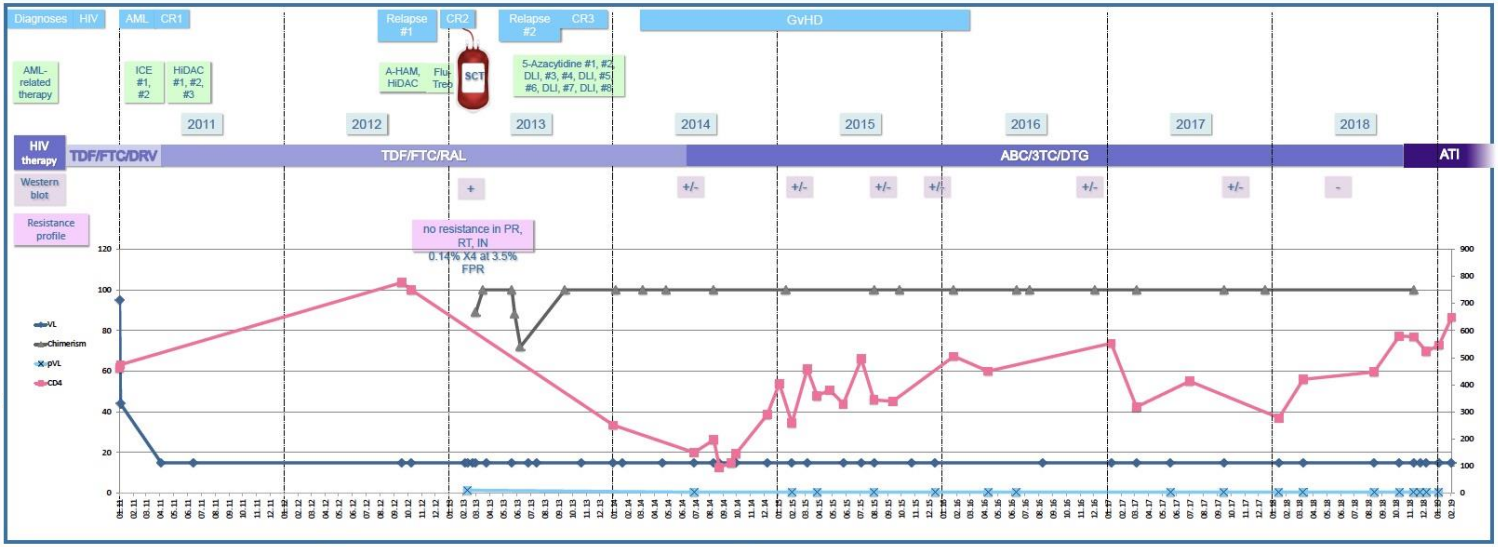
[1] Department of Gastroenterology, Hepatology and Infectious Diseases, University of Düsseldorf, Germany; [2] Department of Hematology, Oncology and Clinical Immunology, University of Düsseldorf, Germany; [3] Institute of Virology, University of Cologne, Germany; [4] Institute for Virology, University of Düsseldorf, Germany; [5] University Medical Center Utrecht, Netherlands; [6] IrsiCaixa Institute for AIDS Research, Badalona, Spain; [7] Medicine 3, University Hospital Erlangen, Germany; [8] I. Medical Clinic and Polyclinic, Medical Center Hamburg-Eppendorf, Germany [9] Heinrich Pette Institute, Leibniz Institute for Experimental Virology, Hamburg, Germany; [10] Division of Pathobiology and Immunology, Oregon National Primate Research Center, Oregon Health & Science University, USA

BACKGROUND

- As reported before (CROI 2016) a now 49y old HIV-infected male patient did receive unmodified HSCT from a female 10/10 CCR5-d32 DKMS-donor in February 2013 because of acute myeloid leukemia while being in 2nd complete remission (CR).
- By then proviral DNA load was 29400 cop/mL and all anticipated bands could be detected by western blot.
- At the time of HSCT coreceptor-usage was predicted as R5-tropic (Sanger: FPR 44.5%; NGS: 0.14% X4 at 3.5% FPR, geno2pheno), confirmed by phenotypic testing (TropChase).
- During HSCT and until November 2018 the patient remained on ART with undetectable viral load in plasma. He had a 2nd relapse of AML in June 2013 but after 8 courses of 5-azacytidine and 4 donor lymphocyte infusions CR was achieved and immunosuppression was stopped in October 2017.

METHODS

PBMC and tissues were analysed by ddPCR, qPCR and in situ hybridization in several laboratories as well as humeral and T-cell responses. Infectious virus was analysed on CD4+ T-cells (qVOA, MVOA). Patient was registered to IciStem as patient #19.

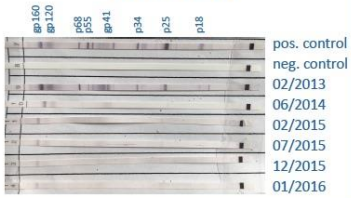


TropChase

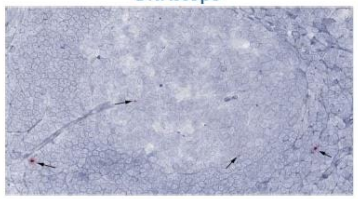
Clone	gp120-V3 amino acid sequence	# sequencing reads	genotypic prediction FPR (%)	phenotypic analysis in Tcells Magi (R5/X4)	MT2 (X4)
D1	CTRPNNNTREGIHIGPGRAFFTTGEIIGNIREASC	4	95,78	R5	R5
D2	CTRPNNNTRKSIHIGPGRAFFTTGEIIGNIKEAYC	2	95,64	R5	R5
D3	CTRPNNNTRKSIHIGPGRAFFTTGEIIGNIGEAYC	2	95,64	R5	R5
D4	CTRPNNNTRKGIHIGPGRAFFTTGEIIGNIREASC	2062	77,33	R5	R5
D5	CTRPNNNTRKGITIGPGRAFFTTGEIIGDIRQAHC	4866	30,67	R5	R5
D6	CTRPNNNTRKGIHIGSRKAFFTTGGIIGDIRQAYC	2	10,61	R5/X4	X4
D7	CTRPHTNTRKRIHIGPGRAFFTTGEIIGDIRQAYC	7	1,74	R5/X4	X4
D8	CTKPNNNTRKRIHIGPGRAFFTTGEIIGNIRQASC	2	1,74	R5	R5
D9	CTRPNNNIRKRIHIGPGRAFFTTGEIIGNIREAYC	3	1,16	R5/X4	X4
HxB2V3Bal		control R5	51,8	R5	R5
HxB2		control X4	0	X4	X4

Monique Nijhuis, Utrecht, ICISTEM

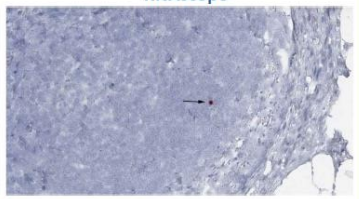
WESTERN BLOT



DNAscope



RNAscope



POST-TRANSPLANTATION

- Concerning HIV, all PBMC samples were negative for proviral DNA by conventional and digital droplet PCR in different labs at multiple time points.
- Liquor (July 2014), rectum (April 2015, March 2016), ileum (March 2016) and bone marrow (August 2015) showed also negative test results.
- Further testing with 0.1 Mio cells from the ileum showed 1/4 replicates positive with LTR-, but negative with gag-primers. There were also 2 positive signals in T-cell subsets (T_{CM} 0.2 Mio cells: ddPCR 6.7 cop/10^6cells, qPCR neg., T_{EM} 0.36 Mio cells: qPCR 5 cop/10^6cells, ddPCR neg.) with all other subsets negative in ddPCR and qPCR.
- No HIV-DNA could be detected by PCR in lymph nodes collected 05/17, but via in situ hybridization assays (RNAscope, DNAscope) few positive signals were detected.
- Viral outgrowth assays (VOA) were negative February 2016, March 2016 and May 2016 (23 Mio CD4+ Tcells, IUPM <0.031/10^6 CD4 T cells).
- Mouse viral outgrowth assays (mVOA, April 2016 Rag2-/-γc-/-, April 2017 NOD-SCID IL2gR-/-) also showed negative test results.
- CTL-assays showed a strong response against HLA-A2-epitope YV9 (RT) and HLA-B7-epitope YL9 (Gag-P6), which was not present in cells from the stem-cell donor.
- The Western blot shows an incomplete pattern (gp160 slightly positive, others negative).

SUMMARY & CONCLUSION

- Despite low signals in ultrasensitive assays no virus could be detected in qVOA/mVOA in the Duesseldorf patient. Taking into account the homozygous CCR5-d32 status we consider a viral rebound to be unlikely. Since the functional relevance is unclear an ATI is the only way to find out whether HIV has been eradicated by allogeneic CCR5-d32 HSCT.
- Therefore ART was stopped in November 2018 after thorough discussion with the patient.
- Plasma viral load and proviral DNA is measured twice weekly since stopping cART, immunological follow-up is performed monthly.
- Despite all plasma samples being negative after ATI longer surveillance is essential.

We are grateful to the patient for his participation and commitment.

Research

JAMA | Original Investigation

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance

A Randomized Clinical Trial

Patrick N. A. Harris, MBBS; Paul A. Tambyah, MD; David C. Lye, MBBS; Yin Mo, MBBS; Tau H. Lee, MBBS; Mesut Yilmaz, MD; Thamer H. Alenazi, MD; Yaseen Arabi, MD; Marco Falcone, MD; Matteo Bassetti, MD, PhD; Elda Righi, MD, PhD; Benjamin A. Rogers, MBBS, PhD; Souha Kanj, MD; Hasan Bhally, MBBS; Jon Iredell, MBBS, PhD; Marc Mendelson, MBBS, PhD; Tom H. Boyles, MD; David Looke, MBBS; Spiros Miyakis, MD, PhD; Genevieve Walls, MB, ChB; Mohammed Al Khamis, MD; Ahmed Zikri, PharmD; Amy Crowe, MBBS; Paul Ingram, MBBS; Nick Daneman, MD; Paul Griffin, MBBS; Eugene Athan, MBBS, MPH, PhD; Penelope Lorenc, RN; Peter Baker, PhD; Leah Roberts, BSc; Scott A. Beatson, PhD; Anton Y. Peleg, MBBS, PhD; Tiffany Harris-Brown, RN, MPH; David L. Paterson, MBBS, PhD; for the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

MERINO Çalışması

- 379 hasta, 26 merkez, 9 ülke
- *Pip-tazo S, E. coli* or *Klebsiella spp*. bakteremisi olan erişkin hastalar
- Randomize, pip-tazo (4 X 4.5 g) veya meropenem (3 X 1g)
- 30 günlük mortalite
  - %12.3 pip-tazo vs % 3.7%
  - P=.90 non-inferiority için
- Ciddi adverse olay ve direnç gelişimi açısından fark yok

Harris PNA, et al. JAMA 2018;320:984

MERINO-Diğer Ayrıntılar

- Suşların %86'sında ESBL (+)
  - *E. coli* %85
  - *K. pneumoniae* %92.5
- Suşların
  - sadece 12'si (%3.9) pip-tazo dirençli
  - %67.6 suşta ESBL ile birlikte OXA-1 veya varyanları mevcut (inhibtör dirençli)

Harris PNA, et al. JAMA 2018;320:984

THE LANCET
Infectious Diseases

ARTICLES | VOLUME 18, ISSUE 4, P391-400, APRIL 01, 2018

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial

Mical Paul, MD • Prof George L Daikos, MD • Emanuele Durante-Mangoni, MD • Dafna Yahav, MD • Prof Yehuda Carmeli, MD • Yael Dishon Benattar, MA • et al. Show all authors

Published: February 15, 2018 • DOI: https://doi.org/10.1016/S1473-3099(18)30099-9 • Check for updates

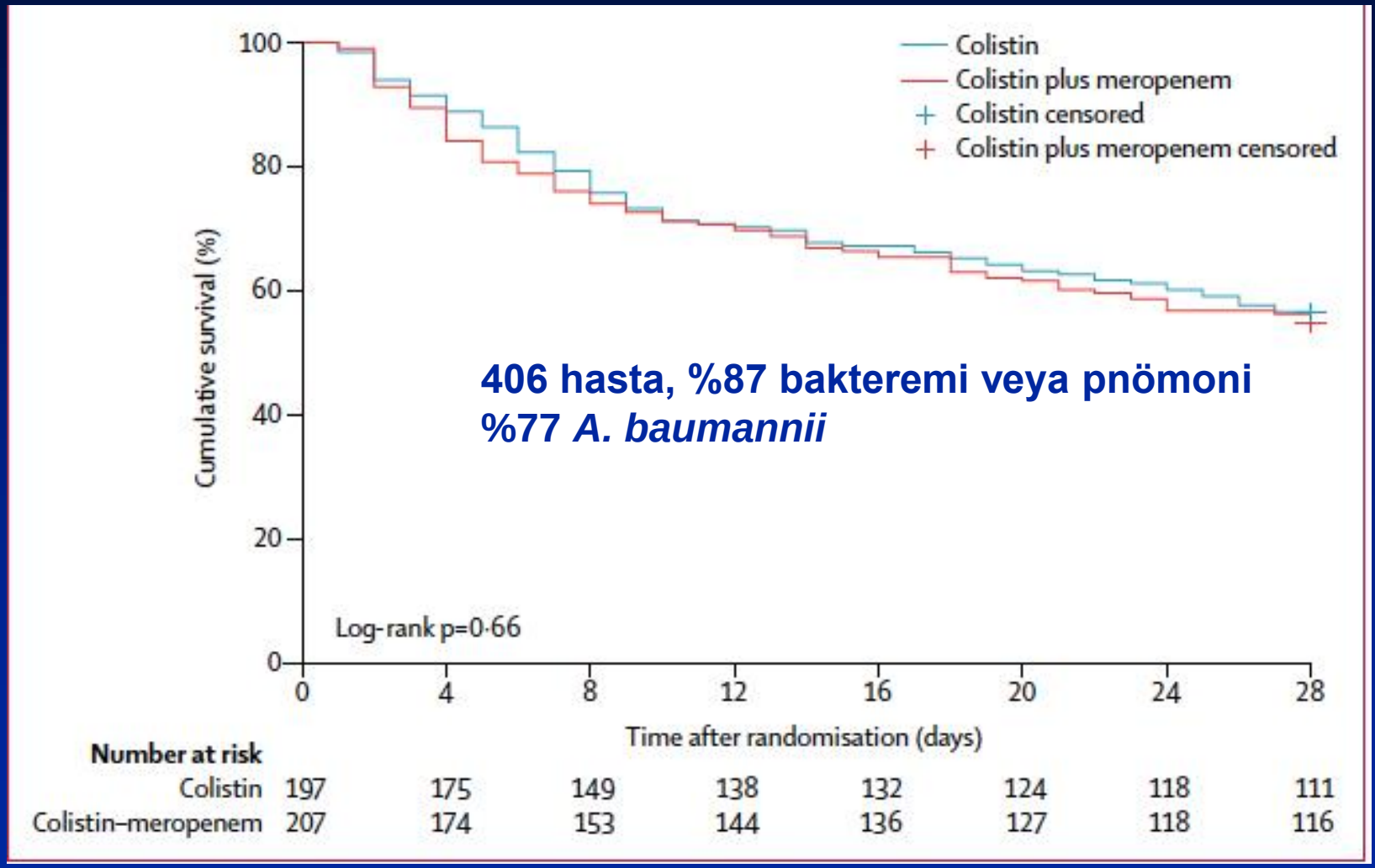
Summary
References
Article Info
Linked Articles
Related Specialty Collections

Summary

Background

Colistin–carbapenem combinations are synergistic in vitro against carbapenem-resistant Gram-negative bacteria. We aimed to test whether combination therapy improves clinical outcomes for adults with infections caused by carbapenem-resistant or carbapenemase-

Karbapenem-R Gram (-) Bakteri İnfeksiyonlarının Tedavisinde Kolistin *vs* Kolistin + Meropenem



Paul M, et al. Lancet Infect Dis 2018;18:391

The Association Between Empirical Antibiotic Treatment and Mortality in Severe Infections Caused by Carbapenem-resistant Gram-negative Bacteria: A Prospective Study

Yael Zak-Doron, Yael Dishon Benattar, Iris Pfeffer, George L Daikos, Anna Skiada, Anastasia Antoniadou, Emanuele Durante-Mangoni, Roberto Andini, Giusi Cavezza, Leonard Leibovici, ... Show more

Clinical Infectious Diseases, Volume 67, Issue 12, 28 November 2018, Pages 1815–1823, https://doi.org/10.1093/cid/ciy371

Published: 27 April 2018 **Article history** ▾

Abstract

Background

Empirical colistin should be avoided. We aimed to evaluate the association between covering empirical antibiotics (EAT) and mortality for infections caused by carbapenem-resistant gram-negative bacteria (CRGNB).

Sonuç

- **Karbapenem dirençli ciddi Gram (-) bakteri infeksiyonlarının tedavisinde kolistin veya kolistin ve meropenm kombinasyonunun empirik olarak başlanmasının sağkalım üzerine etkisi yok…**

Zak-Doron Y, et al. Clin Inferct Dis 2018;67:1815

FDA News Release

FDA approves new drug to treat influenza

For Immediate Release October 24, 2018

Release

Español

Today, the U.S. Food and Drug Administration approved Xofluza (baloxavir marboxil) for the treatment of acute uncomplicated influenza (flu) in patients 12 years of age and older who have been symptomatic for no more than 48 hours.

“This is the first new antiviral flu treatment with a novel mechanism of action approved by the FDA in nearly 20 years. With thousands of people getting the flu every year, and many people becoming seriously ill, having safe and effective treatment alternatives is critical. This novel drug provides an important, additional treatment option,” said FDA Commissioner Scott Gottlieb, M.D. “While there are several FDA-approved antiviral drugs to treat flu, they’re not a substitute for yearly vaccination. Flu season is already well underway, and the U.S. Centers for Disease

Inquiries

Media

Alison Hunt
240-402-0764

Consumers

888-INFO-FDA

Related Information

- FDA - Influenza (Flu) Antiviral Drugs and Related Information
- CDC – About Flu

Follow FDA

Follow @US_FDA

Follow FDA

Diğer Bilgiler…

- 20 yıldan uzun bir süre sonra onaylanan ilk influenza ilacı
  - İnfluenza *cap-dependent* endonükleaz inhibitörü
- Baloxavir verilen hastaların
  - Faz 2 çalışmada %2'sinde
  - Faz 3 çalışmada %10'unda direnç gelişimi söz konusu

The NEW ENGLAND JOURNAL of MEDICINE

5 Temmuz 2018

ORIGINAL ARTICLE

Oral Tecovirimat for the Treatment of Smallpox

Douglas W. Grosenbach, Ph.D., Kady Honeychurch, Ph.D., Eric A. Rose, M.D., Jarasvech Chinsangaram, D.V.M., Ph.D., Annie Frimm, B.S., Biswajit Maiti, Ph.D., Candace Lovejoy, B.S., Ingrid Meara, M.S., Paul Long, B.S., and Dennis E. Hruby, Ph.D.

ABSTRACT

BACKGROUND

Smallpox was declared eradicated in 1980, but variola virus (VARV), which causes smallpox, still exists. There is no known effective treatment for smallpox; therefore, tecovirimat is being developed as an oral smallpox therapy. Because clinical trials in a context of natural disease are not possible, an alternative developmental path to evaluate efficacy and safety was needed.

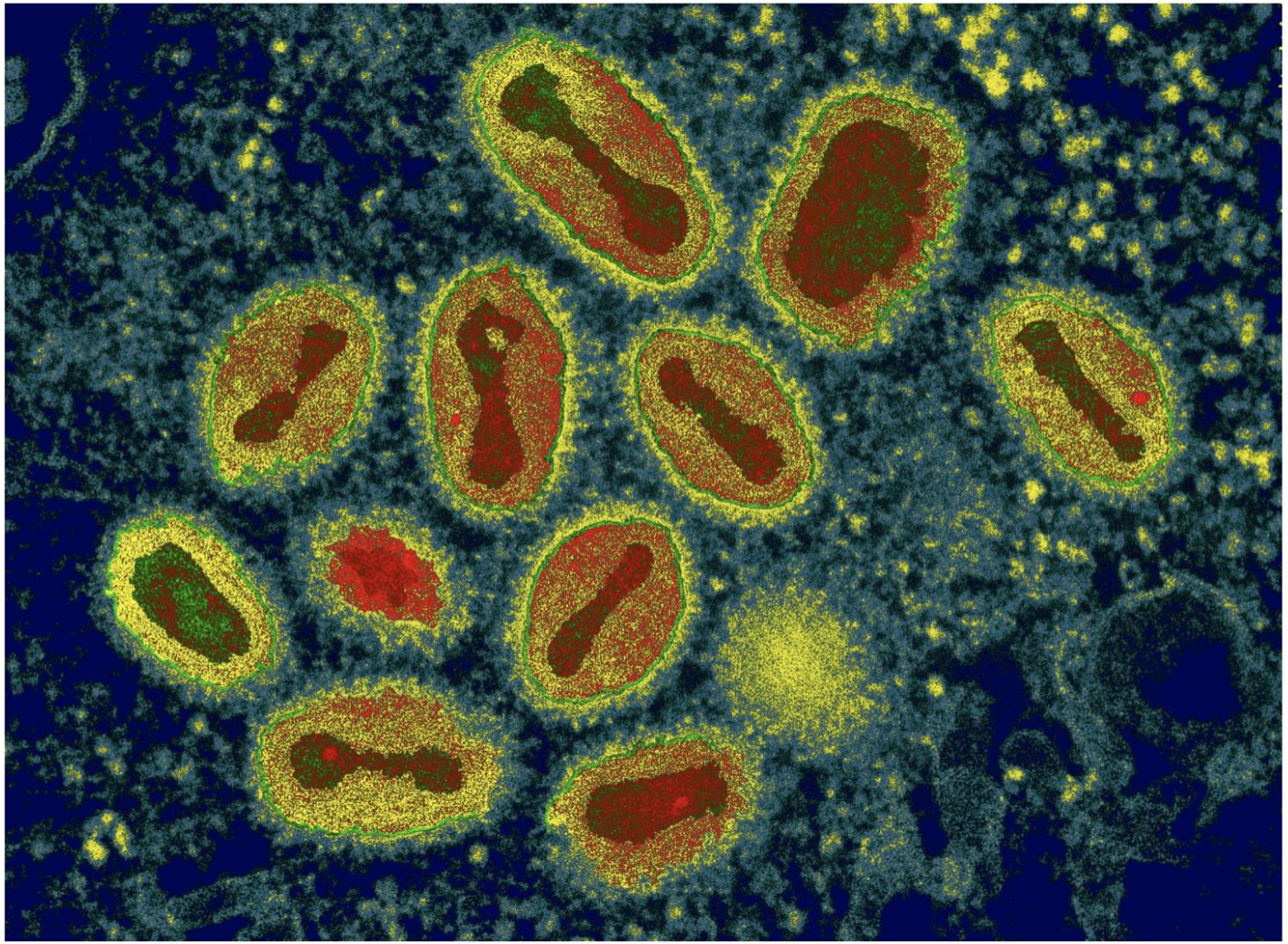
METHODS

From SIGA Technologies, Corvallis, OR. Address reprint requests to Dr. Hruby at SIGA Technologies, Suite 110, 4575 SW Research Way, Corvallis, OR 97333, or at dhruby@siga.com.

N Engl J Med 2018;379:44-53.
DOI: 10.1056/NEJMoa1705688

The New York Times 13 Temmuz 2018

Drug to Treat Smallpox Approved by F.D.A., a Move Against Bioterrorism



Smallpox was eliminated in 1980, but experts have feared the virus, above, may return via laboratory accident or terrorist attack. Eye of Science/Science Source

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 17, 2019 VOL. 380 NO. 3

Single-Dose Tafenoquine to Prevent Relapse of *Plasmodium vivax* Malaria

M.V.G. Lacerda, A. Llanos-Cuentas, S. Krudsood, C. Lon, D.L. Saunders, R. Mohammed, D. Yilma, D. Batista Pereira, F.E.J. Espino, R.Z. Mia, R. Chuquiyauri, F. Val, M. Casapía, W.M. Monteiro, M.A.M. Brito, M.R.F. Costa, N. Buathong, H. Noedl, E. Diro, S. Getie, K.M. Wubie, A. Abdissa, A. Zeynudin, C. Abebe, M.S. Tada, F. Brand, H.-P. Beck, B. Angus, S. Duparc, J.-P. Kleim, L.M. Kellam, V.M. Rousell, S.W. Jones, E. Hardaker, K. Mohamed, D.D. Clover, K. Fletcher, J.J. Breton, C.O. Ugwuegbulam, J.A. Green, and G.C.K.W. Koh

ABSTRACT

BACKGROUND

Treatment of *Plasmodium vivax* malaria requires the clearing of asexual parasites, but relapse can be prevented only if dormant hypnozoites are cleared from the liver (a treatment termed "radical cure"). Tafenoquine is a single-dose 8-aminoquinoline that has recently been registered for the radical cure of *P. vivax*.

METHODS

This multicenter, double-blind, double-dummy, parallel group, randomized, placebo-controlled trial was conducted in Ethiopia, Peru, Brazil, Cambodia, Thailand, and the

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Koh at GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT, United Kingdom, or at gavin.c.koh@gsk.com.

Drs. Lacerda and Llanos-Cuentas and Drs. Green and Koh contributed equally to this article.

P. vivax İnfeksiyonu İçin Standart Tedavi

- 3 gün klorokin (şizontosit-aseksüel parazitler için) + 14 gün primakin (hipnozoitler için)
- 3 gün klorokin tedavisi sonrası tek doz tafenokin (yarı ömrü 15 gün) standart tedavi kadar etkili

Clinical Infectious Diseases

MAJOR ARTICLE

October 11, 2018

doi: 10.1093/cid/ciy859. [Epub ahead of print]

Voriconazole Resistance and Mortality in Invasive Aspergillosis: A Multicenter Retrospective Cohort Study

Pieter P. Lestrade,[1,2,a,b] Robbert G. Bentvelsen,[3,a] Alexander F. A. D. Schauwvlieghe,[4,a] Steven Schalekamp,[5] Walter J. F. M. van der Velden,[2,6] Ed J. Kuiper,[3] Judith van Paassen,[7] Ben van der Hoven,[8] Henrich A. van der Lee,[1,2] Willem J. G. Melchers,[1,2] Anton F. de Haan,[9] Hans L. van der Hoeven,[2,10] Bart J. A. Rijnders,[4] Martha T. van der Beek,[3] and Paul E. Verweij[1,2,]

[1]Department of Medical Microbiology, Radboud University Medical Center, and [2]Center of Expertise in Mycology Radboud University Medical Center/CWZ, Nijmegen, [3]Department of Medical Microbiology, Leiden University Medical Center, [4]Department of Medical Microbiology and Infectious Disease, Erasmus Medical Center, Rotterdam, Departments of [5]Radiology and Nuclear Medicine and [6]Hematology, Radboud University Medical Center, Nijmegen, [7]Department of Intensive Care, Leiden University Medical Center, [8]Department of Intensive Care, Erasmus Medical Center, Rotterdam, and Departments of [9]Health Evidence and [10]Intensive Care, Radboud University Medical Center, Nijmegen, the Netherlands

Background. Triazole resistance is an increasing problem in invasive aspergillosis (IA). Small case series show mortality rates of 50%–100% in patients infected with a triazole-resistant *Aspergillus fumigatus*, but a direct comparison with triazole-susceptible IA is lacking.

Methods. A 5-year retrospective cohort study (2011–2015) was conducted to compare mortality in patients with voriconazole-susceptible and voriconazole-resistant IA. *Aspergillus fumigatus* culture-positive patients were investigated to identify patients with proven, probable, and putative IA. Clinical characteristics, day 42 and day 90 mortality, triazole-resistance profiles, and antifungal treatments were investigated.

Results. Of 196 patients with IA, 37 (19%) harbored a voriconazole-resistant infection. Hematological malignancy was the underlying disease in 103 (53%) patients, and 154 (79%) patients were started on voriconazole. Compared with voriconazole-susceptible

Vorikonazol Direnci ve Mortalite

- 5 yıllık retrospektif çalışma
- 196 invaziv aspergillozlu hasta
  - 37 hastada vorikonazol dirençli infeksiyon
- Mortalite (dirençli *vs* duyarlı)
  - 42. günde %49 *vs* %28 (p=.017)
  - 90. günde %62 *vs* %37 (p=.0038)
- Başlangıçtaki uygunsuz tedavi 10. günde değiştirilse de mortalite %24 *vs* %47 (p=.016)

Lestrade PP, et al. Clin Infect Dis October 11, 2018

Teşekkürler…