KLİMİK TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ
Bilimle Sağlıkla 32 .Yıl

Yeni Antibiyotikler ve İndikasyonları

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İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji

Gelişim Tıp Laboratuvarları

Sunum Planı

- Antibiyotiklerden Önce Yaşam,
- Neden Antibiyotiklere İhtiyacımız Var?
- FDA Tarafından Onaylanan Antibiyotikler ve İndikasyonları,

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Neanderthal behaviour, diet, and disease inferred from ancient DNA in dental calculus

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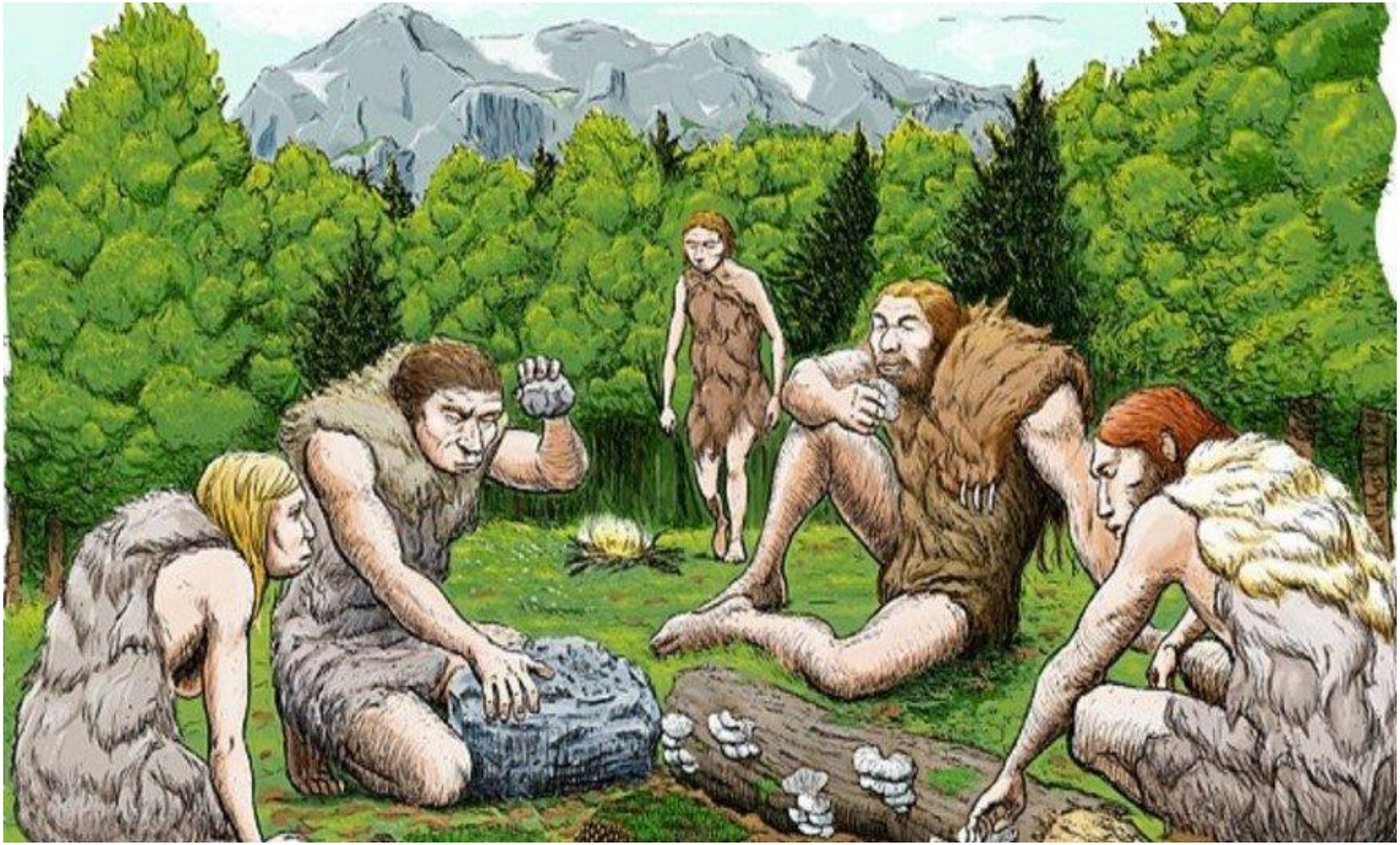
Recent genomic data have revealed multiple interactions between Neanderthals and modern humans[1], but there is currently little genetic evidence regarding Neanderthal behaviour, diet, or disease. Here we describe the shotgun-sequencing of ancient DNA from five specimens of Neanderthal calcified dental plaque (calculus) and the characterization of regional differences in Neanderthal ecology. At Spy cave, Belgium, Neanderthal diet was heavily meat based and included woolly rhinoceros and wild sheep (mouflon), characteristic of a steppe environment. In contrast, no meat was detected in the diet of Neanderthals from El Sidrón cave, Spain, and dietary components of mushrooms, pine nuts, and moss reflected forest gathering[2,3]. Differences in diet were also linked to an overall shift in the oral bacterial community (microbiota) and suggested that meat consumption contributed to substantial variation within Neanderthal microbiota. Evidence for self-medication was detected in an El Sidrón Neanderthal with a dental abscess[4] and a chronic gastrointestinal pathogen (*Enterocytozoon bieneusi*). Metagenomic data from this individual also contained a nearly complete genome of the archaeal commensal *Methanobrevibacter oralis* (10.2× depth

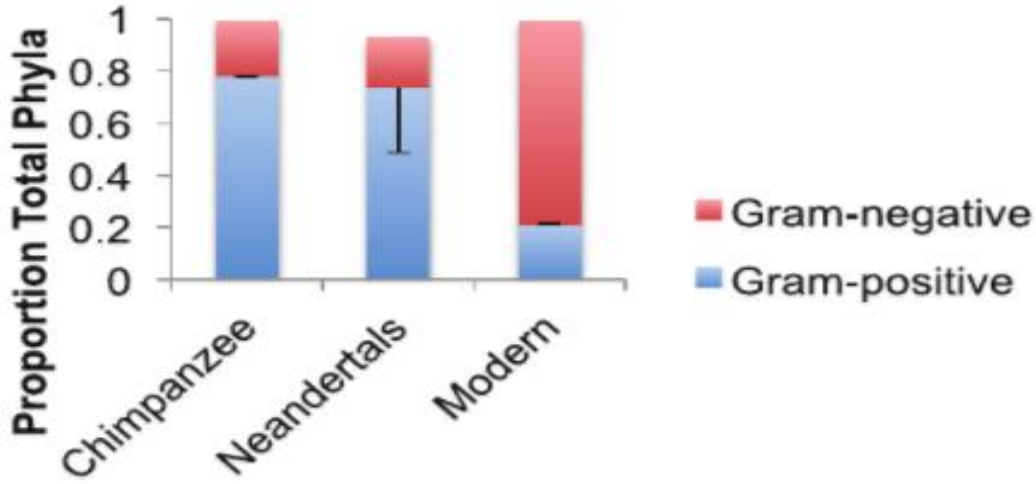
purposes[8]. As a result, Neanderthal diet remains a topic of considerable debate, with limited data on the specific animals and plants directly consumed or the potential effects on Neanderthal health and disease.

Although genomic studies continue to reveal evidence of interbreeding between anatomically modern humans and Neanderthals across Eurasia[9], little is known about the health consequences of these interactions. The genetic analysis of Neanderthal dental calculus represents an opportunity to examine this issue and to reconstruct Neanderthal diet, behaviour, and disease[10]. Here, we report the first genetic analysis of dental calculus from five Neanderthals (two individuals from El Sidrón cave in Spain; two individuals from Spy cave in Belgium; and one individual from Breuil Grotta in Italy) and compare these data to a historic wild-caught chimpanzee ($n = 1$) and modern human ($n = 1$), as well as to low coverage sequencing of calculus from a wide-range of ancient humans (Supplementary Table 1). To provide increased resolution of the diseases that may have affected Neanderthals, we also deeply sequenced (>147 million reads) dental calculus from the best-preserved Neanderthal, El Sidrón 1, which suffered from a dental abscess[4].

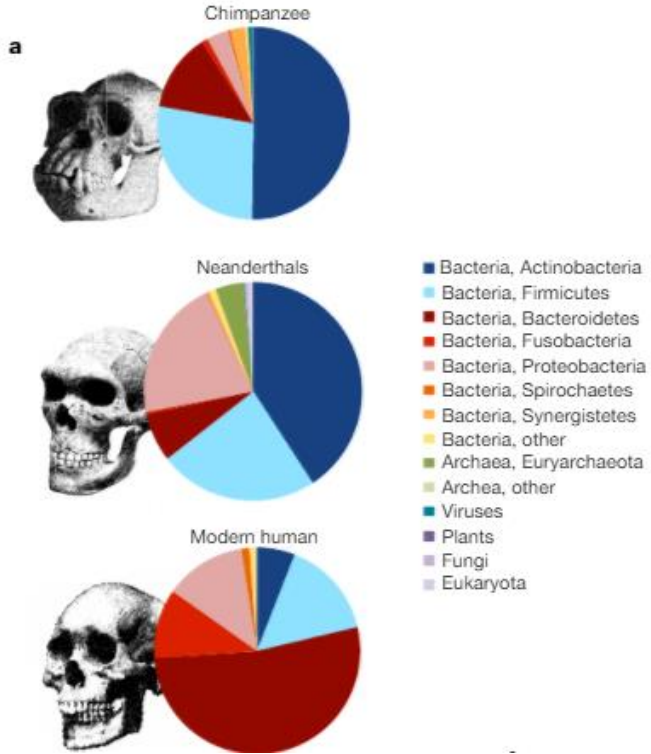
- El Sidron mağarasında bulunan üst çene,
- Maksilla, 1.- 2. molar diş, apse izi, DNA sekans analizi,
- Oyukta, **asetil salisilik asit**, kavak, aspirin
- Apse çevresinde, kalıplaşmış bitki örtüsü, **Penisilium fungus**, doğal bir antibiyotik
- Tesadüf olabilir mi?

Neanderthaller bizden 50 bin yıl önce antibiyotikleri keşfetmiş

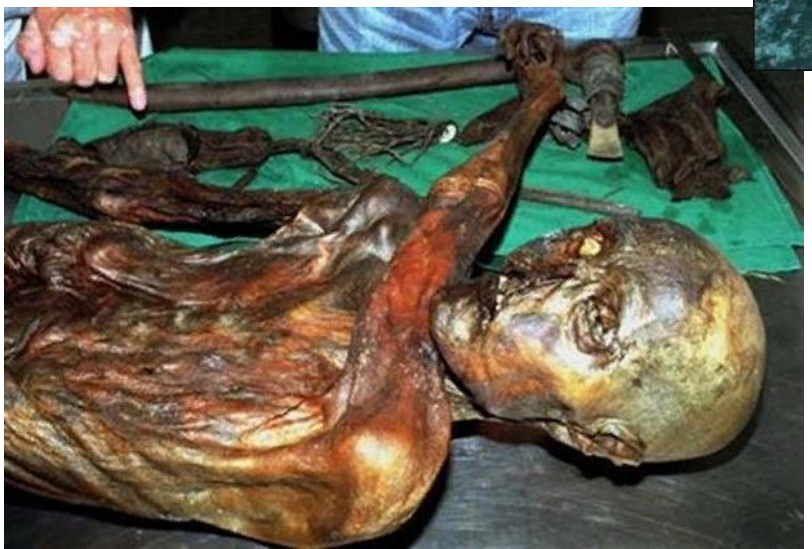




Extended Data Figure 9 | Neanderthal microbiota compared to other ancient and modern calculus specimens. a, UPGMA clustering of Bray–Curtis values were calculated from filtered rarefied shotgun data. **b**, The groups in **a** split on the basis of their differences in proportion of Gram-positive and Gram-negative phyla in shotgun datasets and were plotted for each group (chimpanzee and modern human, $n = 1$; Neanderthals, $n = 3$). Error bars represent s.d.



Buz adam Ötzi



Buz adam Ötzi

- 1991, İtalya Alplerinde, 5.300 yıl önce
- Rektumunda **mantar kalıntıları**
- Pelvisten, **DNA sekans analizi**,
- Kemerine 3 çeşit mantar
- **Piptoporus betulinus** - Huş mantarı
- **Fomes fomentarius** - Kav mantarı
- **Ice man fungus = Buz adam mantarı**

- Anadolu’ da **beyaz peynirdeki küf,**
- **Penicilum notatum** isimli yeşil küf mantarı,
- **Yörükler,** Yaraların iyileştirilmesinde,
- Antibiyotiklerin Anadolu’ daki çok eski zamanlardan beri kullanıldığı

PLoS One. 2012;7(4):e34953. doi: 10.1371/journal.pone.0034953. Epub 2012 Apr 11.

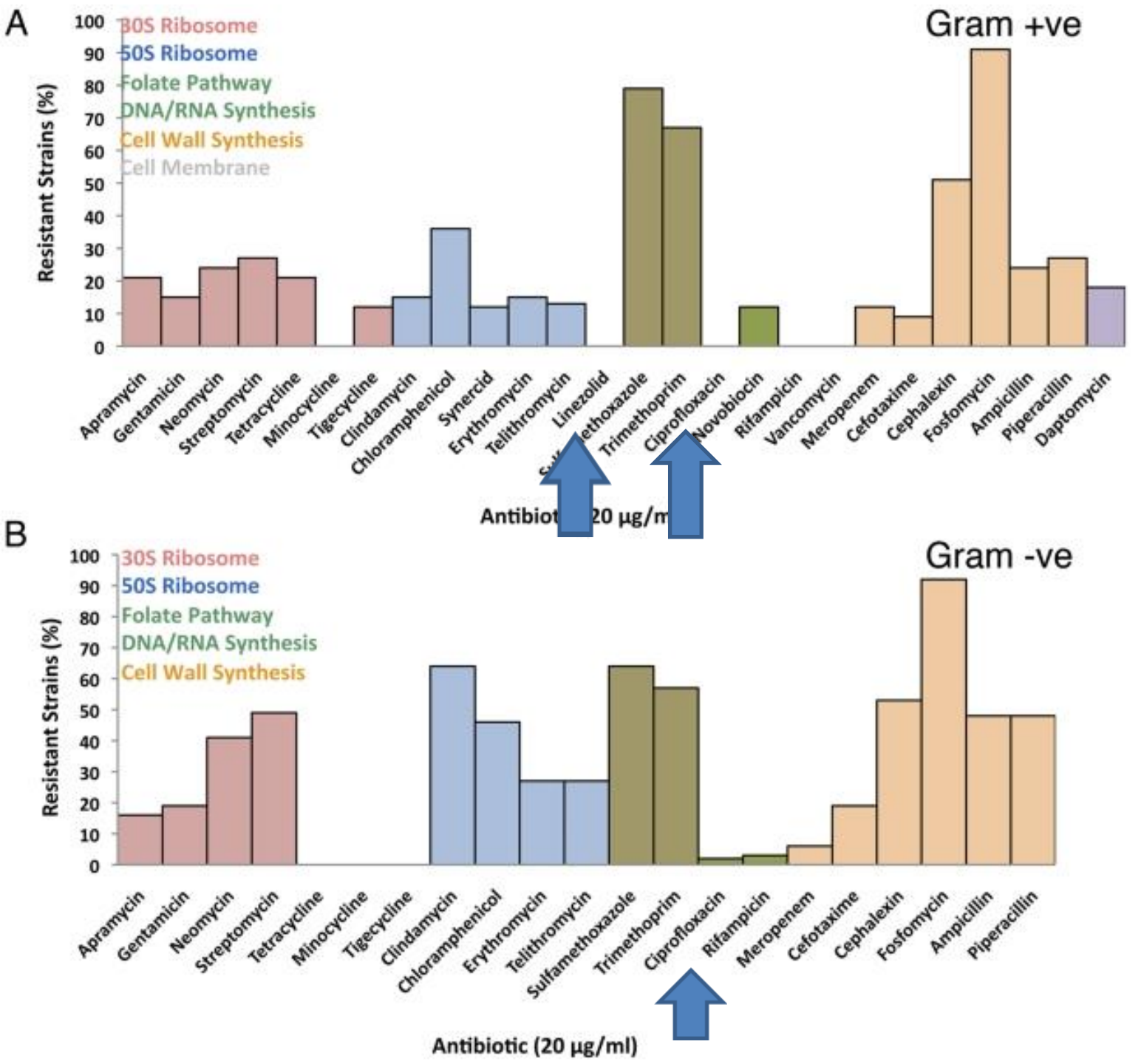
Antibiotic resistance is prevalent in an isolated cave microbiome.

Bhullar K[1], Waglechner N, Pawlowski A, Koteva K, Banks ED, Johnston MD, Barton HA, Wright GD.

Author information

We surveyed the antibiotic susceptibility of 93 bacterial strains isolated from Lechuguilla Cave. This was a genetically diverse collection of oligotrophic organisms (Figure S1), highly adapted to survive in a nutrient limited environment [22]. Like surface organisms [11], the majority of these strains were multidrug resistant indicating that antibiotic resistance is a common and widespread phenotype in pristine, unimpacted environments; however, there are differences in the pattern of resistance. For example, we measured little resistance to the synthetic antibiotics ciprofloxacin and linezolid, while resistance to natural product antibiotics was more prevalent. Unlike surface bacteria, we also detected very little resistance to tetracycline, glycopeptide (vancomycin), rifamycin (rifampicin) and lipopeptide (daptomycin) natural product antibiotics. There are several possible reasons for these differences. First, this survey includes

resistant bacteria identified a macrolide kinase encoding gene and characterization of its product revealed it to be related to a known family of kinases circulating in modern drug resistant pathogens. The implications of this study are significant to our understanding of the prevalence of resistance, even in microbiomes isolated from human use of antibiotics. This supports a growing understanding that antibiotic resistance is natural, ancient, and hard wired in the microbial pangenome.


A
Gram +ve
30S Ribosome
50S Ribosome
Folate Pathway
DNA/RNA Synthesis
Cell Wall Synthesis
Cell Membrane
Resistant Strains (%)
100
90
80
70
60
50
40
30
20
10
0
Apramycin
Gentamicin
Neomycin
Streptomycin
Tetracycline
Minocycline
Tigecycline
Clindamycin
Chloramphenicol
Synercid
Erythromycin
Telithromycin
Linezolid
Trimethoprim
Ciprofloxacin
Novobiocin
Rifampicin
Vancomycin
Meropenem
Cefotaxime
Cephalexin
Fosfomycin
Ampicillin
Piperacillin
Daptomycin
B
Gram -ve
30S Ribosome
50S Ribosome
Folate Pathway
DNA/RNA Synthesis
Cell Wall Synthesis
Resistant Strains (%)
Apramycin
Gentamicin
Neomycin
Streptomycin
Tetracycline
Minocycline
Tigecycline
Clindamycin
Chloramphenicol
Erythromycin
Telithromycin
Sulfamethoxazole
Trimethoprim
Ciprofloxacin
Rifampicin
Meropenem
Cefotaxime
Cephalexin
Fosfomycin
Ampicillin
Piperacillin
Antibiotic (20 µg/ml)

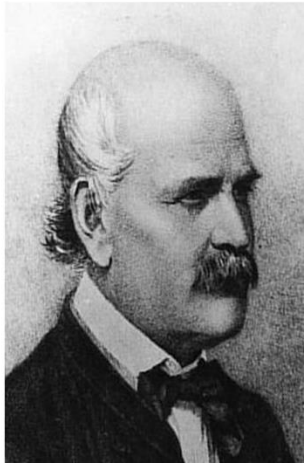
Antibiyotiğin keşfinden önce hayat nasıldı?

Ignaz Semmelweis (1850)

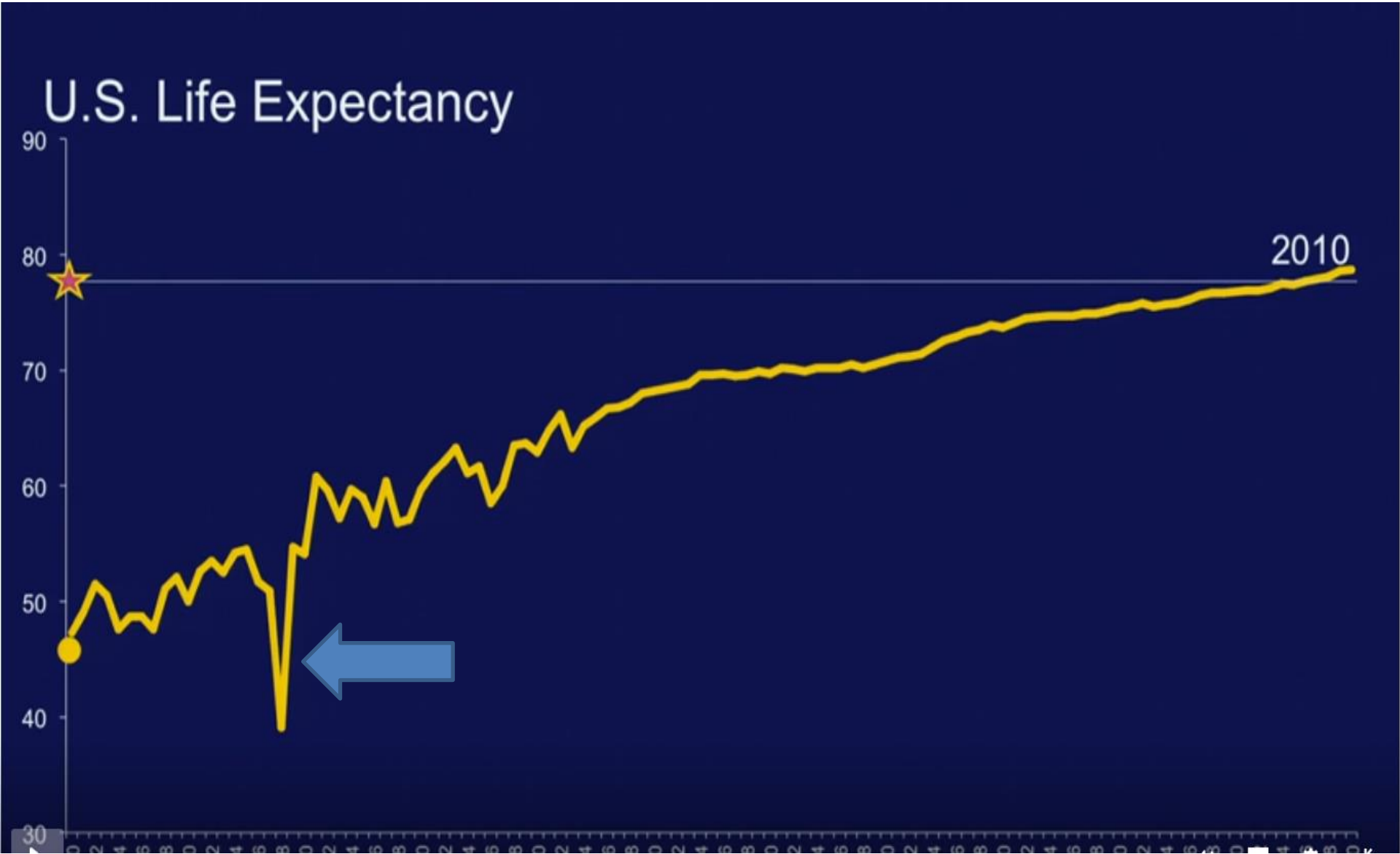
Observed that women in the maternity wards died of childbed fever. He proposed that it was caused by doctors doing autopsies on the deceased women and then carrying the disease causing agent to healthy women who were in labor.

His solution: Wash your hands before delivering babies!

*The Germ Theory did not exist at this time



Antibiyotikler ve Yaşam Beklentisi



- İnsanoğlu “antibiyotik kıyametinin” eşiğinde mi?

Antibiyotik Direncine Dikkat!

ANTİBİYOTİK ÇAĞININ SONUNA GELİYORUZ

Mesude ERŞAN

Tıbbın en önemli buluşlarından antibiyotiklere karşı direnç çok ciddi alarm veriyor. 2050'de antibiyotiğe dirençli süper bakterilerin her yıl 10 milyon can almasından endişe ediliyor ve uzmanlar uyarıyor: "Antibiyotik öncesi çağa dönebiliriz!"

PENİSİLİN ilk defa 1943 yılında kullanılmaya başlandığında tedavide o kadar başarılı oldu ki, tüm enfeksiyonların kökünün kısa süre içerisinde kazınacağı düşünüldü.

Ancak kısa zamanda bakteri ve bazı virüslerde penisiline karşı direnç gelişti. Direnç tedavide başarısızlık demekti. Bu durum bakteriyel enfeksiyon hastalıklarının tedavisi için yeni antibiyotiklerin keşfini hızlandırdı. Yeni antibiyotiklere karşı da kısa sürede direnç gelişti ve sorun giderek büyüdü.

ŞU ANDA YILDA 700 BİN CAN ALIYOR

Geldiğimiz noktada, antimikrobiyal ilaçlara (bakteri, virüs, mantar, parazitlere karşı etkili) dirençli enfeksiyonlar nedeniyle tüm dünyada her yıl ortalama 700 bin kişi hayatını kaybediyor. Bu kişilerin önemli bir kısmı, antibiyotiklere karşı gelişen direnç nedeniyle ölüyor.

Bu ciddi ve endişe verici duruma karşı, WHO (Dünya Sağlık Örgütü) Türkiye'nin de aralarında bulunduğu CAESAR'ın (Orta Asya ve Doğu Avrupa Ülkeleri Antibiyotik Direnci Ağı) yeni raporuna dikkat çekti.

BU ÜLKELER RİSK ALTINDA

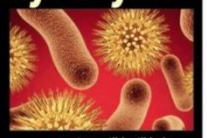
Beyaz Rusya, Bosna-Hersek, Rusya Federasyonu, Sırbistan, İsviçre, Makedonya ve Kosova'nın da yer aldığı CAESAR'da, son seçenek olan antibiyotiklere karşı bazı bakterilerde direnç oranlarının giderek arttığı görülüyor. Toplam 74 üniversite ve devlet hastanesinden veri yollayan Türkiye, yüksek direnç grubundaki ülkeler arasında yer alıyor. Türk Klinik Mikrobiyoloji ve Infeksiyon Hastalıkları Derneği (KLİMİK), Antibiyotik Direnci Çalışma Grubu Başkanı Prof. Dr. A. Çağrı Büke, gelinen endişe verici noktayı şöyle özetliyor:

TÜRKİYE ANTİBİYOTİK 'CANAVARI'

"Türkiye kişi başına antibiyotik tüketimi açısından dünyada üst sıralarda yer alıyor. Her 100 reçeteden ortalama 30-40'ında antibiyotik var. Antibiyotik direncinden nasibini almayan ülke yok. Direnç tüm dünya için bir sorun, hatta tehdit. Antibiyotiklere karşı bizdeki direnç oranları AB üyesi komşularımız Yunanistan, Romanya, Bulgaristan ile benzer. Ne yazık ki hızla artan antibiyotiklere dirençli enfeksiyonları tedavi edebileceğimiz yeni antibiyotik yok."


Prof. A. Çağrı Büke

Bakterilere karşı savaşı kaybediyoruz



PROF. Dr. Çağrı Büke'nin verdiği bilgiye göre, antibiyotiklere direnç gelişimi her geçen yıl artıyor.

Bir taraftan mevcut antibiyotiklere karşı direnç oranlarında artış yaşanırken, diğer taraftan yeni antibiyotik keşfinde ciddi azalma, bakteriyel enfeksiyon hastalıklarının tedavisinde ciddi sorunlar yaratıyor, basit enfeksiyonlardan ölüm riskini artırıyor. Prof. Dr. A. Çağrı Büke, "Antibiyotiklerin altın çağı, yani çok sayıda farklı gruptan antibiyotiklerin mevcut olduğu ve bunlara direnç oranlarının düşük düzeyde görüldüğü dönem çoktan geçti. Antibiyotik çağının sonuna doğru bir süreç yaşıyoruz. Hızla, evrensel önlemler alınmalı. Eldeki antibiyotikler doğru kullanılmalı" diyor.

'10 reçetenin 3'ünde antibiyotik var'

Türk Klinik Mikrobiyoloji ve İnfeksiyon Hastalıkları Derneği (KLİMİK) ve Avrupa Klinik Mikrobiyoloji ve Enfeksiyon Hastalıkları Derneği iş birliğiyle antimikrobiyal direncin azaltılması amacıyla İstanbul'da iki günlük kurs düzenlendi. KLİMİK Yönetim Kurulu Üyesi Prof. Dr. Önder

KLİMİK BÜLTENİ
Türk Klinik Mikrobiyoloji ve İnfeksiyon Hastalıkları Derneği Yayın Organıdır

ABD Hükümetinden Yeni Antibiyotik Geliştirilmesine Mali Destek

- Çok önemli bir savaşın içindeyiz,
- ‘Superbugs’ çok ilaca dirençli bakteriler,
- Kaybetmek üzereyiz,
- **WHO**; No action today, no cure tomorrow
- **IDSA**: Bad bugs, No drugs, **10 by ’20**
- **FDA**, Barack Obama hükümeti

- Generating Antibiotic Incentives Now (**GAIN**),
- Üretilen antibiyotik, **5 sene** aynı jenerik, başka firma tarafından üretilemeyecek,
- Bu ek süre, ilaç şirketlerinin karlılığı 
- **İnovasyon** ve yeni antibiyotikler üretmesi
- FDA ‘fast-track program’

Innovation: Frequent Use of Expedited Development and Review Pathways

CDER used several regulatory pathways to expedite the development and approval of novel drugs in 2017. These pathways utilize a range of approaches that can enhance development efficiency and shorten timelines; these approaches can include more interactions between CDER staff and drug developers, greater program design flexibility, and shortened timelines for review of applications.

Fast Track

Fast Track designated drugs have the potential to address unmet medical needs. Eighteen of the 46 2017 novel drugs (39%) were designated by CDER as Fast Track. Fast Track speeds new drug development and review, for instance, by increasing the level of communication between FDA and drug developers, and by enabling CDER to review portions of a drug application ahead of the submission of the complete application.

Drugs designated with Fast Track status were: Aliqopa, Bavencio, Baxdela, Bevyxxa, Emflaza, Idhifa, Ingrezza, Mavyret, Mepsevii, Ocrevus, Prevymis, Rydapt, Solosec, Vabomere, Verzenio, Vosevi, Xermelo, and Zejula.

1.gün

- 34 yaş, gebe,
- Şiddetli karın ağrısı, bulantı, kusma, ishal ve ateş,
- Göztepe EAH.
- Akut gastroenterit,
- IV sıvı ve semptomatik tedavi,
- Eve gönderiliyor,

2.gün

- 2 yaş erkek çocuk,
- Diyare, kusma, iştahsızlık, ateş,
- HNH, çocuk acil servis,
- Ciddi sıvı kaybı, elektrolit dengesizliği,
- Hastaneye yatırılıyor,

4. gün

- 2 yaşındaki çocuğun laboratuvar sonuçları;
- **Salmonelloz** olduğu tespit ediliyor,
- Sefalosporin ve kinolonlar dahil **tüm antibiyotiklere dirençli**,
- Dehidratasyon ve bakteriyemi, exitus,
- Diğer tarafta, 34 yaş, gebe hastada Salmonella infeksiyonuna bağlı abortus,
- Takiplerinde gebe hasta da kaybediliyor,

5.gün

- 325 ölü,
- Ülkenin farklı şehirlerinde, acillere aynı semptomlarla başvuran binlerce insan var,
- 49 farklı şehirden Salmonella vakaları bildirildi,

6. gün

- **1730** ölüm, 200.000 vaka,
- Tüm şehirlerinden vakalar bildirildi,
- Çevre ülkelerden de vakalar bildiriliyor,
- Ülkeye giriş çıkışlar durduruluyor,
- Doktorlar sadece semptomatik tedavi,
- Spesifik, AB tedavisi verilmiyor

7. gün

- Ölü ve vaka sayıları katlanarak artıyor

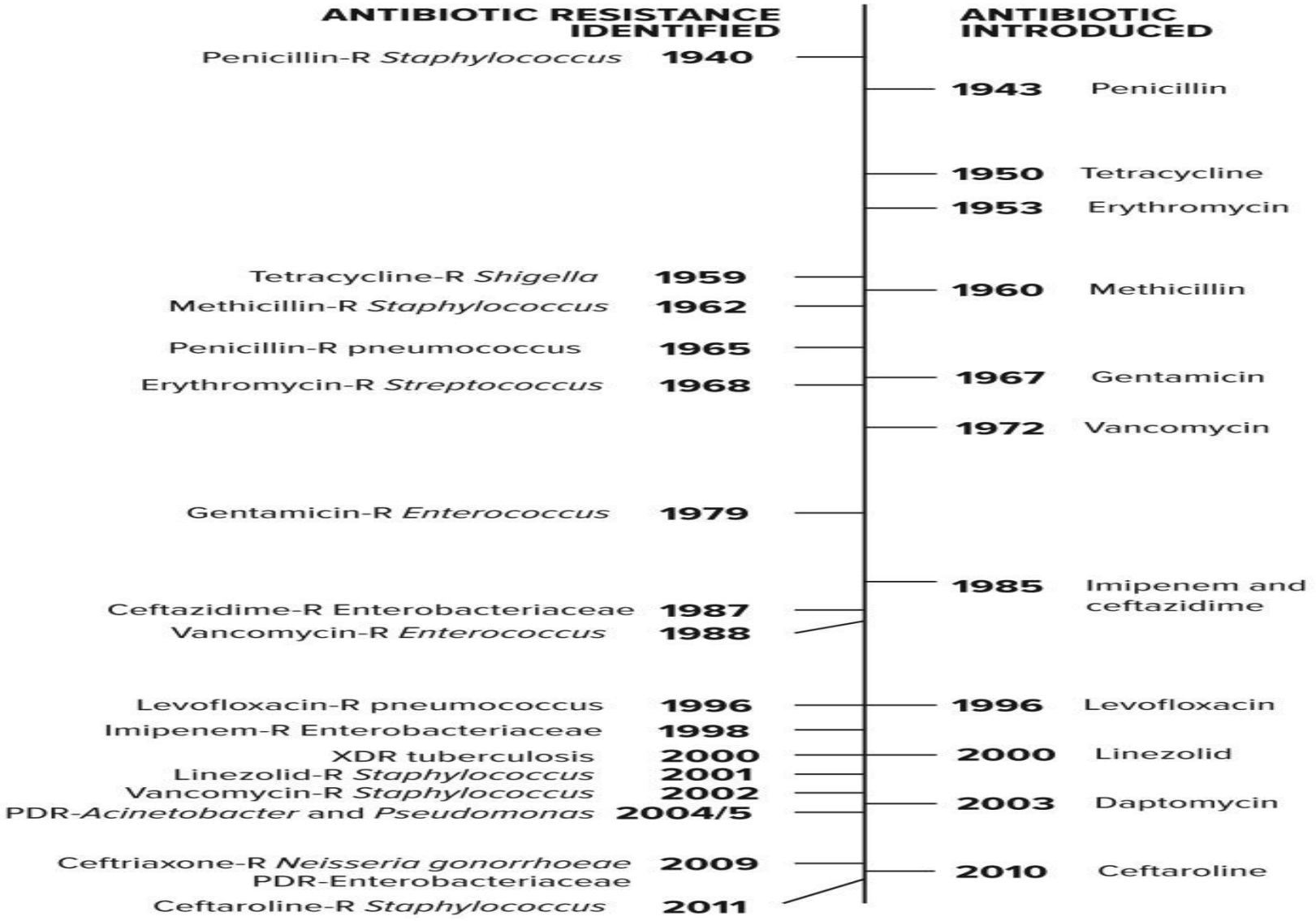
- Abartılı mı?

- 1985’ de ABD’ de ***Salmonella typhimirium*** ile kontamine olmuş süt ,

- 1730 kişi öldü, 200,000 kişi etkilendi,

- O günü vakayı, bizim senaryomuzdan ayıran;
- **Antibiyotik direnci**,

Figure 1 Developing Antibiotic Resistance: A Timeline of Key Events[5]

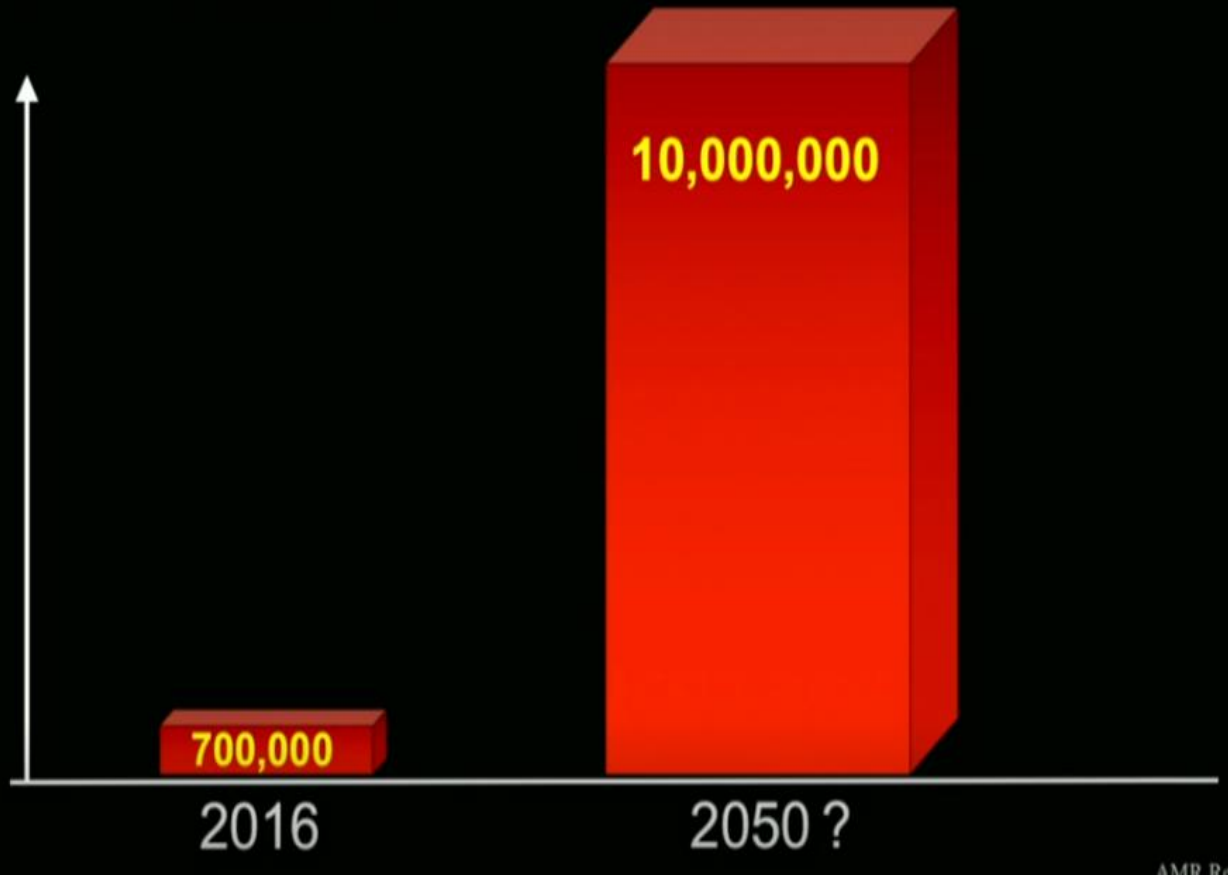


PDR = pan-drug-resistant; R = resistant; XDR = extensively drug-resistant

Dates are based upon early reports of resistance in the literature. In the case of pan-drug-resistant *Acinetobacter* and *Pseudomonas*, the date is based upon reports of health care transmission or outbreaks. Note: penicillin was in limited use prior to widespread population usage in 1943.

Superbugs

Worldwide Annual Death Toll



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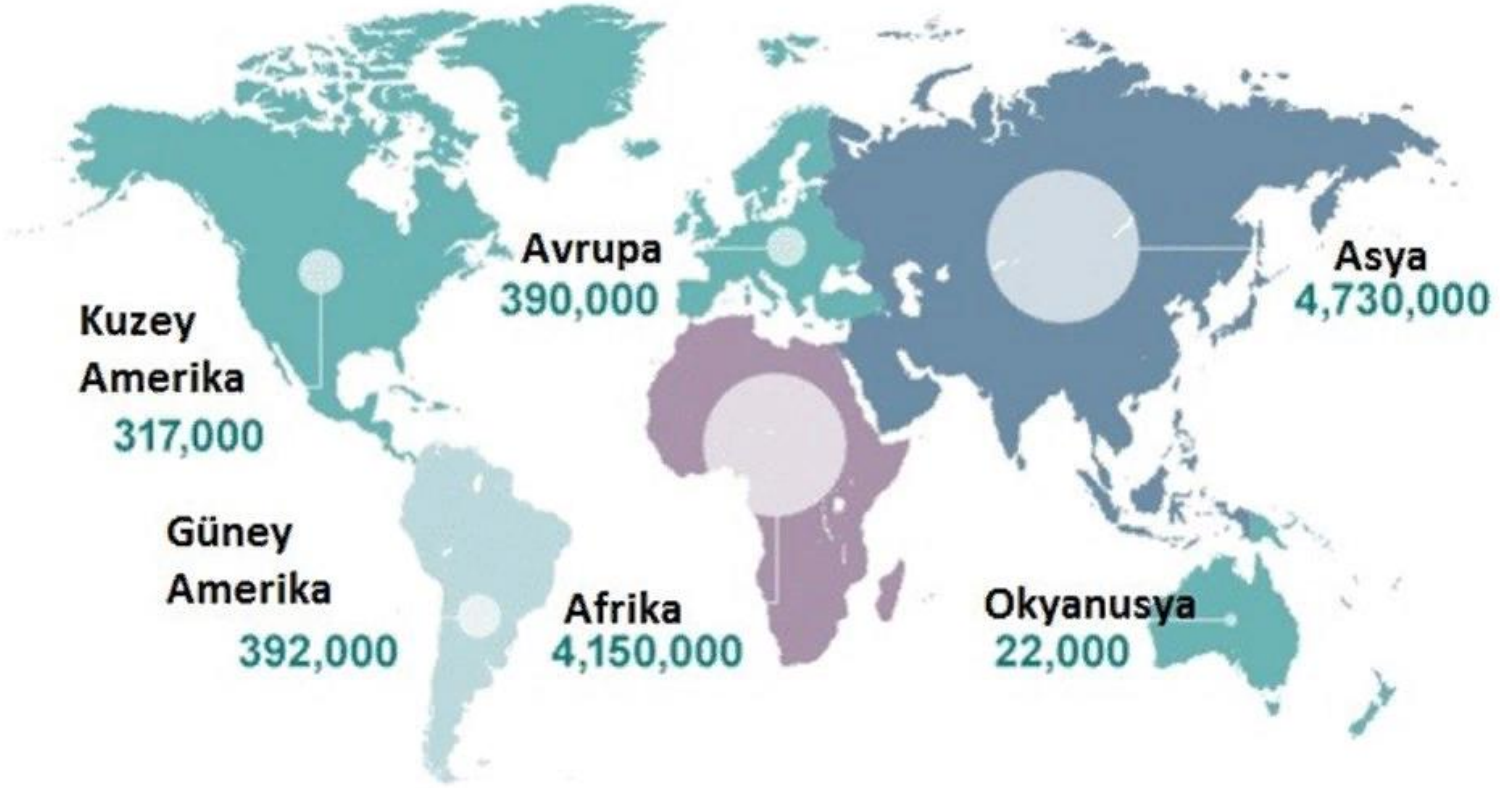
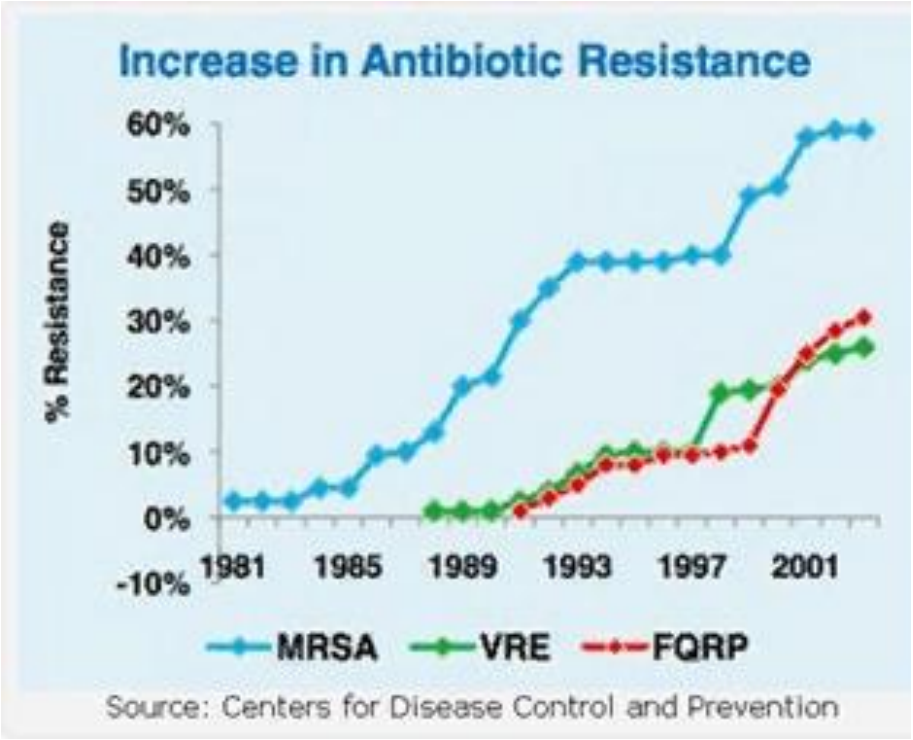
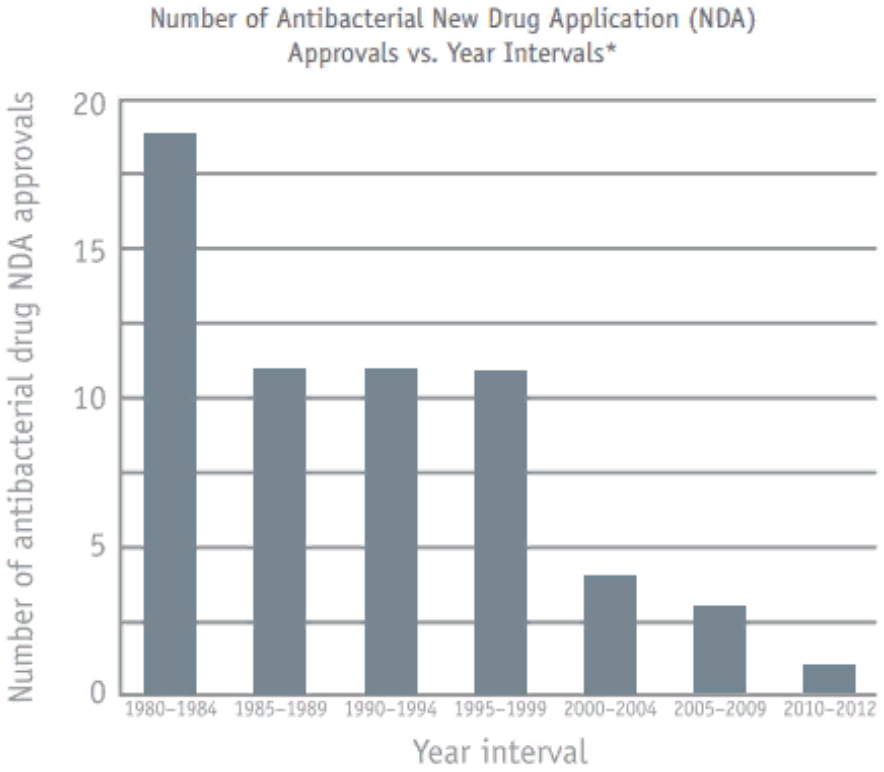
AMR Review 2016

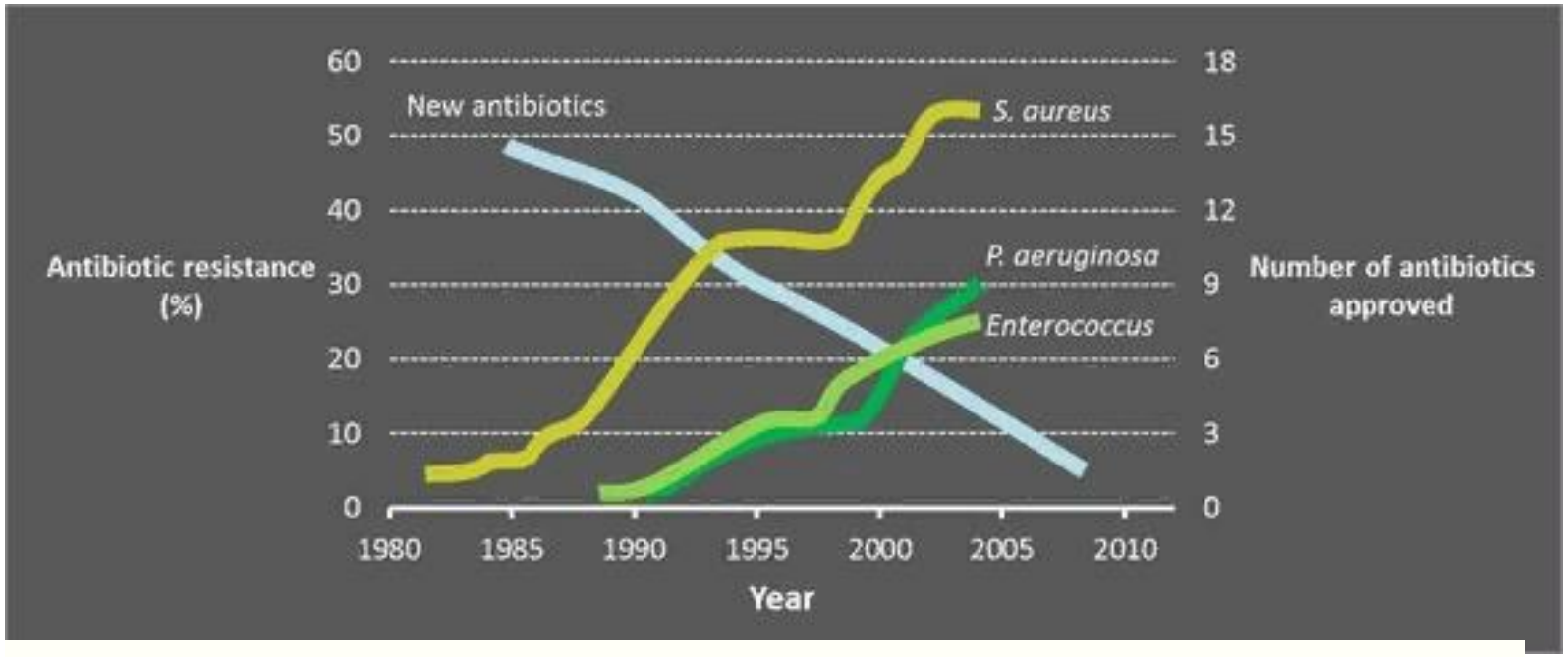
2050 yılı itibariyle kıtalarda beklenen 'yıllık' ölüm sayısı



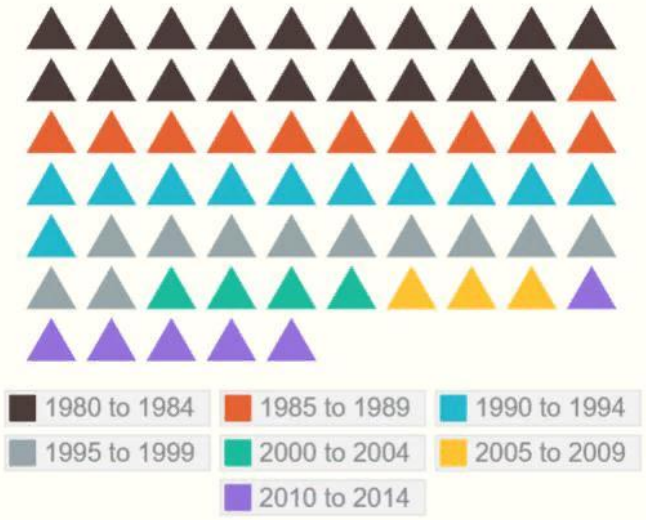
Neden Yeni Antibiyotiklere İhtiyacımız Var?







Newly Approved Antibiotics

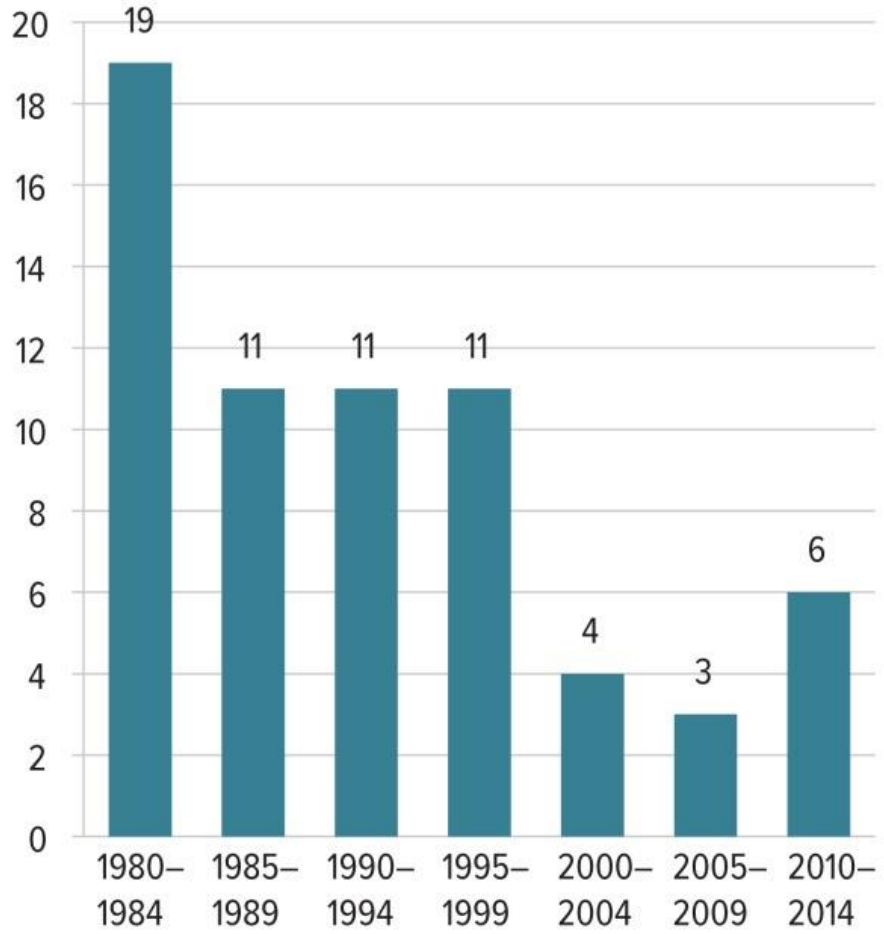


1980 to 1984
19 new antibiotics approved

2010 to 2014
6 new antibiotics approved

Data from CDC, 2013
Graphic by Neil Murthy/MEDILL

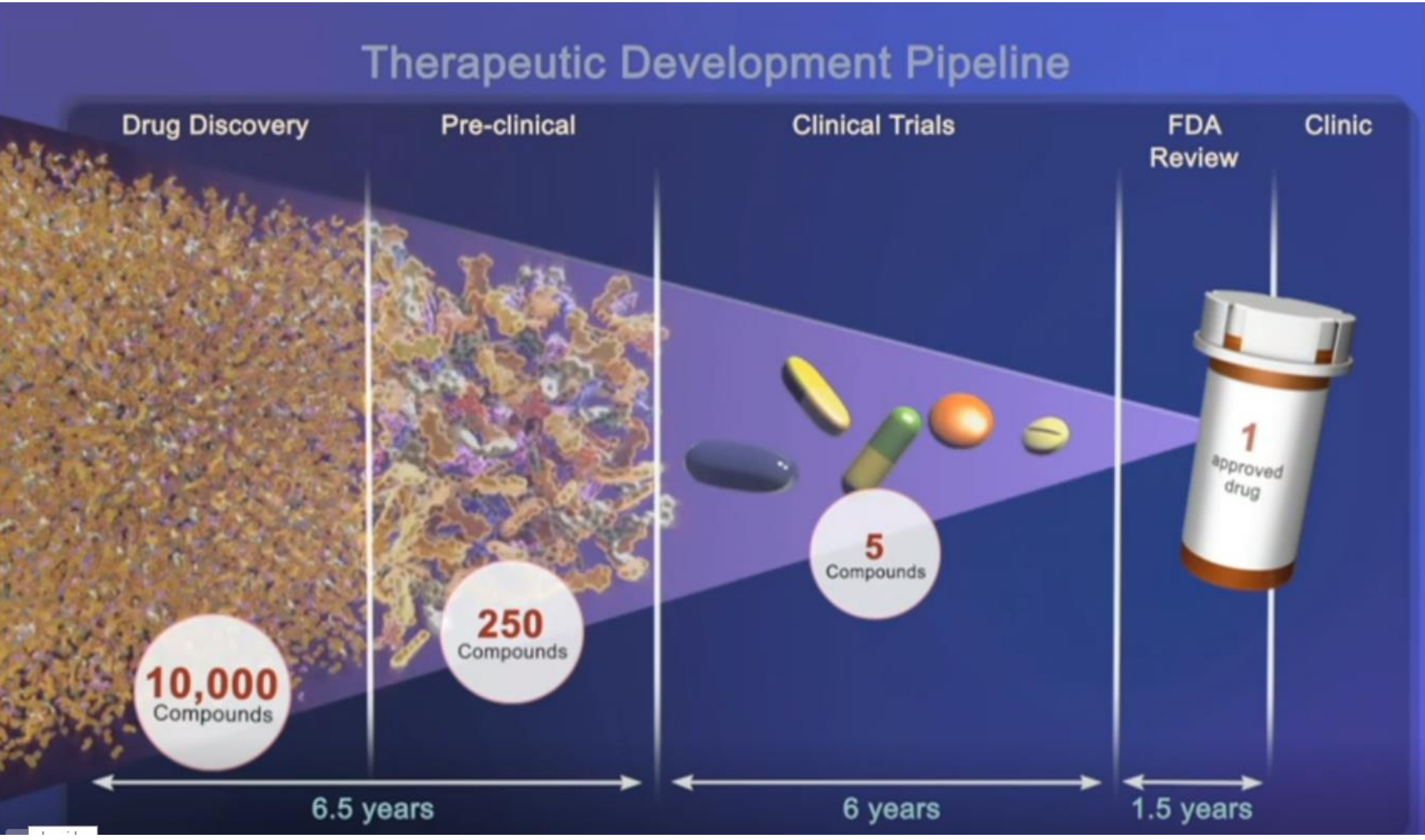
Figure 3 Number of Antibacterial New Drug Application Approvals Versus Year Intervals



The number of new antibiotics developed and approved has decreased steadily over the past three decades (although four new drugs were approved in 2014), leaving fewer options to treat resistant bacteria.

* Drugs are limited to systemic agents. Data courtesy of the CDC[5] and the FDA Center for Drug Evaluation and Research.

İlaç Geliştirme Süreci



2014 Yeni İlaç Onayları 18 Yılın Zirvesine Ulaştı

- 2014 ilaç **inovasyonu** için iyi bir yıldı,
- 1996 yılında endüstrinin tüm zamanların rekoru.

Therapeutic category	No of drugs approved	Percent of total	New modes of action
Infectious diseases	12	27%	4
Cancer	8	18%	4
Rare diseases	5	11%	4
Endocrine System	4	9%	0
Nervous System	4	9%	1
Hematology	4	9%	0
Respiratory	3	7%	2
Cardiovascular	1	2%	1
Digestive System	2	5%	0
Immune system	1	2%	1

Source: Calculated from FDA data

2014 FDA Onaylanmış İlaçlar

Infections and Infectious Diseases

Dalvance (dalbavancin); Durata Therapeutics; For the treatment of acute bacterial skin and skin structure infections, Approved May 2014

Harvoni (ledipasvir and sofosbuvir); Gilead; For the treatment of hepatitis C, Approved October 2014

Impavido (miltefosine); Knight Therapeutics; For the treatment of visceral, cutaneous and mucosal leishmar Approved March 2014

Jublia (efinaconazole) 10% topical gel; Valeant Pharmaceuticals; For the treatment of onychomycosis of the toenails, Approved June 2014

Kerydin (tavaborole); Anacor; For the treatment of onychomycosis of the toenails, Approved July 2014

Metronidazole 1.3% Vaginal Gel; Actavis, Inc.; For the treatment of bacterial vaginosis, Approved April 2014

Orbactiv (oritavancin); The Medicines Company; For the treatment of acute bacterial skin and skin structure infections, Approved August 2014

Rapivab (peramivir injection); Biocryst; For the treatment of acute uncomplicated influenza in adults, Appro December 2014

Sivextro (tedizolid phosphate) ; Cubist Pharmaceuticals; For the treatment of acute bacterial skin and skin structure infections, Approved June 2014

Triumeq (abacavir, dolutegravir, and lamivudine); ViiV HealthCare; For the treatment of HIV-1, Approved A 2014

Viekira Pak (ombitasvir, paritaprevir, ritonavir and dasabuvir) tablets; Abbvie; For the treatment of genc 1 chronic hepatitis C virus, Approved December 2014

Xtoro (finafloxacin otic suspension) 0.3%; Alcon; For the treatment of acute otitis externa, Approved Decen 2014

Zerbaxa (ceftolozane + tazobactam) ; Cubist Pharmaceuticals; For the treatment of complicated intra-abdor and urinary tract infections, Approved December 2014

2015 FDA Onaylanmış İlaçlar

Infections and Infectious Diseases

Avycaz (ceftazidime-avibactam); Actavis; For the treatment of complicated intra-abdominal and urinary tract infections, Approved February 2015

Bexsero (Meningococcal Group B Vaccine); Novartis; For the treatment of invasive meningococcal disease caused by serogroup B, Approved January 2015

Cresemba (isavuconazonium sulfate) ; Astellas; For the treatment of invasive aspergillosis and invasive mucormycosis, Approved March 2015

Daklinza (daclatasvir) ; Bristol-Myers Squibb; For the treatment of chronic HCV genotype 3, Approved July 2015

Evotaz (atazanavir and cobicistat) ; Bristol-Myers Squibb; For the treatment of HIV-1 infection, Approved January 2015

Fluad (trivalent influenza vaccine); Seqirus; For the prevention of influenza A and B, Approved November 2015

Genvoya (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide); Gilead Sciences; For the treatment of HIV-1 infection, Approved November 2015

Prezcobix (darunavir and cobicistat); Janssen; For the treatment of HIV-1 infection, Approved January 2015

Technivie, (ombitasvir, paritaprevir and ritonavir); Abbvie; For the treatment of chronic HCV genotype 4, Approved July 2015

2016 FDA Onaylanmış İlaçlar

Infections and Infectious Diseases

Anthim (obiltoxaximab); Elusys Therapeutics; For the treatment of inhalational anthrax , Approved March 2016

Descovy (emtricitabine and tenofovir alafenamide); Gilead; For the treatment of HIV-1 infection, Approved April 2016

Epclusa (sofosbuvir and velpatasvir) ; Gilead Sciences; For the treatment of hepatitis C, Approved June 2016

Odefsey (emtricitabine, rilpivirine, and tenofovir alafenamide); Gilead Sciences; For the treatment of HIV-1 as initial therapy, Approved March 2016

Syndros (dronabinol oral solution); Insys Therapeutics; For the treatment of anorexia associated with AIDS and nausea and vomiting associated with cancer chemotherapy, Approved July 2016

Vaxchora (Cholera Vaccine, Live, Oral); PaxVax; For active immunization against Cholera, Approved June 2016

Vemlidy (tenofovir alafenamide); Gilead Sciences; For the treatment of chronic hepatitis B , Approved November 2016

Zepatier (elbasvir and grazoprevir); Merck; For the treatment of chronic HCV genotypes 1 or 4 , Approved January 2016

Zinplava (bezlotoxumab); Merck; For the treatment of recurrent Clostridium difficile infection in patients receiving antibacterial treatment, Approved October 2016

2017 FDA Onaylanan İlaçlar

Infections and Infectious Diseases

Baxdela (delafloxacin) tablets and injection; Melinta Therapeutics; For the treatment of acute bacterial skin and skin structure infections, Approved June 2017

Benznidazole; Chemo Group; For the treatment of Chagas disease , Approved August 2017

Heplisav-B [Hepatitis B Vaccine (Recombinant), Adjuvanted] ; Dynavax; For the prevention of hepatitis B virus infection, Approved November 2017

Juluca (dolutegravir and rilpivirine); ViiV Healthcare; For the treatment of HIV-1 infection in adults, Approved November 2017

KedRab [Rabies Immune Globulin (Human)]; Kedrion Biopharma ; For the post-exposure prophylaxis of rabies infection, Approved August 2017

Mavyret (glecaprevir and pibrentasvir) ; AbbVie; For the treatment of chronic HCV genotype 1, 2, 3, 4, 5 or 6, Approved August 2017

Prevymis (letermovir) ; Merck; For the prevention of cytomegalovirus following allogenic hematopoietic stem cell transplant, Approved November 2017

Shingrix (Zoster Vaccine Recombinant, Adjuvanted) ; GlaxoSmithKline; For the prevention of herpes zoster (shingles), Approved October 2017

Solosec (secnidazole) ; Symbiomix Therapeutics; For the treatment of bacterial vaginosis , Approved September 2017

Vabomere (meropenem and vaborbactam); The Medicines Company; For the treatment of complicated urinary tract infections , Approved August 2017

Xepi (ozenoxacin) ; Medimetriks; For the treatment of impetigo, Approved December 2017

Approval Date	Trade Name	Active Ingredient	First-in-Class	Orphan	Fast Track	Breakthrough	Priority	Accelerated Approval	Met PDUFA Goal	First Cycle Approval	First in the United States	Dosage Form
7/13/2017	Tremfya	guselkumab										Injection
7/17/2017	Nerlynx	neratinib maleate										Tablet
7/18/2017	Vosevi	voxilaprevir; velpatasvir; sofosbuvir										Tablet
8/1/2017	Idhifa	enasidenib										Tablet
8/3/2017	Mavyret	glecaprevir; pibrentasvir										Tablet
8/17/2017	Besponsa	inotuzumab ozogamicin										Injection
8/29/2017	benznidazole	benznidazole										Tablet
8/29/2017		vaborbactam; meropenem										Injection
9/14/2017	Aliqopa	copanlisib hydrochloride										Injection
9/15/2017	Solosec	secnidazole										Granules
9/28/2017	Verzenio	abemaciclib										Tablet
10/31/2017	Calquence	acalabrutinib										Capsule
11/2/2017	Vyzulta	latanoprostene bunod										Ophthalmic Solution
11/8/2017	Prevymis	letermovir										Tablet
11/14/2017	Fasenra	benralizumab										Injection

Yeni Antibiyotikler

- **GLİKOPEPTİDLER**
- Telavancin
- Oritavancin
- Dalbavancin

- **OKSAZOLİDİNON**
- Tedizolid

- **KİNOLON**
- Delafloksasin

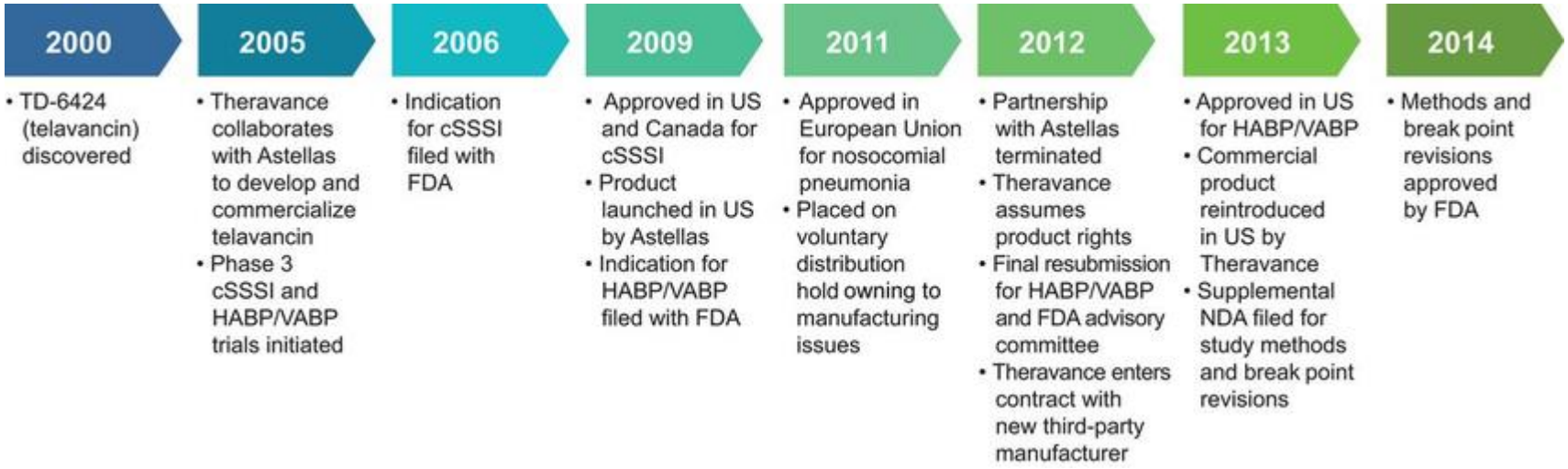
- **KOMBİNASYONLAR**
- Seftazidim–Avibakatam
- Seftolozan-Tazobaktam
- Vaborbaktam-Meropenem

Yeni (ikinci kuşak) Glikopeptitler

- Telavansin (vankomisin derivesi)
- Oritavansin (vankomisin derivesi)
- Dalbavansin (teikoplanin derivesi)

TELAVANSİN (Vibativ)

- 2013’ de FDA,
- Vankomisin’ in lipoglikopeptid türevi
- Gr (+) bakterilere etkili bakterisidal

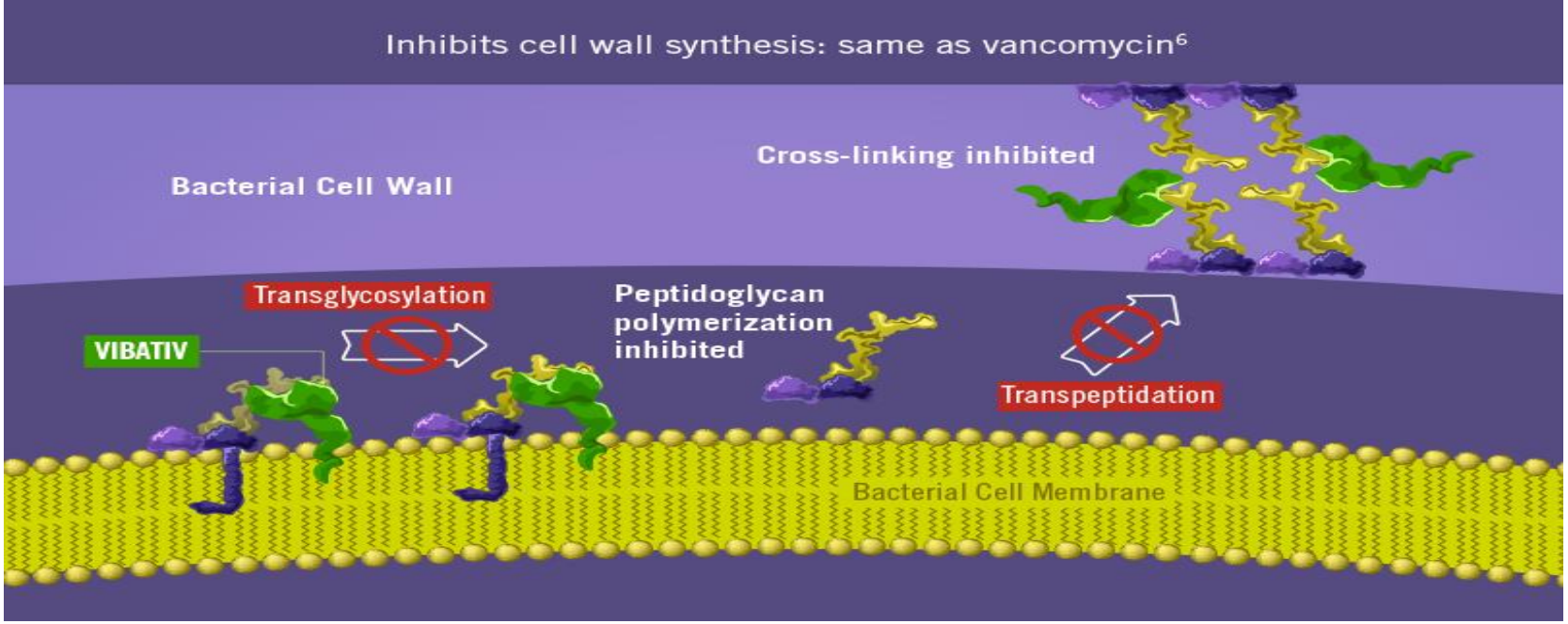


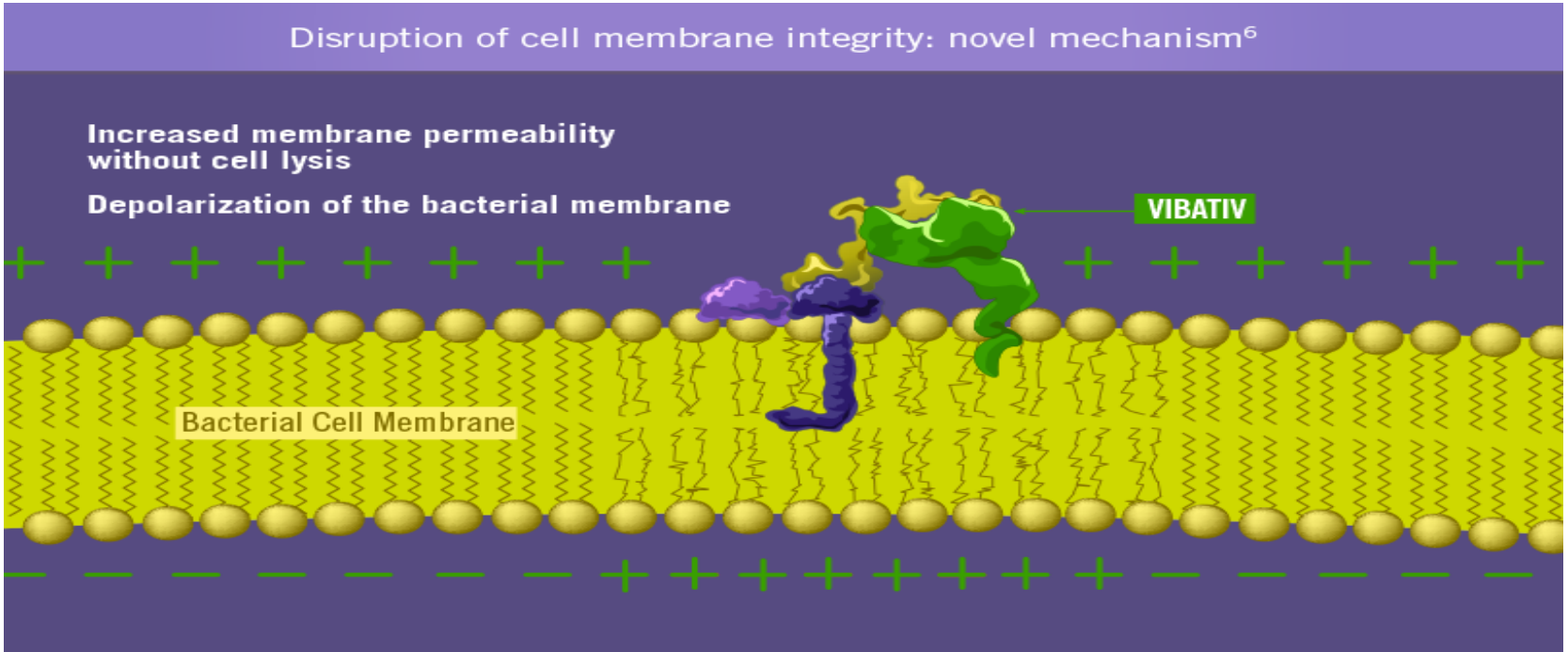
TELAVANSİN

- Bakteriyel hücre duvar sentezi,
- **Çift etki** mekanizması inhibisyonu

1- Peptidoglikan zincir öncülerine bağlanır,
Hücre duvarı sentezini inhibe eder ,
(**Vankomisin' den 10 kat güçlü**)

2- Hücre membranına bağlanır,
Membran bariyer fonksiyonunu bozar,


Inhibits cell wall synthesis: same as vancomycin[6]
Bacterial Cell Wall
Cross-linking inhibited
Transglycosylation
VIBATIV
Peptidoglycan polymerization inhibited
Transpeptidation
Bacterial Cell Membrane


Disruption of cell membrane integrity: novel mechanism[6]
Increased membrane permeability without cell lysis
Depolarization of the bacterial membrane
VIBATIV
Bacterial Cell Membrane

TELAVANSİN
Etki Spektrumu

- Metisilin Dirençli S. Aureus (**MRSA**)
- Vankomisin Orta Duyarlı S. Aureus (**VISA**)
- Vankomisin Dirençli S. Aureus (**VRSA**)
- Pnömokoklar dahil Gr (+) bakterilere karşı **Bakterisidal** etkisi vardır
- **Anaerob** Gr (+) bakterilere karşı etki (Actinomyces, Laktobacillus dahil)

TELAVANSİN
Etki Spektrumu

- Vankomisin ve Linezolid **dirençli MRSA**' lara karşı da etkili,
- In vitro stafilokok biyofilm modellerinde;
- Vankomisin, Teikoplanin, Linezolid ve Moksifloksasin' e göre **daha güçlü bakterisidal**
- Hayvan modellerinde, **bakterisidal etki vankomisin' e göre,**

  MRSA' da 5-30 kat, MSSA' da 16-40 kat

TELAVANSİN

- **Günde bir kez**, 10mg/kg,
- IV, 1 saat infüzyon

- CrCl 30-50 ml/dk: 7,5 mg/kg /gün,
- CrCl 10-30 ml/dk: 48 saatte 10 mg/kg/gün

- Gebelik kategori C

TELAVANSİN İndikasyonları

- FDA onayı,

- MRSA dahil Gram (+) komplike **DYDE**
- S. aureus kaynaklı **Nozokomiyal Pnömoni**
- S. aureus kaynaklı **Ventilatör İlişkili Pnömoni** ,

Telavancin Versus Vancomycin for the Treatment of Complicated Skin and Skin-Structure Infections Caused by Gram-Positive Organisms

Martin E. Stryjewski,[1,9] Donald R. Graham,[3] Samuel E. Wilson,[4] William O'Riordan,[5] David Young,[6] Arnold Lentnek,[8] Douglas P. Ross,[10] Vance G. Fowler,[1,2] Alan Hopkins,[7] H. David Friedland,[7] Steven L. Barriere,[7] Michael M. Kitt,[7] and G. Ralph Corey,[1,2] on behalf of the Assessment of Telavancin in Complicated Skin and Skin-Structure Infections Study[a]

[1]Duke Clinical Research Institute and [2]Division of Infectious Diseases, Duke University Medical Center, Durham, North Carolina; [3]Springfield Clinic, Springfield, Illinois; [4]University of California, Irvine School of Medicine, Orange, [5]eStudy Site, San Diego, [6]San Francisco General Hospital–University of California, San Francisco, and [7]Theravance, South San Francisco, California; [8]WellStar Health System, Marietta, Georgia; [9]Department of Medicine and Division of Infectious Diseases, Centro de Educación Médica e Investigaciones Clínicas, Buenos Aires, Argentina; and [10]St. Mary's Hospital, Durban, South Africa

Background. Telavancin is an investigational, rapidly bactericidal lipoglycopeptide with a multifunctional mechanism of action.

Methods. We conducted 2 parallel, randomized, double-blind, active-control, phase 3 studies with a prespecified pooled analysis design. Patients aged ≥18 years who had complicated skin and skin-structure infections caused by suspected or confirmed gram-positive organisms were randomized to receive either telavancin (10 mg/kg intravenously every 24 h) or vancomycin (1 g intravenously every 12 h).

Results. A total of 1867 patients were randomized and received ≥1 dose of study medication. In the clinically evaluable population, at 7–14 days after receipt of the last antibiotic dose, success was achieved in 88% and 87% of patients who received telavancin and vancomycin, respectively (95% confidence interval for the difference, −2.1 to 4.6). Methicillin-resistant *Staphylococcus aureus* was isolated at baseline from samples from 579 clinically evaluable patients. Among these patients with methicillin-resistant *S. aureus* infection, cure rates were 91% among patients who received telavancin and 86% among patients who received vancomycin (95% confidence interval for the difference, −1.1 to 9.3). Microbiologic eradication among patients infected with methicillin-resistant *S. aureus* was 90% in the telavancin treatment group and 85% in the vancomycin treatment group (95% confidence interval for the difference, −0.9 to 9.8). Therapy was discontinued because of adverse events in 8% and 6% of patients who received telavancin and vancomycin, respectively. Except for mild taste disturbance, nausea, vomiting, and serum creatinine concentration elevation in the telavancin treatment group and pruritus in the vancomycin treatment group, adverse events were similar between groups with regard to type and severity.

Conclusions. Telavancin given once daily is at least as effective as vancomycin for the treatment of patients with complicated skin and skin-structure infections, including those infected with methicillin-resistant *S. aureus*.

TELAVANSİN

- **Komplike deri ve yumuşak doku infeksiyonu**,
- 2 randomize kontrollü faz 3 çalışması, akut bakteriyel deri ve yumuşak doku infeksiyonlu **1867** hastada,
- **Kreatinin artışı** telavansin grubunda vankomisine göre daha daha sık (%6,3 - %2.2),
- CrCl ≤ 50 ml/dk olanlarda tedavi başarısı daha düşük bulunmuştur.

TELAVANSİN

- Telavansin – vankomisin, 14 gün sonra tedavi başarısı (%88 - %87)
- **MRSA** infeksiyonu, klinik iyileşme, telavansin - vankomisin (%91 - %86)
- Bakteriyel eradikasyon telavansin - vankomisin (%90 - %85)
- **Sonuç:** Günde tek doz uygulanan telavansin komplike DYDİ'da en az vankomisin kadar etkili

Telavancin versus Vancomycin for Hospital-Acquired Pneumonia due to Gram-positive Pathogens

Ethan Rubinstein,[1] Tahaniyat Lalani,[2,3] G. Ralph Corey,[2,3] Zeina A. Kanafani,[11] Esteban C. Nannini,[12] Marcelo G. Rocha,[15] Galia Rahav,[16] Michael S. Niederman,[4,5] Marin H. Kollef,[6] Andrew F. Shorr,[7] Patrick C. Lee,[8] Arnold L. Lentnek,[9] Carlos M. Luna,[13] Jean-Yves Fagon,[17] Antoni Torres,[18] Michael M. Kitt,[a] Fredric C. Genter,[10] Steven L. Barriere,[10] H. David Friedland,[a] Martin E. Stryjewski,[2,14] for the ATTAIN Study Group[b]

[1]Section of Infectious Diseases Department of Internal Medicine and Medical Microbiology, University of Manitoba, Winnipeg, Manitoba, Canada; [2]Department of Medicine, Duke Clinical Research Institute and [3]Department of Medicine, Division of Infectious Diseases, Duke University Medical Center, Durham, North Carolina; [4]Winthrop-University Hospital, Mineola, and [5]State University of New York at Stony Brook, Stony Brook, New York; [6]Pulmonary and Critical Care Division, Washington University School of Medicine, St. Louis, Missouri; [7]Pulmonary and Critical Care Medicine, Washington Hospital Center, Washington, DC; [8]Baystate Medical Center, Springfield, Massachusetts; [9]Wellstar Infectious Disease, Marietta, Georgia; [10]Theravance Inc., South San Francisco, California; [11]American University of Beirut Medical Center, Beirut, Lebanon; [12]Department of Infectious Diseases, School of Medicine, Universidad Nacional de Rosario, Rosario and [13]Department of Internal Medicine, Pulmonary Diseases Division, Hospital de Clínicas, Universidad de Buenos Aires, and [14]Department of Medicine and Division of Infectious Diseases, Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno, Buenos Aires, Argentina; [15]Intensive Care Unit, Pavilhão Pereira Filho, Irmandade da Santa Casa, Porto Alegre, Brazil; [16]Division of Infectious Diseases Department of Medicine, Sheba Medical Center, Tel Hashomer, Israel; [17]Assistance Publique-Hôpitaux de Paris, Université Paris-Descartes, Paris, France; [18]Division of Pulmonary Medicine, Clinic Institute of Thorax, Hospital Clinic of Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Ciber de Enfermedades Respiratorias, Barcelona, Spain

Background. Telavancin is a lipoglycopeptide bactericidal against gram-positive pathogens.

Methods. Two methodologically identical, double-blind studies (0015 and 0019) were conducted involving patients with hospital-acquired pneumonia (HAP) due to gram-positive pathogens, particularly methicillin-resistant *Staphylococcus aureus* (MRSA). Patients were randomized 1:1 to telavancin (10 mg/kg every 24 h) or vancomycin (1 g every 12 h) for 7–21 days. The primary end point was clinical response at follow-up/test-of-cure visit.

Results. A total of 1503 patients were randomized and received study medication (the all-treated population). In the pooled all-treated population, cure rates with telavancin versus vancomycin were 58.9% versus 59.5% (95% confidence interval [CI] for the difference, –5.6% to 4.3%). In the pooled clinically evaluable population ($n = 654$), cure rates were 82.4% with telavancin and 80.7% with vancomycin (95% CI for the difference, –4.3% to 7.7%). Treatment with telavancin achieved higher cure rates in patients with monomicrobial *S. aureus* infection and comparable cure rates in patients with MRSA infection; in patients with mixed gram-positive/gram-negative infections, cure rates were higher in the vancomycin group. Incidence and types of adverse events were comparable between the treatment groups. Mortality rates for telavancin-treated versus vancomycin-treated patients were 21.5% versus 16.6% (95% CI for the difference, –0.7% to 10.6%) for study 0015 and 18.5% versus 20.6% (95% CI for the difference, –7.8% to 3.5%) for study 0019. Increases in serum creatinine level were more common in the telavancin group (16% vs 10%).

Conclusions. The primary end point of the studies was met, indicating that telavancin is noninferior to vancomycin on the basis of clinical response in the treatment of HAP due to gram-positive pathogens.

Telavansin
Yan Etki

- **<u>Telavansin-Vankomisin Yan Etki Karşılaştırması</u>**

- Herhangi bir yan etki,
- Ciddi yan etki,
- Yan etki nedeniyle tedaviyi yarıda kesme

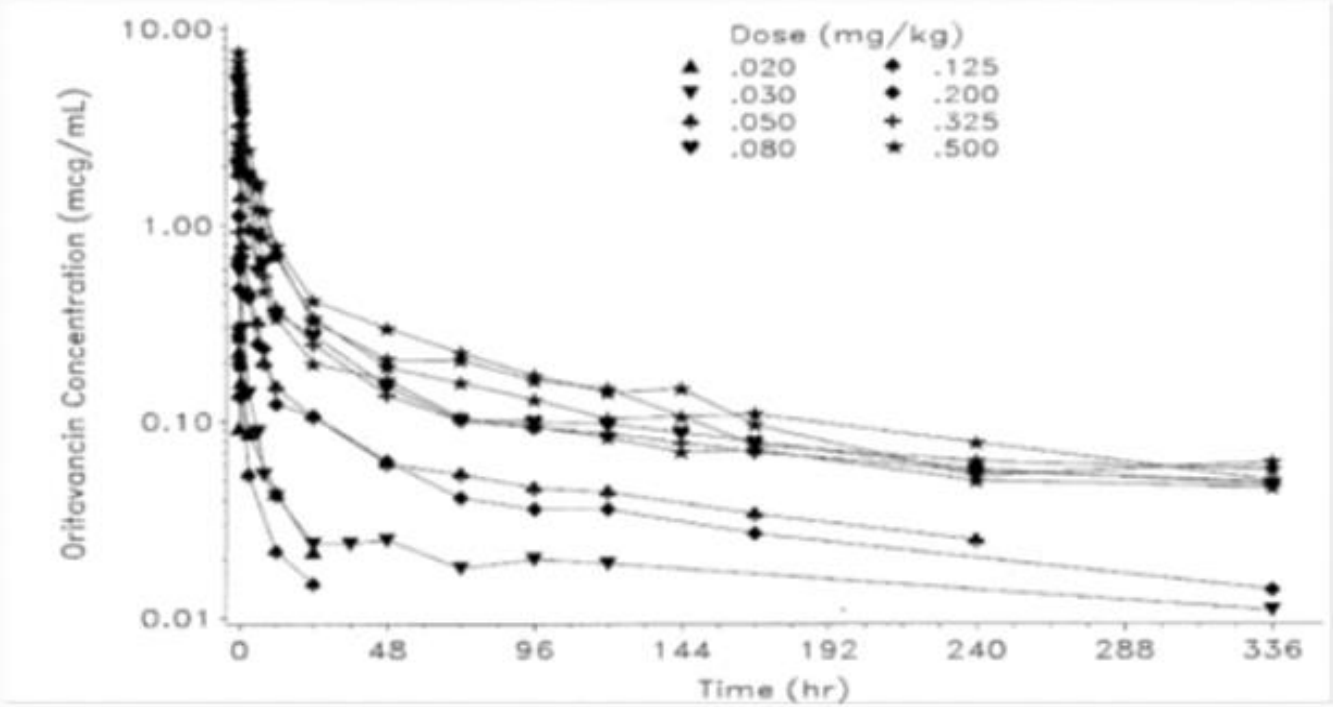
Variable	No. (%) of patients	
	Telavancin treatment arm (n = 929)	Vancomycin treatment arm (n = 938)
Any adverse event	735 (79)	676 (72)
Serious adverse event	69 (7)	42 (4)
Discontinued treatment because of an adverse event	73 (8)	53 (6)
Adverse event term		
Taste disturbance	311 (33)	62 (7)
Nausea	249 (27)	142 (15)
Headache	130 (14)	120 (13)
Vomiting	127 (14)	69 (7)
Urine abnormality (foamy urine)	122 (13)	27 (3)
Insomnia	90 (10)	86 (9)
Constipation	96 (10)	61 (7)
Diarrhea	67 (7)	76 (8)
Dizziness	55 (6)	53 (6)
Rash	35 (4)	43 (5)
Infusion site pain	41 (4)	40 (4)
Fatigue	41 (4)	31 (3)
Chills	41 (4)	21 (2)
Generalized pruritus	28 (3)	60 (6)
Infusion site erythema	24 (3)	24 (3)
Decreased appetite	25 (3)	19 (2)
Anxiety	26 (3)	22 (2)
Renal dysfunction	27 (3)	10 (1)
Abdominal pain	17 (2)	26 (3)

Oritavansin (orbactive)

- FDA ve EMA onayı 2014.
- **Uzun** etkili glikopeptid, **tek doz**
- Hücre duvarı sentezini inhibe eder,
- Yarılanma zamanı 195 saat
  (% 90 protein e bağlanma)
- Konsantrayona bağlı **bakterisidal** aktivite
- **Deri ve yumuşak doku infeksiyonlarında,**

Oritavansin

Plasma Concentration: Oritivancin



Glikopeptidlerin Yarılanma Ömürleri Kıyaslaması

Parameter	Oritavancin	Dalbavancin	Televancin	Vancomycin
Peak concentration (mg/L)	31	279	186	60
Protein binding (%)	90	>99	93	**10-50**
Vd	1.08/L/kg	9.75-15.5 L	0.12 L/kg	0.4- 1 L/kg
Terminal half-life (hrs)	**195**	**257**	**7.5**	**6-12**

Oritavansin

Etki Spektrumu

- Gr (+) bakterilerden, penisilin dirençli suşlar dahil Pnömokoklara,
- VISA, VRSA,
- Streptokok,
- Listeria, Clostridium, Corynbacterium türlerine
- Enterococcus faecalis (vancomisin-duyarlılar)
- Tavşan deneylerinde; **MRSA endokarditi ve pnömokoksik menenjit**

Clin Infect Dis. 2015 Jan 15;60(2):254-62. doi: 10.1093/cid/ciu778. Epub 2014 Oct 6.

Single-dose oritavancin versus 7-10 days of vancomycin in the treatment of gram-positive acute bacterial skin and skin structure infections: the SOLO II noninferiority study.

Corey GR[1], Good S[2], Jiang H[2], Moeck G[2], Wikler M[2], Green S[3], Manos P[4], Keech R[5], Singh R[6], Heller B[7], Bubnova N[8], O'Riordan W[9]; SOLO II Investigators.

Author information

Abstract

BACKGROUND: Oritavancin is a lipoglycopeptide antibiotic with rapid bactericidal activity against gram-positive bacteria. Its concentration-dependent activity and long half-life allow for single-dose treatment.

METHODS: In a randomized, double-blind trial, adults with acute bacterial skin and skin structure infections (ABSSSIs) received either a single intravenous 1200-mg dose of oritavancin or 7-10 days of twice-daily vancomycin. Three efficacy endpoints were tested for noninferiority: (1) primary composite endpoint at 48-72 hours (cessation of spreading or reduction in lesion size, absence of fever, and no rescue antibiotic); (2) investigator-assessed clinical cure 7-14 days after end of treatment; and (3) ≥20% reduction in lesion area at 48-72 hours.

RESULTS: A total of 503 and 502 patients comprised the modified intent-to-treat population for oritavancin and vancomycin, respectively. All 3 efficacy endpoints met the 10% noninferiority margin: the primary composite endpoint (80.1% vs 82.9%; 95% confidence interval [CI], -7.5 to 2.0), investigator-assessed clinical cure (82.7% vs 80.5%; 95% CI, -2.6 to 7.0), and proportion of patients attaining ≥20% reduction in lesion area (85.9% vs 85.3%; 95% CI, -3.7 to 5.0) for oritavancin vs vancomycin, respectively. Efficacy outcomes by pathogen, including methicillin-resistant Staphylococcus aureus and the frequency of adverse events, were similar between treatment groups.

CONCLUSIONS: A single 1200-mg dose of oritavancin was noninferior to 7-10 days of vancomycin in treating ABSSSIs caused by gram-positive pathogens, and was well tolerated. Oritavancin provides a single-dose alternative to multidose therapies for the treatment of ABSSSIs. Clinical Trials Registration. NCT01252732.

Oritavancin

- SOLO 1, SOLO 2 çalışmaları,
- 7-10 gün, 1200 mg, **tek doz**
- 2x1 gr, Vankomisin karşılaştırmada etki **benzer**,
- IV inf., 3 saat,
- **Avantaj**; TEK doz, yan etki düşük,
- **Gentamisin** ile kombine, sinerjistik etki, dirençli mutant gelişimini önler,

Dalbavansin (Dalvance)

- FDA 2014, Bakterisidal
- Daha **uzun** etkili, lipoglikopeptid, IV
- Akut bakteriyel **DYDİ** onaylı sadece,
- Ama kateter ilişkili bateriyemilerde , faz 2 çalışmasında Vankomisin' den üstün,
- Yarılanma ömrü çok uzun, **9-12** gün, **haftalık** kullanım, 2 doz, 14 gün etki

Dalbavansin

Etki Spektrumu

- S. aureus (MSSA ve MRSA) **ve**
- Streptococcus pyogenes' e vankomisin, teikoplanin ve oritavansin' den **daha etkili**
- Pnömokoklara,
- Vankomisin duyarlı enterokoklara **etkili**,
- Glikopeptit dirençli enterokoklara yeterince **etkin değil**,
- Ampisilin ile sinerjistik etki

N Engl J Med. 2014 Jun 5;370(23):2169-79. doi: 10.1056/NEJMoa1310480.

Once-weekly dalbavancin versus daily conventional therapy for skin infection.

Boucher HW[1], Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW.

Author information

Abstract

BACKGROUND: Dalbavancin, a lipoglycopeptide antibiotic agent that is active against gram-positive pathogens, has a long plasma half-life, allowing for once-weekly dosing. DISCOVER 1 and DISCOVER 2 were identically designed noninferiority trials of dalbavancin for the treatment of acute bacterial skin and skin-structure infection.

METHODS: We randomly assigned patients to receive dalbavancin intravenously on days 1 and 8 or vancomycin intravenously for at least 3 days with the option to switch to oral linezolid to complete 10 to 14 days of therapy. The primary end point, early clinical response, required the cessation of spread of infection-related erythema and the absence of fever at 48 to 72 hours. Secondary end points at the end of therapy included clinical status and investigator's assessment of outcome.

RESULTS: Analysis of the primary end point showed noninferiority of dalbavancin in both DISCOVER 1 and DISCOVER 2. In the pooled analysis, 525 of 659 patients (79.7%) in the dalbavancin group and 521 of 653 (79.8%) in the vancomycin-linezolid group had an early clinical response indicating treatment success (weighted difference, -0.1 percentage point; 95% confidence interval, -4.5 to 4.2). The outcomes were similar in the analyses by study and the pooled analyses of clinical status at the end of therapy and the investigator's assessment of outcome. For patients infected with Staphylococcus aureus, including methicillin-resistant S. aureus, clinical success was seen in 90.6% of the patients treated with dalbavancin and 93.8% of those treated with vancomycin-linezolid. Adverse events and study days with an adverse event were less frequent in the dalbavancin group than in the vancomycin-linezolid group. The most common treatment-related adverse events in either group were nausea, diarrhea, and pruritus.

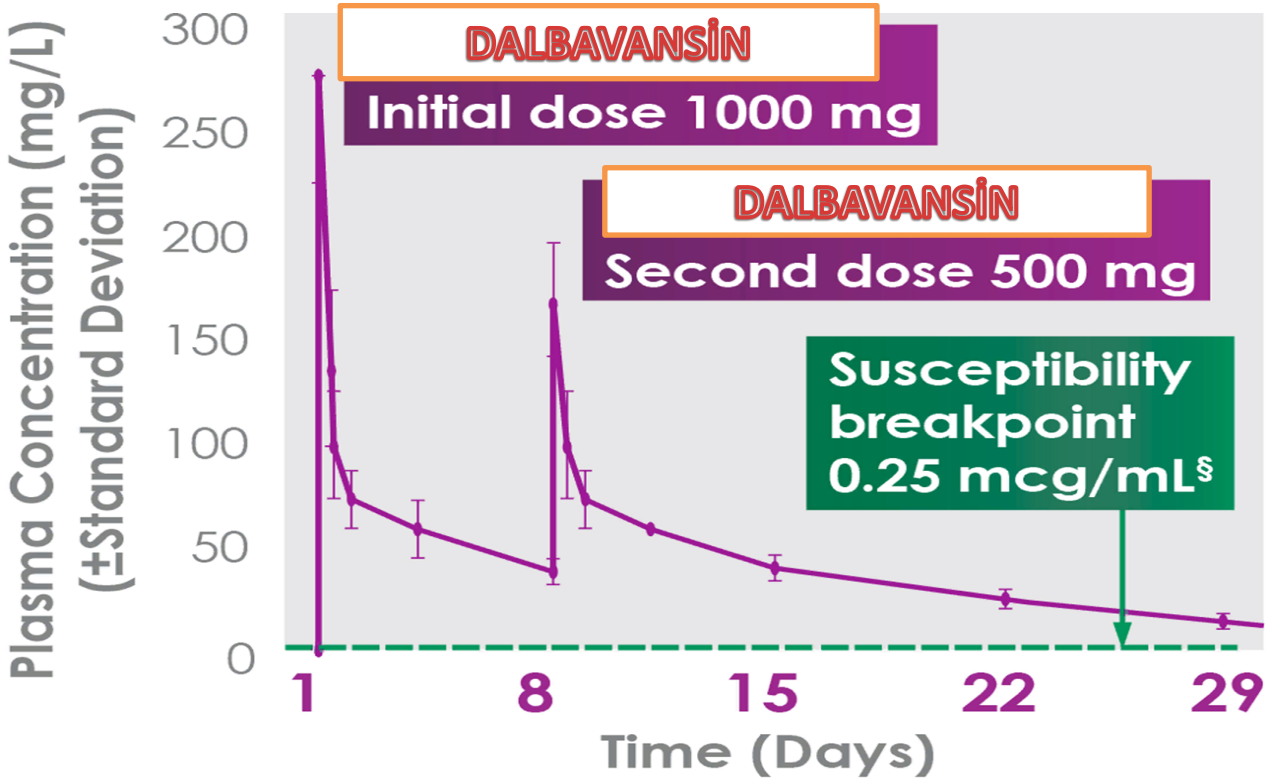
CONCLUSIONS: Once-weekly intravenous dalbavancin was not inferior to twice-daily intravenous vancomycin followed by oral linezolid for the treatment of acute bacterial skin and skin-structure infection. (Funded by Durata Therapeutics; DISCOVER 1 and DISCOVER 2 ClinicalTrials.gov numbers, NCT01339091 and NCT01431339.).

Dalbavansin

- DISCOVER-1 ve DISCOVER-2 çalışmaları,
- Dalbavancin IV, **ilk gün 1000 mg, 8.gün 500 mg,**
- **Vankomisin** IV, en az 3 gün, daha sonra **linezolid** veya IV / oral 12h,
- Tedavi 14 güne tamamlandı,
- Dalbavancin' in etkinliği, Vankomisin / Linezolid ile benzer etkinlikte bulunuyor

Dalbavansin

- Tek doz 1000 mg IV kullanımı, MRSA için 8 gün yüksek serum konsantrasyonu,



Dalbavansin

- 150-250 saat, uzun yarı ömrü
- (protein bağlama >%99)
- MRSA infeksiyonlarında kullanılması,
- Vankomisin’ e göre çok **uzun yarı ömürlü,**
- Haftada 2 doz, **ayaktan** tedavi, avantaj
- Hücre duvarı sentezini inhibe eder,

Maliyet Analizi

IV Agents for MRSA:[skin and soft tissue]

Agent	Usual Adult Dose (70 kg person)	FDA approved duration	Cost ($)
Lipoglycopeptide			
Vancomycin	15 mg/kg q 12		16.50
Dalbavancin ★	1000mg, x1, 500mg 1 week later	14 days →	**2980.00**
Oritavancin ★	1200 mg	Once →	**2900.00**
Televancin	10 mg/kg q 24	7-14 days	309.50
Oxazolidinone			
Linezolid	600 mg q 12	10-14 days	278.90
Tedizolid	200mg/day	6 days	235.00

Oksazolidinonlar

- Linezolid (FDA onayı 2000'de)
- Tedizolid (FDA 2014)
- Radezolid (faz çalışması)

Oksazolidinon
Tedizolid (Sivextro)

- Oral ve IV formu (Linezolid gibi)
- **Deri ve yumuşak doku infeksiyonları** indikasyon
- Protein sentezini inh. eder , 50S ribozom
- Oral / IV, 200 mg, **6 gün**
- Biyoyararlanımı %91.7
- Yarılanma ömrü 9 saat (Linezolid' e göre daha yüksek yarı ömür)

Tedizolid

Gr (+) etkinlik

- Staph. aureus (**MRSA** ve MSSA), KNS
- Pnömokoklar (dirençli dahil), S. pyogenes, S. Agalactiae
- Enterococcus faecalis (**Vankomisine duyarlı ve dirençli**)
- Tedizolid stafilokok ve enterokoklara 4-16 kez daha etkili

JAMA. 2013 Feb 13;309(6):559-69. doi: 10.1001/jama.2013.241.

Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial.

Prokocimer P[1], De Anda C, Fang E, Mehra P, Das A.

Author information

Abstract

IMPORTANCE: Acute bacterial skin and skin structure infections (ABSSSIs), including cellulitis or erysipelas, major cutaneous abscesses, and wound infections, can be life-threatening and may require surgery and hospitalization. Increasingly, ABSSSIs are associated with drug-resistant pathogens, and many antimicrobial agents have adverse effects restricting their use. Tedizolid phosphate is a novel oxazolidinone in development for the treatment of ABSSSIs.

OBJECTIVES: To establish the noninferiority of tedizolid phosphate vs linezolid in treating ABSSSIs and compare the safety of the 2 agents.

DESIGN, SETTING, AND PATIENTS: The Efficacy and Safety of 6-day Oral Tedizolid in Acute Bacterial Skin and Skin Structure Infections vs 10-day Oral Linezolid Therapy (ESTABLISH-1) was a phase 3, randomized, double-blind, noninferiority trial that was conducted from August 2010 through September 2011 at 81 study centers in North America, Latin America, and Europe. The intent-to-treat analysis set consisted of data from 667 adults aged 18 years or older with ABSSSIs treated with tedizolid phosphate (n = 332) or linezolid (n = 335).

INTERVENTIONS: A 200 mg once daily dose of oral tedizolid phosphate for 6 days or 600 mg of oral linezolid every 12 hours for 10 days.

MAIN OUTCOME MEASURES: The primary efficacy outcome was early clinical response at the 48- to 72-hour assessment (no increase in lesion surface area from baseline and oral temperature of ≤37.6°C, confirmed by a second temperature measurement within 24 hours). A 10% noninferiority margin was predefined.

RESULTS: In the intent-to-treat analysis set, the early clinical treatment response rates were 79.5% (95% CI, 74.8% to 83.7%) of 332 patients in the tedizolid phosphate group and 79.4% (95% CI, 74.7% to 83.6%) of 335 patients in the linezolid group (a treatment difference of 0.1% [95% CI, -6.1% to 6.2%]). The sustained clinical treatment response rates at the end of treatment (day 11) were 69.3% (95% CI, 64.0% to 74.2%) in the tedizolid phosphate group and 71.9% (95% CI, 66.8% to 76.7%) in the linezolid group (a treatment difference of -2.6% [95% CI, -9.6% to 4.2%]). Results of investigator-assessed clinical treatment success rates at a posttherapy evaluation visit (1-2 weeks after the end-of-treatment visit) were 85.5% (95% CI, 81.3% to 89.1%) in the tedizolid phosphate group and 86.0% (95% CI, 81.8% to 89.5%) in the linezolid group (a treatment difference of -0.5% [95% CI, -5.8% to 4.9%), and were similar for 178 patients with methicillin-resistant Staphylococcus aureus isolated from the primary lesion.

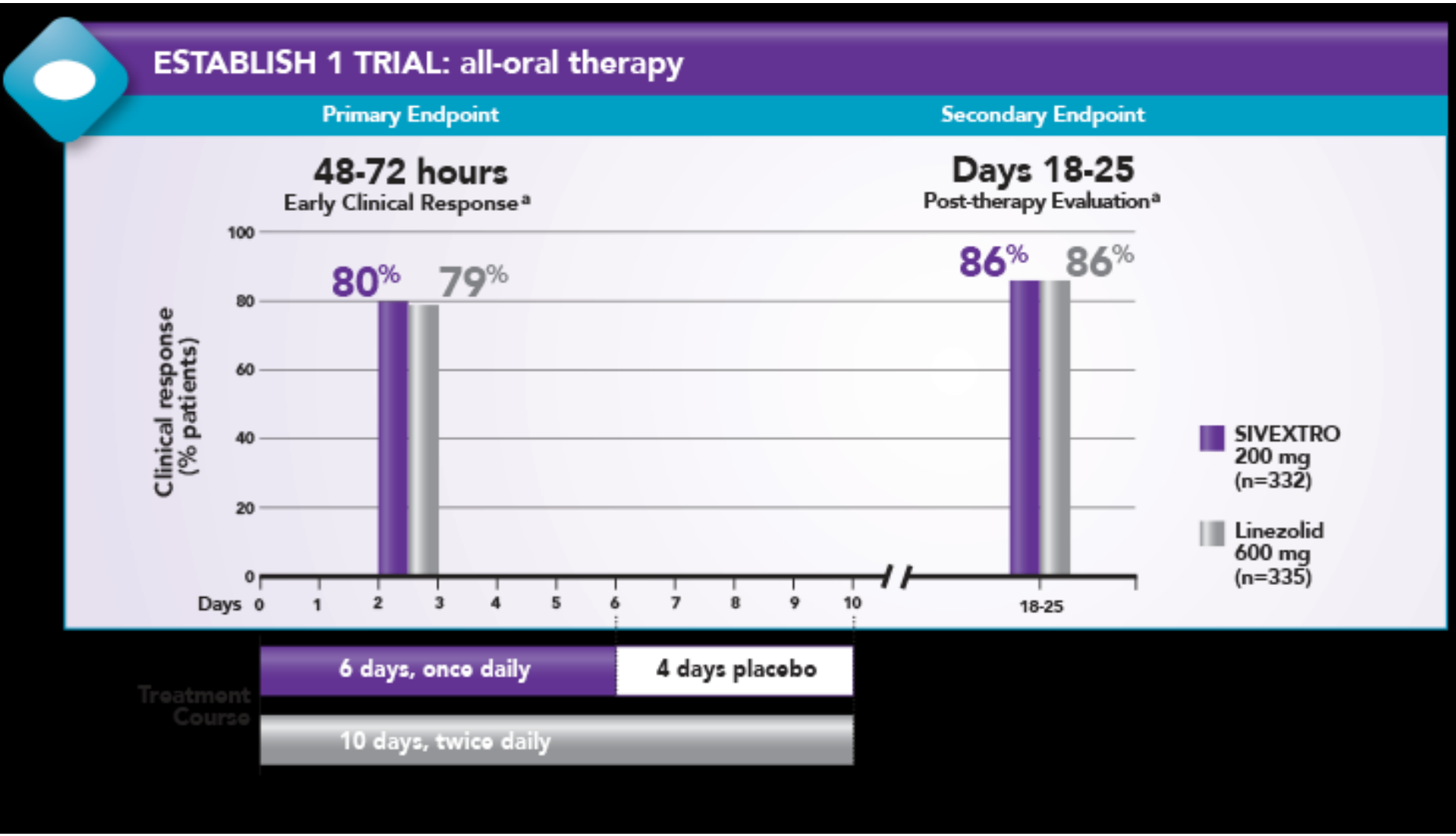
CONCLUSIONS AND RELEVANCE: Tedizolid phosphate was a statistically noninferior treatment to linezolid in early clinical response at 48 to 72 hours after initiating therapy for an ABSSSI. Tedizolid phosphate may be a reasonable alternative to linezolid for treating ABSSSI.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT01170221.

Tedizolid Faz III çalışması

- Establish-1 çalışmasında; 667 hasta,
- Tedizolid, **6 gün**, oral 200 mg, **1x1,**
- Linezolid, **10 gün**, oral 600 mg, **2x1**
- Erken klinik yanıt oranları; tedizolid %79.5 linezolidde %79.4
- Tedizolid'in en az linezolid kadar etkin olduğu gösterilmiş.

Tedizolid


ESTABLISH 1 TRIAL: all-oral therapy
Primary Endpoint
Secondary Endpoint
48-72 hours
Early Clinical Response[a]
Days 18-25
Post-therapy Evaluation[a]
Clinical response (% patients)
100
80
60
40
20
0
80%
79%
86%
86%
Days 0 1 2 3 4 5 6 7 8 9 10
18-25
SIVEXTRO 200 mg (n=332)
Linezolid 600 mg (n=335)
Treatment Course
6 days, once daily
4 days placebo
10 days, twice daily

Tedizolid

Tedizolid: highly differentiated oxazolidinone

Tedizolid

Linezolid (Zyvox)

Generic

Attribute	Linezolid	Vancomycin	Daptomycin	Tedizolid
IV/Oral	✓	X	X	✓
In-Vivo Bactericidal	X	✓	✓	✓
Active in Lung Infections	✓	✓	X	✓
Once Daily Treatment	X	X	✓	✓
Short Course of Therapy	X	X	X	✓

CDC Antibakteriyel Direnç Tehditleri

CDC Assessment of Antibacterial Resistance Threats [5]

Urgent Threats

- Clostridium difficile
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

Seftazidim-avibaktam (Avycaz)

- FDA, 2015
- Bir sefalosporin ve beta-laktamaz inh. kombinasyonu
- **Seftazidim**;
- 3. jenerasyon, veteran, 1985 FDA,
- Tek başına da kullanılır,
- Bakterisidal etkisi, penicillin bağlayıcı proteinlere (PBPs)

Seftazidim-avibaktam

- **Avibaktam**;
- Beta-laktamazı inaktive eder,
- Seftazidim' e Avibaktam ilavesi;
- Seftazidim' in ***Enterobacteriaceae*** ve ***Pseudomonas aeruginosa***' ya karşı etki
- Acinetobacter spp., Gr (-) anaerob basilllere karşı **etkilemez**

Seftazidim-avibaktam

İndikasyonlar

- **Komplike üriner sistem** infeksiyonları,
- **İntra-abdominal** infeksiyonlar**,**

- Seftazidim-Avibaktam, **seftazidim' e dirençli** komplike ÜSİ ve İAİ en az karbapenemler kadar etkili

Seftazidim-avibaktam

- Komplike İAİ' da **Metronidazol**

- *Escherichia coli,*
- *Klebsiella pneumoniae,*
- *Proteus mirabilis,*
- *Providencia stuartii,*
- *Enterobacter cloacae,*
- *Klebsiella oxytoca,*
- *Pseudomonas aeruginosa*

Seftazidim-avibaktam

- Piyelonefrit dahil komplike Üriner Sistem İnfeksiyonları;

- *Escherichia coli,*
- *Klebsiella pneumoniae,*
- *Enterobacter aerogenes,*
- *Enterobacter cloacae,*
- *Citrobacter freundii,*
- *Proteus spp.,*
- *Pseudomonas aeruginosa*

Seftazidim-avibaktam

- Intravenöz,
- Önerilen doz 2.5 gram,
- 2 gram seftazidim ve 0.5 gram avibaktam,
- Her 8 saatte bir uygulanır, 3x1
- IV infüzyon 2 saat

Seftazidim-avibaktam

Phase 3 Clinical Results

cUTI: RECAPTURE

AVYCAZ vs doripenem (N=1020)

A phase 3, multinational, multicenter, double-blind, randomized noninferiority trial studying AVYCAZ vs doripenem for the treatment of cUTI, including acute pyelonephritis and complicated lower urinary tract infections.[1]

cUTI, complicated urinary tract infections.

cUTI: REPRISE

AVYCAZ vs best available therapy (BAT; N=305)

A phase 3, multinational, randomized, open-label trial comparing AVYCAZ vs BAT for the treatment of cUTI due to ceftazidime-nonsusceptible Gram-negative pathogens. BAT options were meropenem, imipenem, doripenem, and colistin.[1]

cIAI: RECLAIM

AVYCAZ plus metronidazole vs meropenem (N=1058)

A phase 3, multinational, double-blind, noninferiority trial studying AVYCAZ plus metronidazole versus meropenem for the treatment of cIAI.[1]

cIAI, complicated intra-abdominal infections.

See the RECAPTURE data

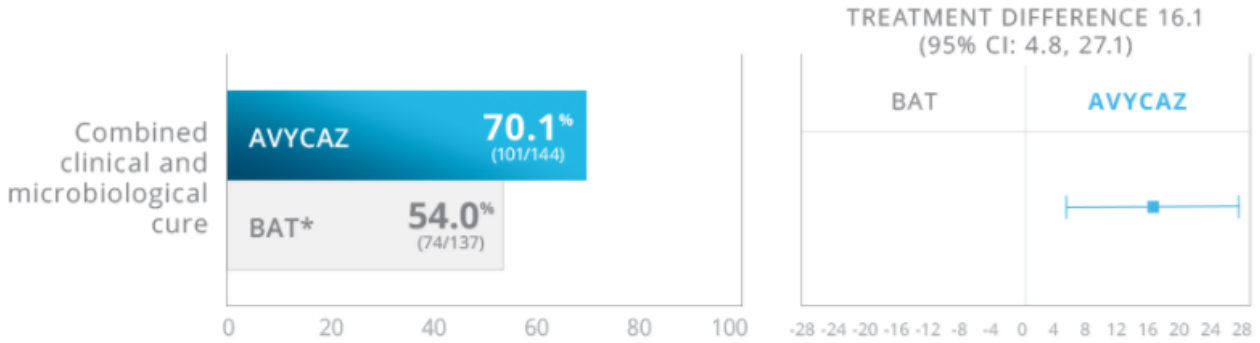
See the REPRISE data

See the RECLAIM data

Clinical efficacy demonstrated in cUTI caused by ceftazidime-NS Gram-negative pathogens[1]

- AVYCAZ demonstrated a higher cure rate with regard to the combined clinical and microbiological cure vs best available therapy (BAT)* at the Day 21 to 25 visit[1]

COMBINED CLINICAL AND MICROBIOLOGICAL CURE RATES AT THE DAY 21 TO 25 VISIT (mMITT)[1]



* Best available therapy (BAT) options were meropenem, imipenem, doripenem, and colistin; the majority of patients received carbapenem monotherapy.[1]

Clinical efficacy in cUTI across baseline ceftazidime-NS Gram-negative pathogens[1]

MICROBIOLOGICAL RESPONSE RATES BY BASELINE CEFTAZIDIME-NS PATHOGEN AT THE DAY 21 TO 25 VISIT (mMITT)[1]

	AVYCAZ®	BAT
Escherichia coli	**76.3%** (45/59)	**57.9%** (33/57)
Klebsiella pneumoniae	**76.4%** (42/55)	**60.0%** (39/65)
Pseudomonas aeruginosa	**57.1%** (8/14)	**60.0%** (3/5)

mMITT, microbiologically modified intent-to-treat.

NS, nonsusceptible.

Lancet Infect Dis. 2017 Dec 15. pii: S1473-3099(17)30747-8. doi: 10.1016/S1473-3099(17)307[illegible] [Epub ahead of print]

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

Torres A[1], Zhong N[2], Pachl J[3], Timsit JF[4], Kollef M[5], Chen Z[6], Song J[6], Taylor D[7], Laud PJ[8], Stone GG[9], Chow JW[10].

Author information

Abstract

BACKGROUND: Nosocomial pneumonia is commonly associated with antimicrobial-resistant Gram-negative pathogens. We aimed to assess the efficacy and safety of ceftazidime-avibactam in patients with nosocomial pneumonia, including ventilator-associated pneumonia, compared with meropenem in a multinational, phase 3, double-blind, non-inferiority trial (REPROVE).

METHODS: Adults with nosocomial pneumonia (including ventilator-associated pneumonia), enrolled at 136 centres in 23 countries, were randomly assigned (1:1) to 2000 mg ceftazidime and 500 mg avibactam (by 2 h intravenous infusion every 8 h) or 1000 mg meropenem (by 30-min intravenous infusion every 8 h) for 7-14 days; regimens were adjusted for renal function. Computer-generated randomisation codes were stratified by infection type and geographical region with a block size of four. Participants and investigators were masked to treatment assignment. The primary endpoint was clinical cure at the test-of-cure visit (21-25 days after randomisation). Non-inferiority was concluded if the lower limit of the two-sided 95% CI for the treatment difference was greater than -12·5% in the coprimary clinically modified intention-to-treat and clinically evaluable populations. This trial is registered with ClinicalTrials.gov (NCT01808092) and EudraCT (2012-004006-96).

FINDINGS: Between April 13, 2013, and Dec 11, 2015, 879 patients were randomly assigned. 808 patients were included in the safety population, 726 were included in the clinically modified intention-to-treat population, and 527 were included in the clinically evaluable population. Predominant Gram-negative baseline pathogens in the microbiologically modified intention-to-treat population (n=355) were Klebsiella pneumoniae (37%) and Pseudomonas aeruginosa (30%); 28% were ceftazidime-non-susceptible. In the clinically modified intention-to-treat population, 245 (68·8%) of 356 patients in the ceftazidime-avibactam group were clinically cured, compared with 270 (73·0%) of 370 patients in the meropenem group (difference -4·2% [95% CI -10·8 to 2·5]). In the clinically evaluable population, 199 (77·4%) of 257 participants were clinically cured in the ceftazidime-avibactam group, compared with 211 (78·1%) of 270 in the meropenem group (difference -0·7% [95% CI -7·9 to 6·4]). Adverse events occurred in 302 (75%) of 405 patients in the ceftazidime-avibactam group versus 299 (74%) of 403 in the meropenem group (safety population), and were mostly mild or moderate in intensity and unrelated to study treatment. Serious adverse events occurred in 75 (19%) patients in the ceftazidime-avibactam group and 54 (13%) patients in the meropenem group. Four serious adverse events (all in the ceftazidime-avibactam group) were judged to be treatment related.

INTERPRETATION: Ceftazidime-avibactam was non-inferior to meropenem in the treatment of nosocomial pneumonia. These results support a role for ceftazidime-avibactam as a potential alternative to carbapenems in patients with nosocomial pneumonia (including ventilator-associated pneumonia) caused by Gram-negative pathogens.

FUNDING: AstraZeneca.

Seftolozan-tazobaktam (Zerbaxa)

- Sefalosporin ve beta-laktamaz inh.,
- **Seftolozan**, “5.jenerasyon” yeni sefalosporin,
- Seftazidim’ e benzer yapısı, anti pseudomonal
- **Tazobaktam**, beta-laktamaz inh.
- Tazobaktam ilavesi, etki spektrumunu artırır (GSBL üreten ve anaerob türler)

Seftolozan-tazobaktam

İndikasyonlar

- Komplike Üriner Sistem İnfeksiyonları
  (piyelonefrit dahil)

- Komplike İntraabdominal İnfeksiyonlar,
  (metronidazol ile kombine kullanıldığında)

Seftolozan-tazobaktam

- **Komplike intra-abdominal infeksiyonlar,** Metronidazole ile
- Gram negatif ve Gram pozitif mikroorganizmalarda;

- *Enterobacter cloacae,*
- *Escherichia coli,*
- *Klebsiella oxytoca, K. pneumoniae,*
- *Proteus mirabilis,*
- *Pseudomonas aeruginosa,*
- *Streptococcus türleri,*
- *Bacteroides fragilis,*
- ***Acinetobacter spp. ye karşı minimal etki***

Clin Infect Dis. 2015 May 15;60(10):1462-71. doi: 10.1093/cid/civ097. Epub 2015 Feb 10.

Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI).

Solomkin J[1], Hershberger E[2], Miller B[2], Popejoy M[2], Friedland I[2], Steenbergen J[2], Yoon M[2], Collins S[2], Yuan G[2], Barie PS[3], Eckmann C[4].

Author information

Abstract

BACKGROUND: Increasing antimicrobial resistance among pathogens causing complicated intra-abdominal infections (cIAIs) supports the development of new antimicrobials. Ceftolozane/tazobactam, a novel antimicrobial therapy, is active against multidrug-resistant Pseudomonas aeruginosa and most extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae.

METHODS: ASPECT-cIAI (Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in Complicated Intra-abdominal Infections) was a prospective, randomized, double-blind trial. Hospitalized patients with cIAI received either ceftolozane/tazobactam (1.5 g) plus metronidazole (500 mg) every 8 hours or meropenem (1 g) every 8 hours intravenously for 4-14 days. The prospectively defined objectives were to demonstrate statistical noninferiority in clinical cure rates at the test-of-cure visit (24-32 days from start of therapy) in the microbiological intent-to-treat (primary) and microbiologically evaluable (secondary) populations using a noninferiority margin of 10%. Microbiological outcomes and safety were also evaluated.

RESULTS: Ceftolozane/tazobactam plus metronidazole was noninferior to meropenem in the primary (83.0% [323/389] vs 87.3% [364/417]; weighted difference, -4.2%; 95% confidence interval [CI], -8.91 to .54) and secondary (94.2% [259/275] vs 94.7% [304/321]; weighted difference, -1.0%; 95% CI, -4.52 to 2.59) endpoints, meeting the prespecified noninferiority margin. In patients with ESBL-producing Enterobacteriaceae, clinical cure rates were 95.8% (23/24) and 88.5% (23/26) in the ceftolozane/tazobactam plus metronidazole and meropenem groups, respectively, and 100% (13/13) and 72.7% (8/11) in patients with CTX-M-14/15 ESBLs. The frequency of adverse events (AEs) was similar in both treatment groups (44.0% vs 42.7%); the most common AEs in either group were nausea and diarrhea.

CONCLUSIONS: Treatment with ceftolozane/tazobactam plus metronidazole was noninferior to meropenem in adult patients with cIAI, including infections caused by multidrug-resistant pathogens.

Seftolozan-tazobaktam

FDA Onayı;

- **Komplike intra-abdominal infeksiyonlarda:**
- Çok uluslu, çift kör, 979 hasta,
- **Seftolozan/tazobaktam** 1 g/0.5 g IV, her 8 saatte + **metronidazole** (500 mg IV, her 8 saatte)
- **Meropenem** (1 g IV, her 8 saatte) 4 ila 14 gün,
- Seftolozan+tazobaktam ve metronidazole, Meropenem , **klinik iyileşme ve bakteriyel eradikasyon**
- 83% and 87.3%,

Lancet. 2015 May 16;385(9981):1949-56. doi: 10.1016/S0140-6736(14)62220-0. Epub 2015 Apr 27.

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

Wagenlehner FM[1], Umeh O[2], Steenbergen J[2], Yuan G[2], Darouiche RO[3].

Author information

Abstract

BACKGROUND: Treatment of complicated urinary-tract infections is challenging due to rising antimicrobial resistance. We assessed the efficacy and safety of ceftolozane-tazobactam, a novel antibacterial with Gram-negative activity, in the treatment of patients with complicated lower-urinary-tract infections or pyelonephritis.

METHODS: ASPECT-cUTI was a randomised, double-blind, double-dummy, non-inferiority trial done in 209 centres in 25 countries. Between July, 2011, and September, 2013, hospital inpatients aged 18 years or older who had pyuria and a diagnosis of a complicated lower-urinary-tract infection or pyelonephritis were randomly assigned in a 1:1 ratio to receive intravenous 1·5 g ceftolozane-tazobactam every 8 h or intravenous high-dose (750 mg) levofloxacin once daily for 7 days. The randomisation schedule was computer generated in blocks of four and stratified by study site. The next allocation was obtained by the study site pharmacist via an interactive voice-response system. The primary endpoint was a composite of microbiological eradication and clinical cure 5-9 days after treatment in the microbiological modified intention-to-treat (MITT) population, with a non-inferiority margin of 10%. This study is registered with ClinicalTrials.gov, numbers NCT01345929 and NCT01345955.

FINDINGS: Of 1083 patients enrolled, 800 (73·9%), of whom 656 (82·0%) had pyelonephritis, were included in the microbiological MITT population. Ceftolozane-tazobactam was non-inferior to levofloxacin for composite cure (306 [76·9%] of 398 vs 275 [68·4%] of 402, 95% CI 2·3-14·6) and, as the lower bound of the two-sided 95% CI around the treatment difference was positive and greater than zero, superiority was indicated. Adverse event profiles were similar in the two treatment groups and were mainly non-serious.

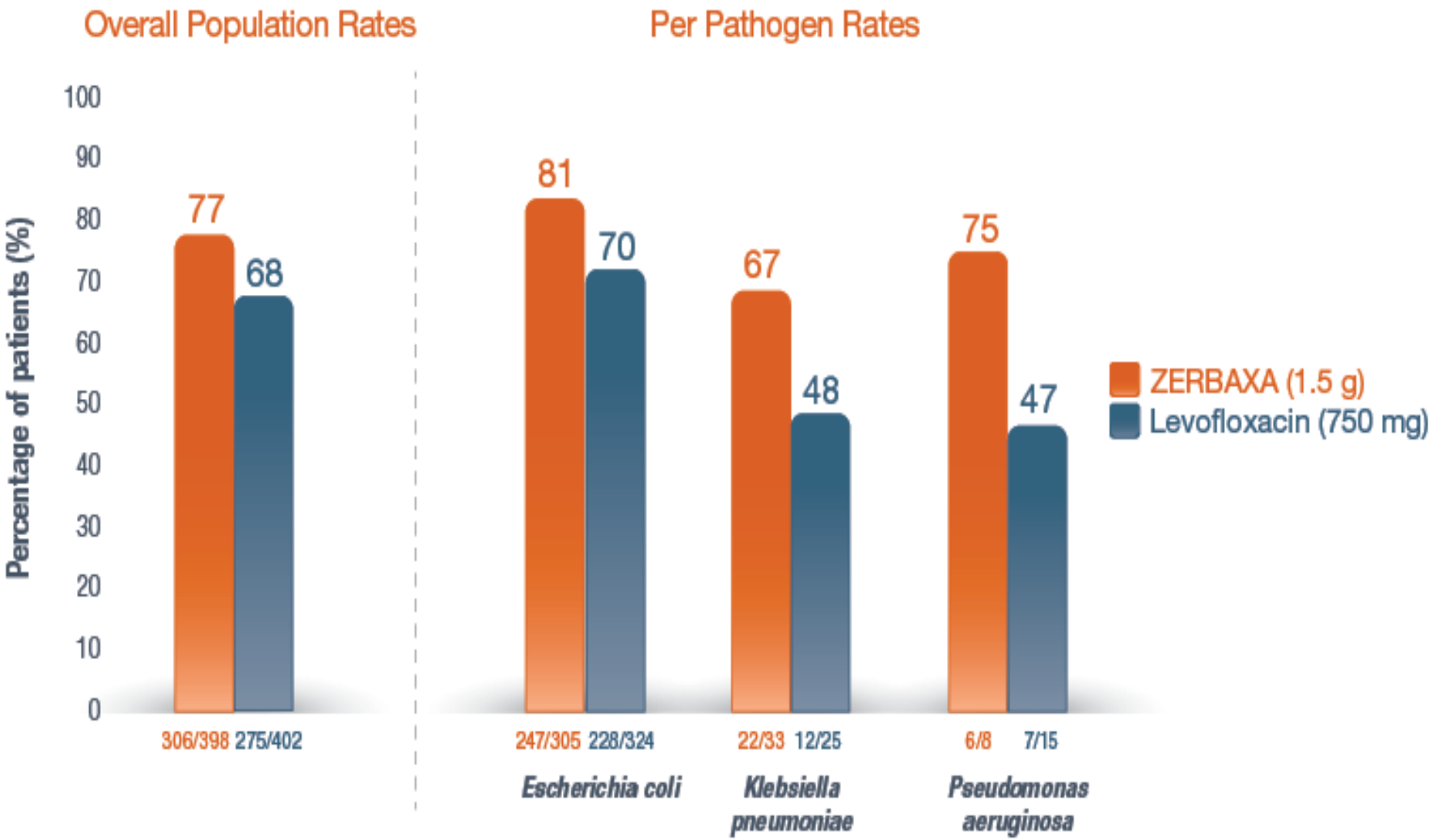
INTERPRETATION: Treatment with ceftolozane-tazobactam led to better responses than high-dose levofloxacin in patients with complicated lower-urinary-tract infections or pyelonephritis.

FUNDING: Cubist Pharmaceuticals.

Seftolozan-tazobaktam

- **Komplike Üriner Sistem İnfeksiyonu:**
- Çok uluslu, çift kör, **1,068** hasta, komplike üriner sistem infeksiyonu (piyelonefrit) hastanede yatan
- Seftolozan/tazobactam 1 g/0.5 gr, IV, 8 saatte bir (3x1)
- Levofloksasin (750 mg IV, günde 1 kez) 7 gün,
- Klinik semptomlar, mikrobiolojik eradikasyon,

Seftolozan-tazobaktam



Seftolozan-tazobaktam

- Komplike Üriner Sistem İnfeksiyonları, Pyelonephritis dahil
- Gram-negatif;
- *Escherichia coli,*
- *Klebsiella pneumoniae,*
- *Proteus mirabilis ve*
- *Pseudomonas aeruginosa*

Meropenem - Vaborbaktam

(Vabomere)

- **Meropenem**, 1996 FDA,
- Pnömoni, bakteriyemi, osteomiyelit, üriner sistem infeksiyonu ve menenjit,
- **Vaborbaktam**, yeni beta-laktamaz inh.
- Antimikrobiyal aktivitesi yok, kombinasyonda
- Avibaktam, aynı tazobaktam gibi, beta laktamazı inh eder.

Meropenem - Vaborbaktam

- **Komplike üriner sistem infeksiyonları, (piyelonefrit)**
- *Escherichia coli, Klebsiella pneumoniae, and Enterobacter cloacae*
- ABD' de ruhsat dışı olarak da kullanılıyor,
- **İlk** Karbapenem–Beta laktamaz inh. komb.
- IV, 4 gram (meropenem 2 gram, vaborbaktam 2 gram), 3x1, infuzyon 3 h, 14 gün
- Doz ayarlaması gerekir, renal yetmezlik

Meropenem - Vaborbaktam

- **Meropenem**, bakterisidal, PBP’ lere bağlanarak hücre duvar sentezi inh.
- **Vaborbaktam**, beta laktamaz ve karbapenemaz üreten bakterilere karşı, Meropenem’ i koruyan beta-laktamaz inh.
- En iyi etki, Meropenem ile kombinasyonda,
- Çok aktif bir beta-laktamaz inh.

Meropenem - Vaborbaktam

- Qualified infectious disease product (ayrıcalıklı infeksiyon hastalıkları ürünleri)
- FDA, fast track
- FDA, gereğinden fazla kullanılmamalı meropenem-vaborbactam,
- Başka duyarlı antibiyotik varsa onlar kulanılmalı,
- En son silah olarak bırakılmalı,

Meropenem - Vaborbaktam

- Etkinlik ve güvenliği, TANGO-1 çalışmasından sonra, FDA tarafından onaylandı

- Piperasilin-Tazobaktam ile karşılaştırıldı,
- İdrar kültürü karşılaştırılması
- Bakteriyel eradikasyon

Meropenem-Vaborbactam Phase 3 Clinical Program

TANGO

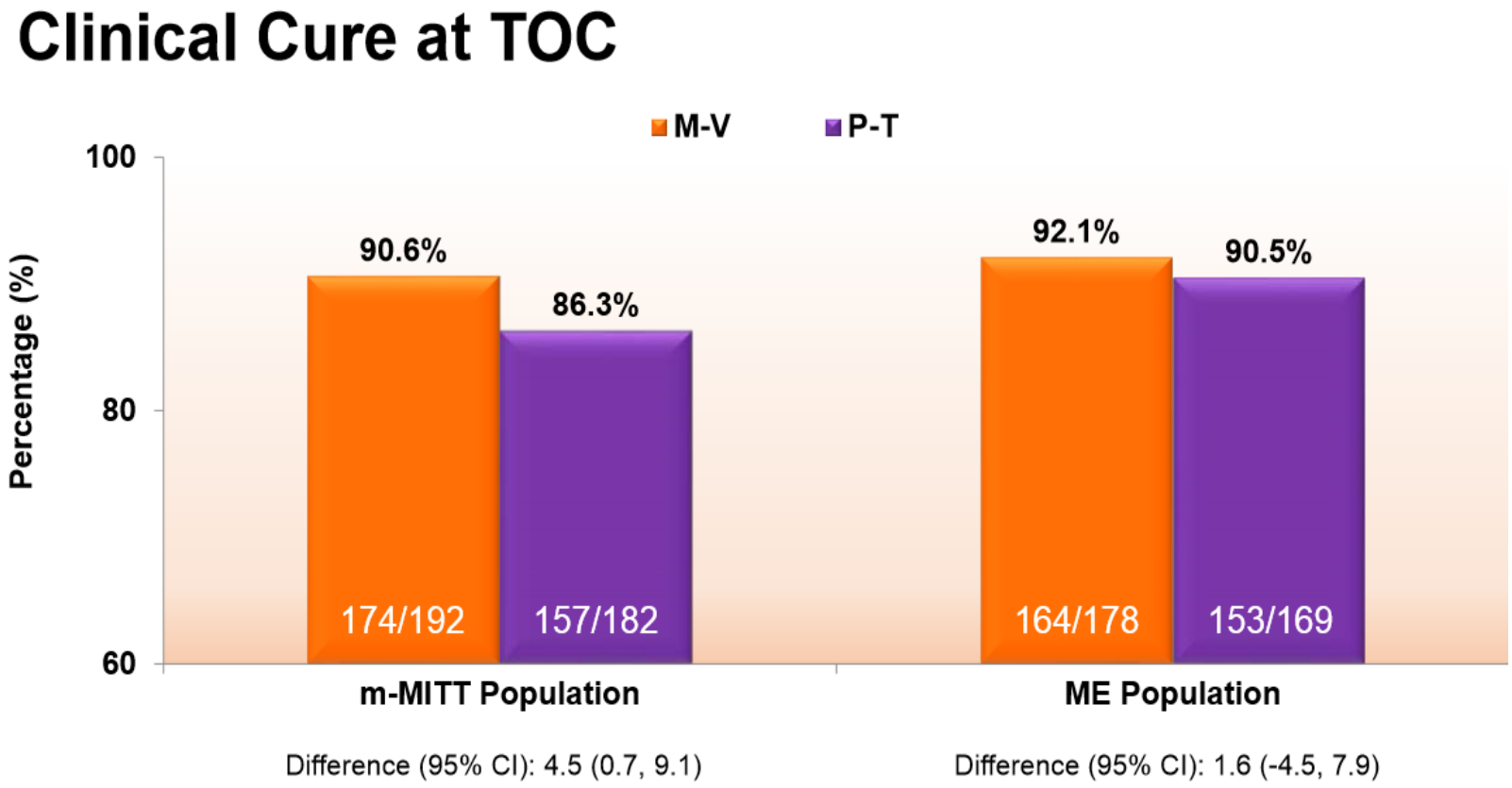
Targeting Antibiotic Non-susceptible Gram-negative Organisms

	TANGO I	TANGO II
Features	*Site/Indication Focus*	*Pathogen-Focused*
Patients	Complicated UTI/AP (n=550)	cUTI/AP, cIAI, HABP, VABP and/or bacteremia known or suspected to be due to CRE
Design	Randomized 1:1 Double-blind	Randomized 2:1 Open-label
Comparator	Piperacillin-tazobactam	"Best available therapy"
Status	*Completed* (this presentation)	*Ongoing*

Meropenem - Vaborbaktam

- FDA onayı; 550 hasta
- Meropenem 2g - vaborbactam 2g, 3 saat IV inf. Her 8 saatte bir,
- Piperasillin 4g - tazobaktam 500mg, 30 dk IV inf. Her 8 saatte bir,
- 10 gün tedavi verildi
- Kültürde < 10^4 CFU/ml,

Meropenem - Vaborbaktam



Delafloksasin (Baxdela)

- 2017 FDA,
- Akut Bakteriyel Deri İnfeksiyonlarında,
- Florokinolon,
- Avantaj; Gr (+)’ ler MRSA dahil, Gr (-), Anaerob’lar
- Yan etki profili düşük,
- IV ve oral

Delafloksasin

- Gram-pozitifler:
- *Staphylococcus aureus* ([MRSA] ve [MSSA] dahil), *Staph. haemolyticus, Staph. lugdunensis,*
- *Streptococcus agalactiae, Streptococcus anginosus* Grup (*Streptococcus anginosus, Streptococcus intermedius*, and *Streptococcus constellatus dahil*), *Streptococcus pyogenes*,
- *Enterococcus faecalis*

Delafloksasin

- Gram-negatifler:
- *Escherichia coli,*
- *Enterobacter cloacae,*
- *Klebsiella pneumoniae*,
- *Pseudomonas aeruginosa*
- Anaerop bakteriler
  (*Bacteroides* sp, *Prevotella* sp, *Clostridium difficile*, *Clostridium perfringens*),
- Hücre içi patojenler
- (*Mycoplasma* sp, *Ureaplasma* sp, *Chlamydia* sp)
- *M. tuberculosis*

Delafloksasin

- Delafloksasin, oral ve IV
- IV olarak 300 mg, 60 dk, her 12 saatte bir
- Oral olarak 450-mg her 12 saatte bir,

- 5 - 14 gün tedavi süresi
- GFR’ ye göre doz ayarlaması gerekir

J Antimicrob Chemother. 2017 Dec 1;72(12):3471-3480. doi: 10.1093/jac/dkx329.

Efficacy and safety of delafloxacin compared with vancomycin plus aztreonam for acute bacterial skin and skin structure infections: a Phase 3, double-blind, randomized study.

Pullman J[1], Gardovskis J[2], Farley B[3], Sun E[4], Quintas M[4], Lawrence L[4], Ling R[5], Cammarata S[4]; PROCEED Study Group.

Author information

Abstract

BACKGROUND: Delafloxacin is an investigational anionic fluoroquinolone in development for oral or intravenous administration for the treatment of infections caused by Gram-positive (including MRSA), Gram-negative, atypical and anaerobic organisms.

OBJECTIVES: To establish the non-inferiority of delafloxacin compared with vancomycin plus aztreonam for the treatment of acute bacterial skin and skin structure infections and to compare the safety of the two antimicrobials.

PATIENTS AND METHODS: A Phase 3, multicentre, randomized, double-blind, active-controlled study with 660 patients compared delafloxacin 300 mg or vancomycin 15 mg/kg plus aztreonam 2 g each administered twice daily intravenously for 5-14 days. Non-inferiority was evaluated by objective response (≥20% erythema reduction) at 48-72 h after initiation of study drug, investigator subjective assessment of outcome and microbiological responses. Clinical Trials Registration: NCT01811732. EudraCT number: 2012-001767-71.

RESULTS: In the ITT analysis set, the objective response was 78.2% in the delafloxacin arm and 80.9% in the vancomycin/aztreonam arm (mean treatment difference, -2.6%; 95% CI, -8.78% to 3.57%). Investigator-assessed cure was similar between the two groups at follow-up (52.0% versus 50.5%) and late follow-up (70.4% versus 66.6%). Bacterial eradication of MRSA was 100% and 98.5% in the delafloxacin group and the vancomycin/aztreonam group, respectively. Frequency of treatment-emergent adverse events in the delafloxacin and vancomycin/aztreonam groups was similar. Treatment-emergent adverse events leading to study drug discontinuation were higher in the vancomycin/aztreonam group compared with the delafloxacin group (4.3% versus 0.9%).

CONCLUSIONS: Delafloxacin, an anionic fluoroquinolone, was statistically non-inferior to vancomycin/aztreonam at 48-72 h following the start of therapy and was well tolerated as monotherapy in the treatment of acute bacterial skin and skin structure infections.

PMID: 29029278 DOI: 10.1093/jac/dkx329

Delafloksasin
FDA Onayı

- **1,510** hasta, **DYDİ**, randomize, çok uluslu,

- **1**. Çalışma; **Delafloksasin** 300 mg, **IV**, 12 h
- **2**. Çalışma; Delafloksasin 300 mg, **IV**, 12 h, 6 doz, devam Delafloksasin 450 mg, **oral**, her 12 h,
- Her 2 çalışmada da, karşıt tedavi, IV, **vancomycin** 15 mg/kg ve **aztreonam**.

- Erken klinik yanıt, 48-72 saat benzer

Delafloksasin

Yan Etki Profili

	BAXDELA N=741	Vancomycin + aztreonam N=751
Nausea	8%	6%
Diarrhea	8%	3%
Headache[a]	3%	6%
Transaminase elevations[b]	3%	4%
Vomiting	2%	2%

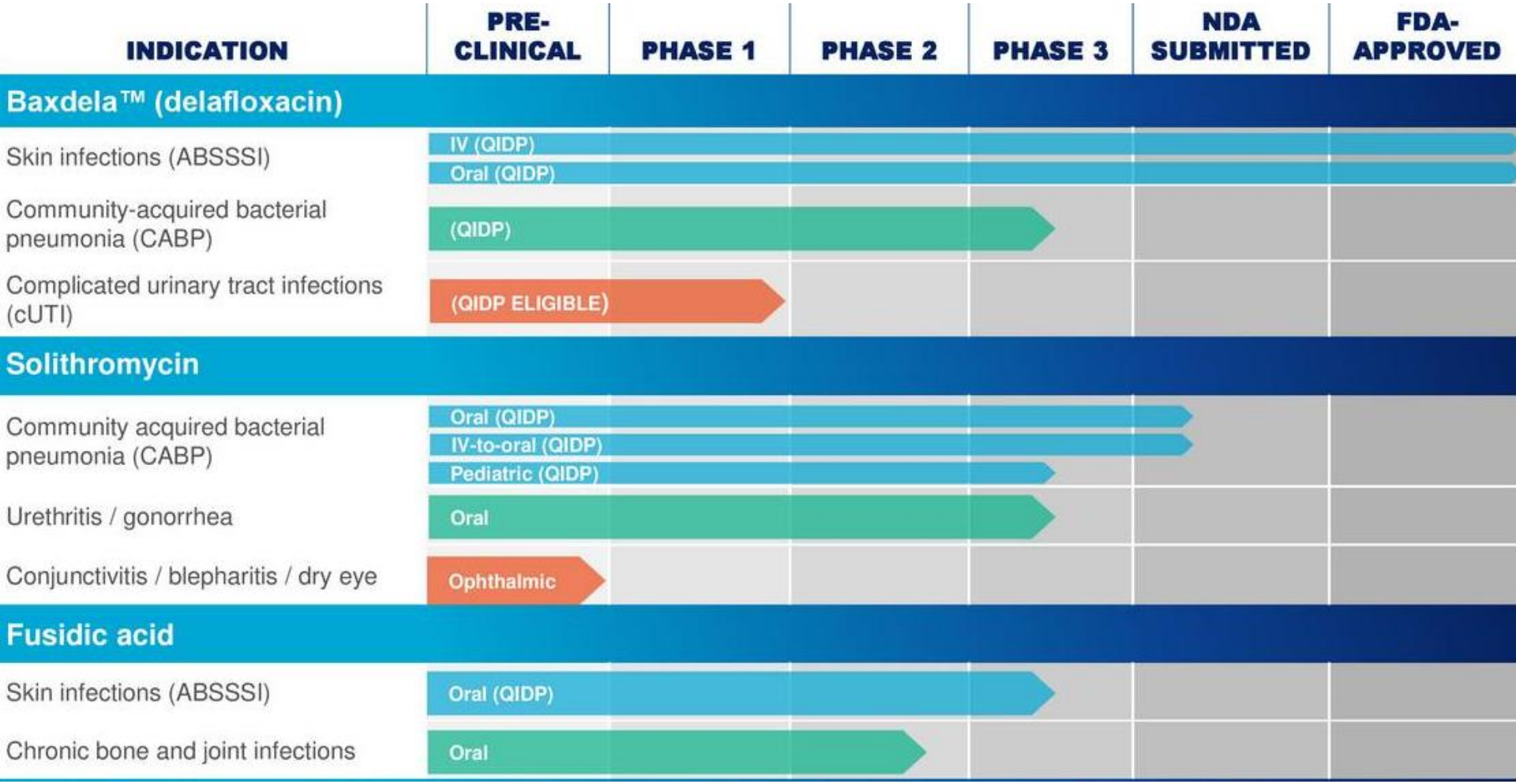
QT aralığında uzama ve aritmiye yok açma yok, Moksifloksasin' e göre avantajı

Diğer kinolonlarla kıyaslandığında fotosensitivite de görülmemiş

Delafloksasin
Potansiyel Tedavi İndikasyonları

- Pnömoni,
- Üriner sistem infeksiyonları,
- Kemik ve eklem infeksiyonları,
- Stafilokoklara bağlı bakteriyemide oral tedavi,
- Cinsel yolla bulaşan hastalıklar

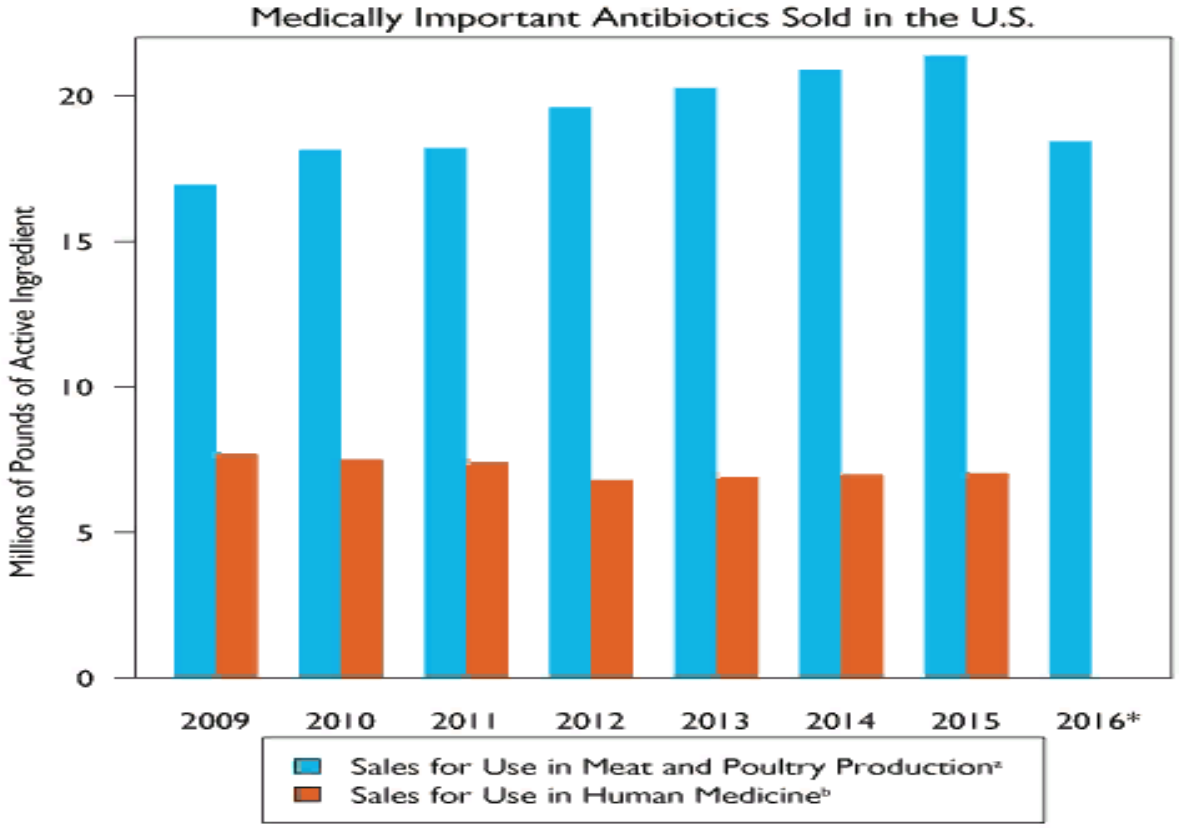
Delafloksasin



Delafloksasin

		Leading Branded Antibiotics				Leading Generic Antibiotics			
	Baxdela (delafloxacin)	Teflaro (ceftaroline)	Sivextro (tedizolid)	Dalvance (dalbavancin)	Orbactiv (oritavancin)	Daptomycin	Linezolid	Vancomycin	Other Quinolones
Broad Spectrum Incl. MRSA and/or Gram Neg	★ ✓	✓	✗	✗	✗	✗	✗	✗	★ ✗
IV and Oral	✓	✗	✓	✗	✗	✗	✓	✗	✓
Fixed Dose	✓	✓	✓	✓	✓	✗	✓	✗	✓
Limited Drug Interaction	✓	✓	✗	✓	✗	✗	✗	✗	✗

Hayvancılıkta Antibiyotik Kullanımı, ABD



- Yıllardan sonra ilk defa, hayvancılık alanında antibiyotik satışı azaldı.
- 2015’ den 2016’ ya %14 oranında düştü.

Teşekkür Ederim

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