New Antibiotics: Are They Really New?

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Antibiotics

The First:
Penicillin was discovered by Alexander Fleming in 1928

More than 100 compounds have been found since, but no new class has been found since 1987.
History of Antibiotics
Drug Resistant Infections Kill

- An estimated 700,000 people around the world die annually from drug-resistant infections.
- If the situation does not change, it is estimated that such infections will kill 10 million people per year by 2050.
In the United States…

at least 2 million patients a year acquire serious resistant infections.

https://www.cdc.gov/drugresistance/index.html
In the United States…

at least 23,000 people die each year as a direct result of these infections.

https://www.cdc.gov/drugresistance/index.html
As a result of our increased use of antibacterials and antibiotics, strains of bacteria have evolved and gotten stronger. We call them superbugs – bacteria that are resistant to common antibiotics and are very hard to treat.

Superbugs, including CRE bacteria, Clostridium difficile and MRSA, are now one of the biggest health concerns of the 21st century.
A Serious Threat!

- The World Health Organization has classified antimicrobial resistance as a “serious threat” to every region of the world which “has the potential to affect anyone, of any age, in any country.”
These gram-negative bacteria elude the mechanisms of antimicrobial agents and some are resistant to most antibiotics in current use.

Of biggest concern are the following:

- *Enterococcus faecium*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Enterobacter*
How are *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* evolving in your institution?

More than 70% of all defined Gram-negative pathogens that caused nosocomial infections were accounted for by the 3 most common Gram-negative pathogens in 2010.
• Analysis of 81,139 pathogens reported from 69,475 healthcare-associated infections in the US during 2009-2010.
According to the Centers for Disease Control and Prevention:

- 19% of healthcare-associated ESBL infections are caused by extended-spectrum beta-lactamase producing *E.Coli* and *Klebsiella spp*

According to the CDC’s National Healthcare Safety Network:

- Approximately 23% of healthcare-associated infections caused by *P.aeruginosa* are resistant to 1 or more carbapenems
ESBL??

- Large family of Gram-negative bacteria that includes many of the more familiar pathogens such as:
  - Salmonella, Escherichia coli, Yersinia pestis, Klebsiella and Shigella, Proteus, Enterobacter, Serratia, and Citrobacter.
- Several are present in the human intestinal tract (normal part of the gut flora).
- Facultative anaerobes. Most also reduce nitrate to nitrite.
- Many have multiple flagella (however, a few species are nonmotile).
- Non-spore forming.
- Variable catalase reactions among the species.
- Some strains produce highly toxic endotoxins

The drug discovery pipeline has been stalled!
Why?

- A spike in drug approvals in the mid-1990s was not the result of any improvement in productivity but due to the FDA clearing a backlog of applications after the introduction of a new system under which companies paid "user fees" to help speed the process.

- Despite pouring billions into research -- more than $65 billion last year in the U.S. alone -- the number of new drugs launched annually has fallen 44% since 1997.

http://www.reuters.com/article/us-bigpharma-specialreport-idUSTRE65F25Q20100616
Why?

- Big Pharma doesn't have nearly enough new drugs in the pipeline to replace all those it is about to lose due to patent expiration.
- Since 1950 a total of 1,256 new drugs have been approved by the U.S. Food and Drug Administration (FDA).
- But the industry today produces roughly the same number of new medicines that it did 60 years ago.

http://www.reuters.com/article/us-bigpharma-specialreport-idUSTRE65F25Q20100616
Why So Few New Antibiotics?

There are issues…

- Antimicrobial resistance problems through the imprudent use of antibiotics over the years.
- Antibiotics are generally used for the short-term, not like the long-term therapies that help bring in revenues for companies.
- Regulatory burden for completely new classes of drugs - trials are so high in cost and society is not willing to pay the high price for antibiotics.

A Glimpse Into Future
Komodo dragon blood may lead to new antibiotics

Each year, more than 23,000 people in the United States die as a result of infections that are resistant to current antibiotics, highlighting the desperate need to develop new antimicrobial medications.
A new study reveals how the blood of the Komodo dragon could help to achieve this goal.

http://www.medicalnewstoday.com/articles/316929.php
Komodo dragon blood may lead to new antibiotics

- The Komodo dragon is a lizard that can be found on five islands in Indonesia: Komodo, Rinca, Flores, Gili Motang, and Padar.
- It is the world's largest living species of lizard, capable of growing up to 10 feet in length. However, that is not the only characteristic that makes it unique. According to van Hoek and team, the reptile rarely becomes ill, despite eating decaying flesh and possessing saliva that is rich in harmful bacteria.
- The researchers say that this is due to a peptide found in their blood called VK25, which they isolated from a Komodo dragon residing at the St. Augustine Alligator Farm Zoological Park in Florida.

http://www.medicalnewstoday.com/articles/316929.php
Komodo dragon blood may lead to new antibiotics

- On closely analyzing this peptide, the team found that it possessed mild antimicrobial properties and had the ability to prevent biofilms, which are microorganisms that stick together in order to thrive and protect themselves. These are often found in wounds.

- The researchers rearranged two amino acids present in VK25 with the aim of making it more effective. This led to the development of a new, synthetic version of the peptide, which they named DRGN-1.

- "The synthesized peptide DRGN-1 is not a Komodo dragon's natural peptide; it's been altered to be stronger in terms of both potency and stability," notes van Hoek.

http://www.medicalnewstoday.com/articles/316929.php
Komodo dragon blood may lead to new antibiotics

Next, the team tested DRGN-1 on mice with wounds that were infected with two strains of antibiotic-resistant bacteria: *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

The synthetic peptide attacked and destroyed the biofilm of the wounds, before killing the two bacterial strains. This led to a faster wound-healing process.

The researchers now plan to test the potential of DRGN-1 as a topical, wound-healing product for animals, but they are hopeful that the peptide could lead to new antibiotics for human use.

http://www.medicalnewstoday.com/articles/316929.php
The Future?

Synthetic Germ-Fighter Peptides

• "Synthetic germ-fighter peptides are a new approach to potentially defeat bacteria that have grown resistant to conventional antibiotics. The antimicrobial peptides we're tapping into represent millions of years of evolution in protecting immune systems from dangerous infections."

Monique van Hoek

http://www.medicalnewstoday.com/articles/316929.php
Soil Rich in Promise...

- Scientists have always believed that the soil was teeming with new and potent antibiotics because bacteria have developed novel ways to fight off other microbes.

http://www.telegraph.co.uk/science/2016/03/14/first-new-antibiotic-in-30-years-discovered-in-major-breakthrough/
However…99% of the microbes will not grow in laboratory conditions

- A team from Northeastern University in Boston, Massachusetts, have discovered a way of using an electronic chip to grow microbes in the soil and then isolate their antibiotic chemical compounds.

http://www.telegraph.co.uk/science/2016/03/14/first-new-antibiotic-in-30-years-discovered-in-major-breakthrough/
First New Antibiotic in 30 years Discovered in Major Breakthrough…

- The discovery of teixobactin could pave the way for a new generation of antibiotics because of the way it was discovered.

- Teixobactin has been found to treat many common bacterial infections such as tuberculosis, septicaemia and C.diff, and could be available within 5 years.

http://www.telegraph.co.uk/science/2016/03/14/first-new-antibiotic-in-30-years-discovered-in-major-breakthrough/
A new drug to combat MRSA is buried inside human noses! A close relative of MRSA that lives in nasal passages and produces a chemical weapon against its kin.

*Staphylococcus lugdunensis* – eradicated MRSA by producing a compound the researchers dubbed lugdunin (lug-done-in)

In one experiment, mice with MRSA skin infections recovered quickly after treatment with topical lugdunin ointments.

http://www.pbs.org/newshour/rundown/new-antibiotic-deadly-mrsa-infections-found-right-noses/
Right Under Our Noses… May Already be Working in Humans

- 187 hospitalized patients examined:
  - *S. aureus* and *S. lugdunensis* rarely hang out in the same nose.
  - *S. aureus* was present in only 5.9% of individuals who also carried *S. lugdunensis*, compared with 34.7% in people without *S. lugdunensis*.

- Given that *S. lugdunensis* is present in only around 10% of the population and *S. aureus* is found in about 30% of the population, there are probably more antibiotics yet to be discovered that are responsible for *S. aureus* colonization resistance.

http://www.pbs.org/newshour/rundown/new-antibiotic-deadly-mrsa-infections-found-right-noses/
What’s New?
Launched in 2010 by the Infectious Disease Society of America

Nine New Antibiotics have been approved

- The 21st Century Cures Act, enacted in 2016 created a new FDA approval pathway for antibiotics and antifungals that treat critical or life-threatening infections in patients with unmet medical needs.

- In February 2017, WHO released its first-ever list of antibiotic resistant “priority pathogens”.
WHO Priority 1: CRITICAL #

*Acinetobacter baumannii*, carbapenem-resistant

*Pseudomonas aeruginosa*, carbapenem-resistant

*Enterbacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

# Mycobacteria (including *Mycobacterium tuberculosis*) was subjected to review for inclusion in this prioritization exercise as it is already a globally established priority for which innovative new treatments are urgently needed.

WHO Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant
Staphylococci aureus, methicillin-resistant, vancomycin intermediate and resistant
Helicobacter pylori, clarithromycin-resistant
Campylobacter, fluoroquinolone-resistant
Salmonella spp., fluoroquinolone-resistant
Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant
WHO Priority 3: MEDIUM

*Streptococcus pneumoniae*, penicillin-non-susceptible

*Haemophilus influenzae*, ampicillin-resistant

*Shigella* spp, fluoroquinolone-resistant
Antibiotics Approved Since 2010

- Ceftaroline fosamil (Teflaro)
- Fidaxomycin (Dificid)
- Bedaquiline (Sirturo)
- Dalbavancin (Dalvance)
- Oritavancin (Orbactiv)
- Tedizolid (Sivextro)
- Ceftolozane/tazobactam (Zerbaxa)
- Ceftazidime/avibactam (Avycaz)
- Delafloxacin (Baxdela)
Ceftaroline (Teflaro)

- **Date approved by the FDA:** 2010
- **What is it:** 5th generation cephalosporin
- **For:**
  - Community-Acquired Bacterial Pneumonia - 600 mg IV q12hr; infuse over 5-60 minutes for 5-7 days
  - Skin & Skin Structure Infections - Indicated for acute bacterial skin and skin structure infections, including MRSA. 600 mg IV q12hr; infuse over 5-60 minutes for 5-14 days
- **Microbiology:** Teflaro is a sterile, semi-synthetic, prodrug antibacterial drug of the cephalosporin class of beta-lactams (β-lactams).
- **Manufactured by:** Allergan
- **Routes:** IV
Ceftaroline (Teflaro)

- **Pro:** Good adjuvant for MRSA high grade infection (bacteremia, endocarditis, bone) – add it to vancomycin until blood clears then – stop and continue vancomycin.
- **Con:** No Pseudomonas coverage
- **Cost:** $49 AWP per vial (both 400 and 600 mg.)
Fidaxomicin (Dificid)

- **Date approved by the FDA:** June 7, 2011
- **What is it:** macrolide antibacterial drug
- **For:** indicated in adults (≥ 18 yrs of age) for treatment of *Clostridium difficile* – associated diarrhea (CDAD).
- **Microbiology:** *C difficile*.
- **Manufactured by:** Merck
- **Route:** Oral
- **Dosage:** 200mg BID
- **Note:** Should not be used for systemic infections
Fidaxomicin (Dificid)

Fidaxomicin
200mg BID
Vancomycin
125 mg QID

Comparable initial clinical response rate vs. vancomycin at end of 10-day treatment

Clinical response rate (primary end point)

<table>
<thead>
<tr>
<th>Trial 1</th>
<th>Trial 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>88% n=289</td>
<td>88% n=253</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>2.6% (2.9%, 8.0%)</td>
<td>1.0% (-4.8%, 6.8%)</td>
</tr>
</tbody>
</table>

*CI was derived using the Wilson score method.
Fidaxomicin (Dificid)

- **Pro:** Less relapse than after vancomycin.
- **Con:** $220.85 AWP per 200 mg. tab @ 1 tab bid = $4,417 for 10 days.
Bedaquiline (Sirturo)

- **Date approved by the FDA:** December 2012
- **What is it:** a diarylquinoline antimycobacterial a First-in-Class ATP Synthase Inhibitor
- **For:** for Pulmonary Multi-drug Resistant TB (MDR-TB) in combination therapy.
- **Microbiology:** pulmonary MDR-TB.
- **Manufactured by:** Janssen
- **Routes:** oral (with food) by directly observed therapy (DOT) with other agents.
Bedaquiline (Sirturo)

- **Pro:** Increased armamentarium of drugs for MDR-TB
- **Con:** The cost of drug
- **Cost:** $191.49 AWP per 100 mg tab
- **Dose:**
  - Weeks 1–2: **400 mg once daily.**
  - Weeks 3–24: **200 mg 3 times per week** (with at least 48 hours between doses).
  - The total duration of treatment is 24 weeks
Dalbavancin (Dalvance)

- **Approved by the FDA:** May 23, 2014
- **Phase II -additional studies:** for osteomyelitis
- **What: is it:** long-acting lipo-glycopeptide antibiotic
- **For:** Phase II for adult osteomyelitis. Approved for acute bacterial skin and skin structure infections
- **Microbiology:** gram-positive bacterial infections, including methicillin-resistant *Staphylococcus aureus*
- **Manufactured by:** Alergan
- **Routes:** Intravenous therapy
- **Dosing:** Two dose, once-weekly regimen eliminates need for prolonged IV access and optimizes medication adherence for infections requiring treatment duration for 4-6 weeks
Dalbavancin (Dalvance)

- **Pro**: Ease of administration. Good MRSA drug
- **Con**: cost
- **Cost**: $1841.64 per 500 mg vial = $5524.92 (1500mg)
- **Dose**: administered as a 30-minute IV infusion of one 1500 mg dose = full course of therapy,
Oritavancin (Orbactive)

- **Date approved by the FDA:** 2014
- **What is it:** Glycopeptide
- **For:** is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSIs)
- **Microbiology:** Susceptible isolates of gram-positive microorganisms
  - *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant *S. aureus* [MRSA] isolates)
  - *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus group* (includes *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*)
  - *Enterococcus faecalis* (vancomycin-susceptible isolates only)
- **Manufactured by:** The Medicines Company
- **Trade name:** Orbactiv
- **Routes:** injection, a single 1200-mg dose administered IV over 3 hr. Lyophilized powder for reconstitution - 400mg per 50 mL vial supplied in a package of 3 vials for a 1200mg dose
Oritavancin (Orbactive)

- **Pro**: Ease of administration
- **Con**: Not for Enterococcus faecium.
- **Cost**: $1,160.00 per 400 mg vial $ \times 3 = $3,480
- **Dose**: IV, lyophilized powder for reconstitution—a single 1200-mg dose over 3 hr.
**Tedizolid phosphate (Sivextro)**

- **Date approved by the FDA:** June 20, 2014
- **What is it:** oxazolidinone-class antibacterial
- **For:** treatment of adults with acute bacterial skin and skin structure infections (ABSSI) caused by
  - **Microbiology:** *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus Group* (including *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), and *Enterococcus faecalis*.
- **Manufactured by:** Merck
- **Routes:** Oral
  - 200 mg tablet, 6 days, once daily.
Tedizolid phosphate (Sivextro)

- **Pro:** “once a day Linezolid”.
- **Con:** “Me Too” drug.
- **Cost:** $319.64 – 200 mg vial (one dose)
  $401.27 - 200 mg tablet (one dose)
  $2407.61 for a total course of therapy
  (one tablet daily x 6 days)
ceftolozane – tazobactam (Zerbaxa)

- **Date approved by the FDA**: December 19, 2014 with other indications, September 2015 and January 16, 2016.
- **What is it**: a combination product consisting for a cephalosporin-class antibacterial drug and beta-lactamase inhibitor
- **For**: treatment of adults (over 18yrs.)
  - complicated Intra-abdominal infections in combination with metronidazole.
  - complicated urinary tract infections, including pyelonephritis, caused by the following
- **Microbiology**: Gram-negative microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *proteus mirabilis* and *Pseudomonas aeruginosa*
- **manufactured by**: Merck
- **Routes**: injection adm. Every 8 hrs by IV infusion over 1 hour
  - 1.5 g (ceftolozane 1g and tazobactam 0.5gm). Adjusted doses in patients with impaired renal function
ceftolozane – tazobactam (Zerbaxa)

- **Pro:**
  - Aztreonam – like B-lactamase
  - Active against those bacteria with w/ESBL
  - Cephalosporin/B-lactamase like penicillin/tazobactam

- **Con:** Minimal gram+ coverage

- **Cost:** $120.61 for a 1.5 gm vial (1 dose) = $361.30/day

- **Dose:**
<table>
<thead>
<tr>
<th>Infection</th>
<th>Dose</th>
<th>Frequency</th>
<th>Infusion time</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complicated Urinary Tract Infections, including Pyelonephritis</td>
<td>1.5 g</td>
<td>Every 8 hours</td>
<td>1 hour</td>
<td>7 days</td>
</tr>
<tr>
<td>Complicated Intra-Abdominal Infections*</td>
<td>1.5 g</td>
<td>Every 8 hours</td>
<td>1 hour</td>
<td>4 to 14 days</td>
</tr>
</tbody>
</table>

*Complicated Intra-Abdominal Infections*
Ceftazidime – avibactam (Avycaz)

- **Date approved by the FDA:** Feb 25, 2015
- **What is it:** is a fixed-dose combination drug containing an antibiotic—3rd generation cephalosporin ceftazidime and a novel non-β-lactam β-lactamase inhibitor avibactam.
- **Manufactured by:** Allergan
- **Routes:** IV
Ceftazidime – avibactam (Avycaz)

**For:** Intra-abdominal Infections - indicated in combination with metronidazole for complicated intra-abdominal infections (cIAIs)

**Microbiology:** *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae, Klebsiella oxytoca, Citrobacter freundii complex, and Pseudomonas aeruginosa.*

**For:** Urinary Tract Infections - Indicated for complicated urinary tract infections (cUTIs) including pyelonephritis

**Microbiology:** *Escherichia coli, Klebsiella pneumoniae, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, Citrobacter freundii, Proteus spp., and Pseudomonas aeruginosa*
Ceftazidime – avibactam (Avycaz)

- **Pro:** Covers ESBL.
- **Con:** Noninferior to meropenem in HAP, including VAP.
- **Cost:** $359.10 - 2.5 gm vial (one dose)
- **Dose:**
  - Intra-abdominal infections: 2.5 g (2 g/0.5 g) IV q8hr infused over 2 hr for 5-14 days
  - UTI: 2.5 g (2 g/0.5 g) IV q8hr infused over 2 hr for 7-14 days
Delafloxacin (Baxdela)

- **Approved by the FDA:** June 19, 2017
- **What is it:** meglumine salt delafloxacin meglumine, is a fluoroquinolone antibiotic
- **For:** acute bacterial skin and skin structure infections
- **Microbiology:**
  - **Gram-positive organisms:** *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Staphylococcus haemolyticus*, *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (including *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), *Streptococcus pyogenes*, and *Enterococcus faecalis*;
  - **Gram-negative organisms:** *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.
- **Manufactured by:** Melinta Therapeutics.
- **Routes:** Oral administration, Intravenous therapy
Delafloxacin (Baxdela)

- **Pros:** Covers MRSA and Pseudomonas. Oral option with no renal adjustment.
- **Con:** Black-box warning of all quinolones
- **Cost:** Baxdela – No pricing info available as it has been FDA approved but is not available from the manufacturer
What We Need For Real Progress?

- Not “Look – Alike” drugs
- Less cost
- Better coverage of resistant organisms
just getting started...
- What is Vaborbactem? 
- Meropenem + Vaborbactem 
- QIDP – expedited by FDA 
  - Approved August 29, 2017