Resistance Is (Not) Futile – Confronting the Post-Antibiotic Era

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Objectives

- Describe the scope of the problem of antimicrobial resistance.
- Explain factors that promote antimicrobial resistance.
- Analyze challenges and opportunities related to the development of new antimicrobials.
- Evaluate the clinical role of new antimicrobials, including ceftazidime-avibactam, ceftolozane-tazobactam, dalbavancin, oritavancin, and tedizolid.
- Recognize antimicrobials that are currently in the developmental pipeline.
Antimicrobial resistance - are we doomed?
Antibiotics - miracle drugs...

“For most of the infectious diseases on the wards of Boston City Hospital in 1937, there was nothing that could be done beyond bed rest and good nursing care.

Then came the explosive news of sulfanilamide, and the start of the real revolution in medicine.

I remember the astonishment when the first cases of pneumococcal and streptococcal septicemia were treated with antibiotics in Boston in 1937…it was the opening of a whole new world. We knew that other molecular variations of sulfanilamide were on their way from industry, and had heard about the possibility of penicillin and other antibiotics; we became convinced, overnight, that nothing lay beyond reach for the future.”

“the public will demand [the drug and]…then will begin an era…of abuses. The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save. In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope the evil can be averted.”
The impact of infectious diseases

Antimicrobial development

Antimicrobial development versus resistance

Antimicrobial development versus resistance

The impact of antimicrobial resistance

The impact of antimicrobial resistance
Carbapenem-resistant Enterobacteriaceae (CRE)

Carbapenem-resistant Enterobacteriaceae (CRE)

CRE susceptibility

Notable antimicrobial resistance challenges

**Urgent Threats**

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*
Notable antimicrobial resistance challenges

**Serious Threats**

- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella Typhi*
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

Notable antimicrobial resistance challenges

Concerning Threats

- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*
The drug discovery process

Profitability of antibiotics

http://amr-review.org/sites/default/files/SECURING%20NEW%20DRUGS%20FOR%20FUTURE%20GENERATIONS%20FINAL%20WEB_0.pdf. 
The antibiotic pipeline

High priority
Potential for activity against at least 90% of carbapenemase-producing bacteria in the UK

Medium priority
Targets at least one CDC 'Urgent' threat (Clostridium difficile, carbapenem-resistant Enterobacteriaceae or drug-resistant Neisseria gonorrhoea, but is not classed as a potential breakthrough)

Low priority
Does not meet the criteria for "clinically useful"
What can we do to solve this crisis?
What can we do?

1. **Reduce** the need for antibiotics through improved water, sanitation, and immunization

2. **Improve** hospital infection control and antibiotic stewardship

3. **Change** incentives that encourage antibiotic overuse and misuse to incentives that encourage antibiotic stewardship

4. **Reduce** and eventually phase out subtherapeutic antibiotic use in agriculture

5. **Educate** health professionals, policy makers, and the public on sustainable antibiotic use

6. **Ensure** political commitment to meet the threat of antibiotic resistance

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Antibiotic use in livestock

U.S. Children Getting Majority Of Antibiotics From McDonald’s Meat

WASHINGTON, DC—According to a Department of Health and Human Services report released Monday, McDonald’s meat from antibiotics-injected livestock is now the primary source of antibiotics for U.S. children, particularly for uninsured youths from low-income households.

“Some children still fall through the cracks in our healthcare system, but luckily, McDonald’s is there to lend a helping hand,” the Secretary of Health and Human Services said at a press conference announcing the findings. “So even if a child’s family has no health insurance and can’t afford medicine, virtually anyone can afford a delicious 99-cent Big Mac with pickles, cheese, and [the antibiotic] quinupristin-dalfopristin.”

Children at McDonald’s.
Antibiotic use in livestock - continued

Estimated Annual Antibiotic Use in the United States.
Data are shown as approximate numbers of kilograms of antibiotics used per year.

Antimicrobial-containing commercial products

French’s Introduces Antibacterial Mustard

ROCHESTER, NY—In response to increasing demand for tangier, more hygienic meals, condiment giant French’s has introduced a new antibacterial mustard.

“Each year, 15 million cases of bacterial food poisoning originate in U.S. home kitchens, resulting in nausea, diarrhea, fever, and even death,” read a press release French’s issued Monday. “All-new French’s Antibacterial Mustard is the perfect way to add flavor to, and subtract harmful disease-causing bacteria from, your family’s favorite meals!”

The mustard is orange in color and somewhat medicinal in flavor. In product trials, mothers preferred antibacterial mustard 5 to 1 when told of its sterilizing properties.

The importance of hygiene

A different look at hygiene…

Sanitation

There are 46 countries where less than half the population has access to an improved sanitation facility.
Vaccination (or lack thereof)
Diagnosis

Rapid diagnosis

Antibiotic overuse

“Don’t forget to take a complimentary handful of antibiotics on your way out.”

Stevens M. Don’t forget to take a complimentary handful of antibiotics on your way out. New Yorker. January 12, 1998:34.
Antimicrobial use and resistance

A relationship between antimicrobial use and antimicrobial resistance has been demonstrated.

The figure on the right shows the relationship between outpatient antimicrobial use and the prevalence of penicillin-resistant *Streptococcus pneumoniae*. 

Use of broad-spectrum antimicrobials

Appropriate antimicrobial use

Observations on Spiraling Empiricism: Its Causes, Allure, and Perils, with Particular Reference to Antibiotic Therapy

JEROME H. KIM, M.D., HARRY A. GALLIS, M.D. Durham, North Carolina

**TABLE II**

Fallacies in Antibiotic Therapy

1. Broader is better
2. Failure to respond is failure to cover
3. When in doubt, change drugs, or add another
4. More disease(s), more drugs
5. Sickness requires immediate treatment
6. Response implies diagnosis
7. Bigger disease, bigger drugs
8. Bigger disease, newer drugs
9. Antibiotics are non-toxic

Solving the crisis - new antimicrobial approaches
Antibiotic development initiatives

Bad Bugs Need Drugs

10 x ‘20

Ten new ANTIBIOTICS by 2020

The problem with trials to study antimicrobials

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Design Systematic review of randomised controlled trials.

Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

Study selection: Studies showing the effects of using a parachute during free fall.

Main outcome measure Death or major trauma, defined as an injury severity score > 15.

Results We were unable to identify any randomised controlled trials of parachute intervention.

Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.
A new approach to antimicrobial development?

Do FDA-approved indications make sense?

Standard indication
…indicated for infection X due to [genus or species]

Pathogen-focused indication
…indicated for infections due to [genus or species]

The “anti-indication”
…although safety and efficacy have not been established at other body sites or for other pathogens, it is recognized that consideration of the use of drug X might become necessary for such sites or pathogens in patients with limited treatment options. If such usage is considered, consultation with a physician with experience in the management of infectious diseases is strongly recommended.
## Dalbavancin - Dalvance®

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Actavis - approved May 2014</td>
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<tr>
<td><strong>Class</strong></td>
<td>Lipoglycopeptide</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>Acute bacterial skin and skin structure infections (ABSSSI)</td>
</tr>
</tbody>
</table>
| **Dose**            | 1000 mg IV x 1, followed in one week by 500 mg IV x 1  
|                     | Dose adjustment is required in patients with renal insufficiency |
| **Adverse reactions**| Nausea (5.5%), headache (4.7%), diarrhea (4.4%), rash (2.7%), pruritus (2.1%), “Red Man Syndrome” |
| **Drug interactions**| No major interactions          |
## Oritavancin - Orbactiv®

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<tr>
<td>Manufacturer</td>
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<td>Class</td>
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<tr>
<td>Indications</td>
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</table>
| Dose            | 1200 mg IV x 1  
|                 | No dose adjustment required based on hepatic or renal insufficiency |
| Adverse reactions| Nausea, vomiting, diarrhea, headache (> 3%), “Red Man Syndrome” |
| Drug interactions| Warfarin (increase in serum concentrations of warfarin) |
## Tedizolid phosphate - Sivextro®

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<td><strong>Manufacturer</strong></td>
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<td><strong>Class</strong></td>
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<tr>
<td><strong>Indications</strong></td>
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</tbody>
</table>
| **Dose** | 200 mg PO/IV every 24 hours  
No dose adjustment required based on hepatic or renal insufficiency |
| **Adverse reactions** | Nausea (8%), headache (6%), diarrhea (4%),  
thrombocytopenia (2.3%) |
| **Drug interactions** | Monoamine oxidase inhibitors, serotonergic agents (SSRIs) |
# Ceftolozane-tazobactam - Zerbaxa®

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<tr>
<td><strong>Ceftolozane-tazobactam</strong></td>
<td></td>
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<tr>
<td>Manufacturer</td>
<td>Merck - approved December 2014</td>
</tr>
<tr>
<td>Class</td>
<td>Cephalosporin + beta-lactamase inhibitor</td>
</tr>
<tr>
<td>Indications</td>
<td>Complicated urinary tract infections, including pyelonephritis Complicated intra-abdominal infections (with metronidazole)</td>
</tr>
<tr>
<td>Dose</td>
<td>1.5 gm (1 gm ceftolozane / 0.5 gm tazobactam) IV q8h Dose adjustment is required in patients with renal insufficiency</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>Nausea, diarrhea, headache, fever (&gt; 5%), renal impairment (0.5%)</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>No major interactions</td>
</tr>
</tbody>
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# Ceftazidime-avibactam - Avycaz®

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<thead>
<tr>
<th><strong>Ceftazidime-avibactam</strong></th>
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<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
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<td><strong>Class</strong></td>
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</tbody>
</table>
| **Indications**           | Complicated urinary tract infections, including pyelonephritis  
                           | Complicated intra-abdominal infections (with metronidazole) |
| **Dose**                  | 2.5 gm (2 gm ceftazidime / 0.5 gm avibactam) IV q8h  
                           | Dose adjustment is required in patients with renal insufficiency |
| **Adverse reactions**     | Nausea, vomiting (10%) |
| **Drug interactions**     | Probenecid (may decrease elimination of avibactam) |
## Antimicrobials in the pipeline

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comments</th>
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</table>
| **Plazomicin** - aminoglycoside | Being studied for serious infections due to CRE  
No nephrotoxicity or ototoxicity has been observed |
| **Fusidic acid** - fusidane (protein synthesis inhibitor) | Used widely in Europe to treat MRSA; trials are underway in the US  
Must be used in combination to prevent the emergence of resistance |
| **Solithromycin** - fluoroketolide | Dosing is similar to that of azithromycin  
Trials are underway for community-acquired pneumonia, gonorrhea |
## Antimicrobials in the pipeline - continued

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Delafloxacin</strong></td>
<td>A trial for the treatment of gonorrhea was stopped early because a single dose was not sufficient to treat some patients</td>
</tr>
<tr>
<td><strong>Eravacycline</strong></td>
<td>In September, it was announced that the clinical endpoint in a trial of complicated UTI was not reached</td>
</tr>
<tr>
<td><strong>Meropenem/RPX7009</strong></td>
<td>A study of serious CRE infections (including UTI, pyelonephritis, pneumonia, and bacteremia) is planned</td>
</tr>
</tbody>
</table>
Prospects for the future

“It is time to close the book on infectious diseases, and declare the war against pestilence won.”

“[antibiotic resistance] threatens the achievements of modern medicine. A post-antibiotic era - in which common infections and minor injuries can kill - is a very real possibility for the 21st century.”


Assessment questions
Which of the following statements regarding antimicrobial resistance is true?

A. antimicrobial resistance is widespread, but has little impact on mortality
B. the impact of antimicrobial resistance is greater in North America than in developing nations within Asia and Africa
C. key resistant pathogens, as defined by the CDC, include carbapenem-resistant Enterobacteriaceae and *Clostridium difficile*
D. resistance to an antimicrobial typically develops decades after the introduction of that antimicrobial
E. the large number of innovative antimicrobials nearing FDA approval represents a potential solution to the problem of antimicrobial resistance
Question 2

Which of the following is a factor that promotes antimicrobial resistance?

A. avoidance of antimicrobial use in livestock
B. the use of soaps and other products that do not contain antimicrobials
C. compliance with sanitation protocols in hospitals
D. inappropriate, unregulated antimicrobial use in clinics
E. adherence to childhood vaccination guidelines/schedules
Question 3

Which of the following statements regarding the development of new antimicrobial agents is true?

A. all new antimicrobials that have been approved within the past five years display activity against Gram-negative bacteria and fungi
B. a placebo-controlled superiority trial is the most appropriate study design for an antimicrobial
C. the financial benefit of developing a new antimicrobial is high and thus not a limitation to the development and approval of new agents
D. the use of data from in vitro and animal studies to complement limited clinical data is one approach to facilitate new antimicrobial development
Question 4

Which of the following statements regarding new antimicrobials is true?

A. in comparison to linezolid, tedizolid poses a lower risk of monoamine oxidase inhibition
B. dalbavancin’s short half-life results in an inconvenient dosing schedule
C. ceftolozane/tazobactam displays activity against CRE, whereas ceftazidime/avibactam does not
D. oritavancin is FDA-approved for the treatment of nosocomial pneumonia, complicated UTI, and intra-abdominal infections
Question 5

Which of the following statements regarding new antimicrobials in the developmental pipeline is true?

A. delafloxacin is a fluoroquinolone that has shown conclusive efficacy against infections caused by antimicrobial-resistant *Neisseria gonorrhoeae*
B. solithromycin is a ketolide that is being studied for the treatment of community-acquired pneumonia and gonorrhea
C. plazomicin is a synthetic tetracycline that displays activity against methicillin-resistant *Staphylococcus aureus*
D. fusidic acid will soon be approved by the FDA for the treatment of infections caused by CRE when used as monotherapy
http://www.une.edu/pharmacy/oce/events