Overwhelming Evolution.
Patients, Microbes and the Drug Resistance Problem

Andrew F. Read PhD
Antibiotics

Alexander Fleming

Penicillium mold

Police Const. Albert Alexander (1897-1941)
“Rebecca’s death has changed me, has changed all of us. Once I believed that the dangers that were out there would stay out there. That modern medicine can avert these dangers. I no longer have the confidence in medicine that I did. I believe we have made great advances, that there are cures to be had, but I’ve watched the dismay in the faces of doctors who are supposed to be the best in their field as they told me they didn’t have any more “cures in their bag.”

And I know that it truly is a PRACTICE of medicine, not a finished product.”
Infection with Panresistant *Klebsiella pneumoniae*: A Report of 2 Cases and a Brief Review of the Literature

Azza Elemam, Joseph Rahimian, and William Mandell
Section of Infectious Diseases, Saint Vincent’s Hospital, New York, New York

*Clinical Infectious Diseases* 2009;49:271–4

It is a rarity for a physician in the developed world to have a patient die of an overwhelming infection for which there are no therapeutic options. These cases were the first instance in our clinical experience in which we had no effective treatment to offer. Trends in urban hospitals are often the harbinger of the future. We share these cases to highlight some troubling issues that soon may be relevant to increasing numbers of physicians and patients across the United States.
The World Wakes Up to the Danger of Superbugs

By THE EDITORIAL BOARD

Tuberculosis. Malaria. Syphilis. Gonorrhea. The microbes that cause these diseases are increasingly resistant, and sometimes even impervious, to antibiotics that worked in the past. Last week, amid other pressing business, 193 nations at the United Nations General Assembly signed a declaration summoning each of them to a war against a powerful and resourceful enemy: superbugs that have learned to evade science’s last remaining defenses.
kakapo
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Evolution in Action 2. Malaria drugs

WHO (2006): Drugs eventually undermined by pathogen evolution
Requires open-ended drug discovery pipeline

Hyde 2005, Read and Huijben 2009
Evolution in Action 3. A US hospital

Daptomycin and Vancomycin-Resistant *Enterococcus* (VRE)
Blood stream VRE: daptomycin resistance
How serious is the problem?

CDC estimate:
23,000 Americans die each year from resistant infections
State health departments that count deaths due to the seven most prevalent infections

<table>
<thead>
<tr>
<th>Infection</th>
<th>Number of States Counting Deaths</th>
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</thead>
<tbody>
<tr>
<td>VRE (Vancomycin-resistant Enterococci)</td>
<td>1</td>
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<tr>
<td>Acinetobacter</td>
<td>2</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>3</td>
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<tr>
<td>MRSA (Methicillin-resistant Staphylococcus aureus)</td>
<td>4</td>
</tr>
<tr>
<td>CRE (Carbapenem-resistant Enterobacteriaceae)</td>
<td>6</td>
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<tr>
<td>VISA (Vancomycin intermediate Staphylococcus aureus)</td>
<td>10</td>
</tr>
<tr>
<td>VRSA (Vancomycin-resistant Staphylococcus aureus)</td>
<td>15</td>
</tr>
<tr>
<td>Outbreaks</td>
<td>20</td>
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</table>

* 48 states and Washington, D.C.; Pennsylvania and Georgia did not participate

Source: Reuters survey of state health departments

Deaths due to resistant bacteria (2003-2014)

<table>
<thead>
<tr>
<th>STATE</th>
<th>STATE COUNT</th>
<th>REUTERS COUNT</th>
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<tbody>
<tr>
<td>Alabama</td>
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<td>Alaska</td>
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<tr>
<td>Florida</td>
<td>21</td>
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<td>Georgia</td>
<td>Did not participate</td>
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<td>Illinois</td>
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<td>27</td>
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<tr>
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<td>Tennessee</td>
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<td>2,399</td>
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<tr>
<td>Wyoming</td>
<td>3</td>
<td>157</td>
</tr>
</tbody>
</table>

Source: Reuters survey of state health departments * Does not count superbug deaths
How serious is the problem?

CDC estimate: 23,000 Americans die each year from resistant infections.

Possible upper bound: 100,000
The World Wakes Up to the Danger of Superbugs

By THE EDITORIAL BOARD  SEPT. 28, 2016

Two forces at work:

- Scientists and pharma failing to develop new drugs to keep pace with failing drugs
- Excessive and improper use of existing drugs by doctors, patients, farmers

Solutions:

- Drug discovery
- Reduce antibiotic use in livestock
- Consumers: vaccines
- Doctors and nurses: hygiene
- Regulate and educate doctors

Tuberculosis. Malaria. Syphilis. Gonorrhea. The microbes that cause these diseases are increasingly resistant, and sometimes even impervious, to antibiotics that worked in the past. Last week, amid other pressing business, 193 nations at the United Nations General Assembly signed a declaration summoning each of them to a war against a powerful and resourceful enemy: superbugs that have learned to evade science’s last remaining defenses.
How to treat patients when patient treatment causes resistance?
A patient

Left ventricular assist device
Resistance phenotype
- sensitive
- intermediate
- resistant

MRSA

Enterobactera

What now?

- clindamycin
- daptomycin
- vancomycin
- sulfamethoxazole/tmp
- gentamicin
- aztreonam
- meropenem
- cefepime
- moxifloxacin
- ciprofloxacin
- levofloxacin
- tigecycline

Bold = i.v. drugs

What now?

Choice of drug(s), dose, infusion time, dosing frequency
One regimen until it fails, then switch or fixed rotation of regimens?
Only treat reactively?

‘Simplify’ the problem: choice of drug

Options for resistance management:
1. Impact origin (transmission, mutation, HGT)
2. Impact expansion

Woods & Read (2015) *Evolution, Medicine and Public Health*
What now?
Choice of drug

1. Continue meropenem until that fails, switch to cefepime
2. Switch back to cefepime until that fails, then switch to meropenem
3. Combination therapy, meropenem and cefepime
4. Combination therapy, meropenem or cefepime + levo or cipro
5. Short duration with gentamicin or colistin

Option 1 is standard practice, so.....
MRSA

cillinamycin
daptomycin
vancomycin
sulfamethoxazole/tmp
gentamicin
aztreonam
meropenem
cefepime
moxifloxacin
ciprofloxacin
levofloxacin
tigecycline

Enterobacter

- hospitalization
- drug used

Resistance phenotype:
sensitive, intermediate, resistant

MRSA
Enterobacteria


**bold** = i.v. drugs
How to treat patients when patient treatment causes resistance?

Options for resistance management:
1. Impact origin (transmission, mutation, HGT)
2. Impact expansion
\[
\frac{dH}{dc} = \left\{ \begin{array}{l}
\text{mutation} \\
\text{reproduction}
\end{array} \right. \\
\int_0^a \pi \left( \frac{\partial \lambda}{\partial p} \frac{\partial \lambda}{\partial c} + \frac{\partial \lambda}{\partial c} \right) ds + \int_0^a \lambda \left( \nabla_x \pi \cdot \alpha_c + \frac{\partial \pi}{\partial c} \right) ds + \frac{n}{1 - \pi} \left( \nabla_x \pi^0 \cdot \alpha_c^0 + \frac{\partial \pi^0}{\partial c} \right)
\]

de novo hazard
standing hazard
Cure or containment?

A change of strategy in the war on cancer

Patients and politicians anxiously await and increasingly demand a 'cure' for cancer. But trying to control the disease may prove a better plan than striving to cure it, says Robert A. Gatenby.
Evolution-proofing existing antibiotics

parasite density (number/mouse)

pABA abundant

pABA depleted

day post infection

Susceptible + Resistant

- Susceptible Inoculum
- Resistant Inoculum
- Pyrimethamine
- Treatment

Wale, Sim, Jones, Salathe, Day, Read in prep.
Take home messages

The problem is big, but we don’t really know how big

Science of antibiotic stewardship is just beginning

New approaches to patient treatment are coming

New opportunities for pharma
- drugs for containment not cure
- evolution-proofing compounds

Drug resistance is a hard problem. But it is not the hardest problem facing humanity – so long as we tackle it.