Development of antimicrobial resistance in bacteria

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Antibiotics

- History of bacterial resistance
- Resistance mechanisms
- Where does resistance come from?
ON THE ANTIBACTERIAL ACTION OF CULTURES OF A PENICILLIUM, WITH SPECIAL REFERENCE TO THEIR USE IN THE ISOLATION OF B. INFLUENZÆ.

ALEXANDER FLEMING, F.R.C.S.

From the Laboratories of the Inoculation Department, St. Mary's Hospital, London.

Received for publication May 18th, 1929.

While working with staphylococcus variants a number of culture-plates were set aside on the laboratory bench and examined from time to time. In the examinations these plates were necessarily exposed to the air and they became contaminated with various micro-organisms. It was noticed that around a large colony of a contaminating mould the staphylococcus colonies became transparent and were obviously undergoing lysis (see Fig. 1).

Subcultures of this mould were made and experiments conducted with a view to ascertaining something of the properties of the bacteriolytic substance which had evidently been formed in the mould culture and which had diffused into the surrounding medium. It was found that broth in which the mould had been grown at room temperature for one or two weeks had acquired marked inhibitory, bactericidal and bacteriolytic properties to many of the more common pathogenic bacteria.
ConsumerReports 8/2015
Die Welt 08.06.2015
1. Juni 2015, 18:47 Uhr  Gipfel in Elmau

So schafften es Superkeime auf die G-7-Agenda

Eine Petrischale mit antibiotikaresistenten Keimen: Jedes Jahr sterben in deutschen Kliniken bis zu 15 000 Menschen an Infektionen, gegen die kein Mittel hilft. Mikrobiologen versuchen, Ursachen dafür zu finden. (Foto: REUTERS)

ANTIBIOTIC RESISTANCE THREATS
in the United States, 2013

NATIONAL SUMMARY DATA

Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:
At least 2,049,442 illnesses,
23,000 deaths

*Bacteria and fungus included in this report.

Estimated minimum number of illnesses and death due to Clostridium difficile (C. difficile), a unique bacterial infection that, although not significantly resistant to the drugs used to treat it, is directly related to antibiotic use and resistance:
At least 250,000 illnesses,
14,000 deaths

WHERE DO INFECTIONS HAPPEN?
Antibiotic-resistant infections can happen anywhere. Data show that most happen in the general community; however, most deaths related to antibiotic resistance happen in healthcare settings, such as hospitals and nursing homes.
Development of antibiotics
Illustration of the “discovery void.” Dates indicated are those of reported initial discovery or patent.

Bacterial resistance to AB

**Intrinsic resistance** (species specific)

- *K. pneumoniae*: Ampicillin
- *Enterococci*: cephalosporins

**Acquired resistance**

- *E. coli*: Ampicillin
- *N. gonorrhoeae*: cephalosporins
- *S. aureus*: Methicillin resistance (MRSA)
resistance mechanisms
How do antibiotics work?

- Cell wall synthesis
- Cell membrane

- DNA-/RNA-synthesis
- Metabolism
- Protein biosynthesis
## Resistance mechanisms

<table>
<thead>
<tr>
<th>Target site modification</th>
<th>Enzymatic inactivation</th>
<th>Transport</th>
</tr>
</thead>
<tbody>
<tr>
<td>beta-lactams penicillin-binding proteins (PBPs)</td>
<td>beta-lactams beta-lactamases</td>
<td>beta-lactams porin changes</td>
</tr>
<tr>
<td>quinolones topoisomerase mutations</td>
<td>aminoglycosides aminoglycoside modifying enzymes</td>
<td>tetracyclines, tigecycline efflux pumps</td>
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<tr>
<td>macrolides rRNA modifications</td>
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</table>
When did resistance to antibiotics first occur?

**LETTER**

Antibiotic resistance is ancient

Vanessa M. D’Costa¹,²*, Christine E. King³,⁴*, Lindsay Kalan¹,², Mariya Morar¹,², Wilson W. L. Sung⁴, Carsten Schwarz³, Duane Froese⁵, Grant Zazula⁶, Fabrice Calmels⁵, Regis Debruyne⁷, G. Brian Golding⁴, Hendrik N. Poinar¹,³,⁴ & Gerard D. Wright¹,²

- Permafrost sediment ca. 30,000 years
- detection of resistance genes to betalactam AB, tetracycline, vancomycin

*Nature 477,457–461 (22. September 2011)*
How long does it take to develop resistance to antibiotics?
# Emergence of resistance

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Year deployed</th>
<th>Clinical resistance observed</th>
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</thead>
<tbody>
<tr>
<td>Sulfonamides</td>
<td>1930s</td>
<td>1940s</td>
</tr>
<tr>
<td>Penicillin</td>
<td>1943</td>
<td>1946</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>1943</td>
<td>1959</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>1947</td>
<td>1959</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>1948</td>
<td>1953</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>1952</td>
<td>1988</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1956</td>
<td>1988</td>
</tr>
<tr>
<td>Methicillin</td>
<td>1960</td>
<td>1961</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>1961</td>
<td>1973</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>1960s</td>
<td>Late 1960s</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>1962</td>
<td>1962</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>1980s</td>
<td>1980s</td>
</tr>
<tr>
<td>Linezolid</td>
<td>1999</td>
<td>1999</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>2003</td>
<td>2003</td>
</tr>
</tbody>
</table>
How does resistance develop?

→ genes encoding resistance

spontaneous mutation/selection

plasmid transfer (horizontal gene transfer)
How does resistance develop?
How does resistance develop?

DNA

chromosome

transformation
Why/how does AB resistance spread?
Dissemination of resistant bacteria

Antibiotic pressure
- humans
- animals

Dissemination
- nosocomial
- community
- food chain
Major threats (CDC)

Urgent
- C. difficile
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Cephalosporin-resistant N. gonorrhoeae

Serious
- ESBL-Enterobacteriaceae
- Vancomycin-resistant Enterococcus (VRE)
- MRSA
- MDR/XDR M. tuberculosis
  ...
β-lactamases

- β-lactam AB
- porin
- cell wall
- cell membrane
- β-lactamase
- ESBL
- carbapenemase
K. pneum. Ceph 3G I/R 2013

Ampicillin  R
Amp/Sulb    R
Piperacillin R
Pip/Tazo    R
Cefuroxime  R
Cefotaxime  R
Ceftazidime R
Meropenem   S
Imipenem    S
Ciprofloxacin R

EARS-Net (http://ecdc.europa.eu)
New superbugs

New Delhi metallo-β-lactamase-1, or NDM-1 for short, is an enzyme that can live inside different bacteria. Any bacteria that carry it will be resistant to antibiotics.

Two types of bacteria have been host to NDM-1: the gut bacterium E.coli and another that can invade the lungs called Klebsiella pneumonia. Both can lead to urinary tract infections and blood poisoning.

Daily Mail 11.08.2010
Carbapenem R K. pneumoniae 2013

Ampicillin R
Amp/Sulb R
Piperacillin R
Pip/Tazo R
Cefuroxime R
Cefotaxime R
Ceftazidime R
Cefepim R
Meropenem I/R
Imipenem I/R
Ciprofloxacin R

EARS-Net ECDC (http://ecdc.europa.eu)
Carbapenemases

- Hydrolyze carbapenems
- *K. pneumoniae*, *E. coli*, other Enterobacteriaceae, *P. aeruginosa*, *A. baumannii*
- increasingly reported worldwide: USA, Greece, Turkey, Israel, India
- usually plasmid-encoded
- detection problematic
- reservoir: gut
Therapy of CRE infections

- beta-lactams I/R (aztreonam S in some cases)
- Colistin/polymyxin B, fosfomycin, tigecyclin often S
- combination therapy (+carbapenem, if MIC <8)
- no new AB in the next future
Is resistance an advantage?

- Plasmids/additional genes burden
- Cost of fitness of resistance genes
Conclusion

- resistance to AB rising globally
- Gram-negative bacteria!
- different resistance mechanisms
- need for more diagnostics, blind therapy
- infection control!
Conclusion

- AB pressure ↘ (patients & food chain)
- no/few new antibiotics in the future
- resistance to future AB will develop rapidly -> existing resistance genes
Thank you for your attention