Antibiotics, antibiotic resistance and the human microbiome

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Earth forms

First life

O$_2$ in atmosphere

First multi-cellular organisms

First fungi

Plants, insects

Dinosaurs

Humans

5 x 10$^{30}$ bacteria on Earth

Whitman et al., 1998. PNAS 95:6578
Earth forms

First life

O$_2$ in atmosphere

First multi-cellular organisms

First fungi

Plants, insects

Dinosaurs

Humans

The natural role of antibiotics
Fungi kill bacteria *in vitro*
Fungi + *Salmonella enterica* Typhi: mice survive
Discovery of antibiotics

Sir Alexander Fleming (1881 – 1955)

Not successful in purifying active substance
Discovery of antibiotics

Thanks to PENICILLIN
...He Will Come Home!
http://www.hhmi.org/biointeractive/penicillin-acting-bacteria
Collateral damage of antibiotic use?

Prof. Martin J. Blaser
New York Medical Center
Collateral damage of antibiotic use?

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Trasande et al., 2013. Intl J Obesity 37:16-23
Antibiotic resistance
Antibiotic resistance

“The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily under-dose himself and by exposing his microbes to nonlethal quantities of the drug make them resistant.”

~Alexander Fleming

“The more you use it, the faster you lose it.”

Dr. Robert Weinstein
Resistance to antibiotics could bring "the end of modern medicine as we know it", WHO claim.

The world is entering an antibiotic crisis which could make routine operations impossible and a scratched knee potentially fatal, the head of the World Health Organisation has claimed.

Deaths attributable to antimicrobial resistance every year by 2050

- North America: 317,000
- Europe: 390,000
- Latin America: 392,000
- Africa: 4,150,000
- Asia: 4,730,000
- Oceania: 22,000

Source: Review on Antimicrobial Resistance 2014

2050?
%resistant in bloodstream isolates. Data: EARS-NET

cephalosporin-resistant *Escherichia coli*

vancomycin-resistant *Enterococcus faecium*

methicillin-resistant *Staphylococcus aureus*
Trimethoprim, *Escherichia coli*
Resistance caused by accumulation of mutations

Trimethoprim, *Escherichia coli*. Time-lapse movie taken over 12 days
Baym et al., 2016. Science 353:1147
Acquisition of antibiotic resistance genes

Rapid transfer of antibiotic resistance
Antibiotic resistance
the problem with plasmids

pNDM-HK
*E. coli* strain from Hong Kong

Resistance genes
β-lactams
(*bla*$_{TEM-1}$, *bla*$_{NDM-1}$, Δ*bla*$_{DHA-1}$)
aminoglycosides
(*aacC2*, *armA*)
sulphonamides
(*sul*1)
macrolides
(*mel*, *mph2*)

Ho et al. 2010. PLoS ONE 6(3): e17989
>50% of ICU patients has a hospital-acquired infection

Vincent et al., 2009. JAMA 302:2323-2329
Selective digestive tract decontamination

Decontamination of oropharynx and intestinal tract

Mix of colistin, tobramycin, amphotericin. Intravenous cefotaxime for first 4 days at ICU

Widely used in Dutch ICUs

Lowers patient morbidity & mortality

But effect on resistance?

van der Waaij et al., 1972. J Hyg (Lond) 70:605
Daneman et al., 2013. Lancet Infect. Dis. 13:328
Oostdijk et al., 2014. JAMA 312:1429
Pilot study

10 healthy volunteers, two samples (1 year apart)

10 ICU-patients, stay ≥10 days
intracerebral hemorrhage

post-operative complications after coronary artery bypass grafting
Microbiome of ICU patients
Microbiome of ICU patients

Diversity of the microbiome decreases in ICU patients
Stable in healthy subjects
Resistome of ICU patients

Primers for 81 resistance genes
16S rRNA: for relative quantification

Most common resistance genes in gut microbiota

Clinically relevant resistance genes
ESBLs, carbapenemases, meca, vancomycin resistance genes

Buelow, Bello Gonzalez et al., in preparation
Many different antibiotic resistance genes
Some enriched in ICU patients, but no ‘high-risk’ genes
Good

Important reduction of *E. coli*

No selection for high-risk antibiotic resistance genes

Bad

Microbiota is highly perturbed
Finding the right balance

Emergence of resistance

Therapeutic benefits
Microbiome interventions in critically ill patients are risky

Restoring the balance?

Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind

Marc G H Besselink, Hjalmar C van Santvoort, Erik Buskens, Maria Thomas L Bollen, Bert van Ramshorst, Ben J M Witteman, Camiel Cornelis H C Dejong, Peter J Wahab, Cees J H M van Laarhoven, Enzo Hein G Gooszen, for the Dutch Acute Pancreatitis Study Group

Lactic acid bacteria
Infections with *Clostridium difficile*
After antibiotic treatment
Can cause life-threatening inflammation of the colon

Fecal transplants?

Fecal transplants?

“90% cure rate”
Conclusions

Antibiotics are essential for modern medicine

Antibiotic use may harm human health through effects on the microbiome

Antibiotic use selects for resistance

Use antibiotics only when benefits outweigh risks

Monitoring of resistance
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