CHALLENGES OF ANTIBIOTIC USE AND MITIGATION BY APPLYING HYGIENE

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Contents

- Evolution of antibiotic use and antibiotic resistance
- Priority of infection prevention over therapy
- Elements of infection prevention in healthcare
- Role of biocides in infection prevention
- Risk of biocide resistance
- Risk of biocide use promoting antibiotic resistance
Evolution of antibiotic use

in humans + animals

ECDC report 2010-14

ECDC report 2013-17

in agriculture (NL 1997-2007)

Evidence of increasing antibiotic resistance gene abundance in archived soils since 1940, Environ Sci Technol 2010; 44: 580-587
Evolution of antibiotic use
Probable reasons

- Over-use of antibiotics in humans
  - Lack of knowledge

- Abuse of antibiotics in agriculture
  - Growth promotion
  - Plant and crop protection

- More invasive procedures
  - Increased need for prophylactic use

- Aging population
  - More infectious diseases need therapy
Consequence of this development

Development of *Clostridioides difficile* infections (CDI)

- 2016: 7,711 CDI cases reported by 20 EU countries, 74.6% healthcare-associated [1]
- Increasing number of deaths related to CDI [2]
  - UK 1999-2007
- Antibiotic use being the main driver of this
  - Example: Ciporfloxacin use and CDI [3]

Evidence for beneficial effect to stop CDI [4]

- Antimicrobial stewardship
- Glove use
- Disposable thermometers
- Environmental disinfection

Add. Costs €12,500 extra 5.6 days in hospital per case

Leal et al., Infection Control & Hospital Epidemiology 2019, 1–9
doi:10.1017/ice.2019.178

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1) ECDC *Clostridium difficile* infections - Annual Epidemiological Report for 2016
2) Pearson, J. Hosp Infect 2009; 73: 296-304
3) Borgmann et al. Eurosurveillance 15 No. 5, Feb 4th 2010
4) Hsu et al., American journal of gastroenterology 2010; 105 (11): 2327-239
Evolution of antibiotic resistance

in humans + animals

Evolution of antibiotic resistance in the environment


Evidence of increasing antibiotic resistance gene abundances in archived soils since 1940, Environ Sci Technol 2010; 44: 580-587
Evolution of antibiotic resistance

Antibiotics
- Found in 1928
- In broad use since 1945
- 1st resistance report: 1940 (acquired resistance, penicillinase)
- Resistance of clinical relevance immediately after introduction

Resistance to antibiotics was already out there
- Antibiotics are “natural” substances
- Microbes acquired resistance during evolution
Consequence of this development

Infections, which can no more be treated

- MRSA  multi-resistant *Staphylococcus aureus*
- VRE  Vancomycin resistant Enterococci
- MRGN  multi-resistant gramnegative Bacteria
- CDI  Clostridioides difficile infection

Some epidemiologists declared the “post-antibiotic era”

3,000,000 healthcare associated infections per year

responsible for approximately 50,000 deaths

1) The First European Communicable Disease Epidemiological Report, ECDC June 2007
Consequence of this development

The frequency and rates of ascent and dissemination of antibiotic resistance in bacterial populations are anticipated to be directly related to the volume of antibiotic use\(^1\)

\[ \Rightarrow \text{antibiotic stewardship} \]

Use (formerly) most powerful weapon against infections more carefully and targeted

Focus on infection prevention rather than treatment

\[
\begin{align*}
\text{“The goal of controlling antimicrobial resistance can only be achieved by combining strong infection prevention and control and the prudent use of antimicrobials.”}^2
\end{align*}
\]

1) Anderson & Levin, Current Opinion in Microbiology 1999; 2: 483-493
2) Commission Notice EU Guidelines for the prudent use of antimicrobials in human health (2017/C 212/01)
Elements of infection prevention in healthcare

- Surveillance
- Isolation of cases
- Barrier management
  - Personal protective equipment, probe covers, patient drapes, ….
- Hygienic design of environment and devices
- Disinfection + antisepsis
Elements of infection prevention in healthcare

Disinfection + antisepsis

- Hands
- Patient environment (surfaces)
- Medical instruments
- Pre-invasive skin antisepsis

biocides / medical devices
medical devices
medicinal products
Role of biocides in infection prevention

Hand disinfection reduces infection rates

Overwhelming scientific evidence published by WHO

WHO Guidelines on Hand Hygiene in Health Care: a Summar of
https://www.who.int/gpsc/5may/tools/9789241597906/en/

The preferred measure:
- alcohol based hand disinfection
- Unless hands are visibly soiled
- Unless contaminated with spores
Role of biocides in infection prevention
Hand disinfection reduces infection rates

The risk of non-compliance in hand hygiene

Simulation study: 1 Mio patient-HCW-patient contacts without hand disinfection

Results in
- 42 MRSA infections (1st patient unknown MRSA status)
- 980 MRSA infections (1st patient known MRSA carrier)

Cost of one non-compliant event
- 1.98 $ (1st patient unknown MRSA status)
- 52.53 $ (1st patient known MRSA carrier)

Cummings, Infect Control Hosp Epidemiol 2010;31:357–364
Role of biocides in infection prevention
Environmental disinfection reduces infection rates

Risk of organism transmission from prior room occupants: review and meta-analysis

- MRSA
- VRE
- Klebsiella/E. Coli
- Pseudomonas
- VRE
- C. difficile
- MRSA
- Acinetobacter
- overall

Environmental surfaces play a significant role in pathogen transmission.

Mitchell et al., J Hops Infect 2015; 91: 211-217
Role of biocides in infection prevention
Environmental disinfection reduces infection rates

- Strong interrupted time series study with control group
- Replacing mere cleaning of high touch objects in patient rooms by disinfection
  - Significantly reduced the rate of VRE
  - Significantly reduced rates of CDI and MRSA infection, when disinfection compliance was ≥80%

Alfa et al. AJIC 2014 doi.org/10.1016/j.ajic.2014.10.016
Role of biocides in infection prevention
Environmental disinfection reduces infection rates

“The value of objectively monitoring environmental cleaning in healthcare settings is becoming increasingly recognized…”1)

Application of biocides must be accompanied by
- Appropriate use instructions
- Training tools and systems
- Compliance monitoring
- Feedback

Carling, Am J Unfect Control 2013; 41: S20-S25
Role of biocides in infection prevention
Combination of surface + hand disinfection most effective

Mathematical model to estimate virus infection risk reduction in healthcare

- 15% hand hygiene increase or 1 surface disinfection event yielded similar infection risk reductions.
- 15% hand hygiene increase and 2 cleanings decreased infection risk by 20.93%-47.55%.
- Risk reduction for greater hand hygiene decreased as baseline compliance increased.

Wilson et al., AM J Infect Control 2019, https://doi.org/10.1016/j.ajic.2019.05.023
Role of biocides in infection prevention
Combination of surface + hand disinfection most effective

Relative risk

Wilson et al., AM J Infect Control 2019, https://doi.org/10.1016/j.ajic.2019.05.023
Does more frequent use of biocides promote biocide resistance?

- Long term exposure to subinhibitory concentrations BAC
  - Pre-adaptation to 50 ppm BAC in a fed batch reactor for 3 years!

![Graph showing BAC removal (BAC+) over generations with MIC (mg/L BAC) vs. Generations.](image)
Does more frequent use of biocides promote biocide resistance?

Long term exposure to subinhibitory concentrations

Dramatic?
Relevant?

No!

- MIC does not represent practice conditions
  - high organic burden

- Such long-term exposure under conditions of growth does not occur in practice
  - Max. concentration in waste water of indirect discharge facilities using such disinfectants:
    - <1.5 ppm BAC and <5 ppm overall QAC\(^1\))
    - One single extreme value in a hospital: 6 ppm\(^2\))

- Start of reversion after 300 + generations?

1) Martínes-Carball et al, Environmental Pollution 2007; 145: 489-496
2) Kümmerer et al, Journal of Chromatography A 1997; 774: 281-286
Does more frequent use of biocides promote biocide resistance?
Effects observed in the laboratory do not occur in real life

- effects of a QAC-containing domestic cleaning fluid on the population dynamics and antimicrobial susceptibility of domestic sink drain biofilm communities

- fully characterized drain microcosm was exposed to short-term (12 days) and long-term (3 months) dosing with a QAC-containing domestic detergent

- Although repeated QAC exposure of drain isolates in pure culture results in susceptibility change in some test bacteria, such changes do not necessarily occur within complex communities.

Does more frequent use of biocides promote biocide resistance?
Effects observed in the laboratory do not occur in real life

- Ants disinfect their houses by including conifera woods
  - Using biocides is “natural”
  - Microbes have not acquired resistance during evolution

Figure 1: Mean (± SE) number of colony-forming units of bacteria and fungi per g m⁻¹ of nest material, for nests consuming corn (white bars) and water-free corn (black bars). Tryptic Soy Agar (TSA) is a standard nutritive medium for bacteria. Brain Heart Infusion (BHI) agar (EMB) is specific for gram-negative bacteria, and Dickhouson Glyceral (DG10) agar (DG10) is specific for aerophilic fungi.
Does more stringent hygiene promote antibiotic resistance?

“…increased confinement and cleaning is associated with a loss of diversity…“1)

“…the loss of microbial diversity correlates with increase in (antibiotic) resistance…“

- Determined as availability of resistance genes in the environment of healthcare and cleanroom (space craft assembly) settings

The same was not observed in food manufacturing

- The BIOHYPO project:
  No correlation between biocide and antibiotic susceptibility.2)

- So far, data from the BIOHYPO project do not allow for the indication of any risk of clinically significant antibiotic resistance development following the use of biocides3)

1) Mahnert et al., Nature Communications, DOI: 10.1038/s41467-019-08864-0
2) http://cordis.europa.eu/result/rcn/89974_de.html
Does biocide use promote antibiotic resistance?

- The increased rate of resistance genes is probably not due to biocide use
  - Was not demonstrated in food settings, which are equally confined and disinfected
- The increased rate of resistance genes in healthcare settings may be due to antibiotic use
- The cleanroom situation needs further investigation
Conclusions (1)

- Infection risks must be weighed against the (potential and unknown) effects of reducing microbial diversity
  - In proven cases the benefit in infection prevention outweighs by far the risk of developing biocide resistance or promoting antibiotic resistance
  - Proven cases: hand disinfection, disinfection of high touch surfaces

- Biocides must be used according to use instructions to achieve infection prevention
  - Compliance and correct use must be supervised and instructed
  - Biocides must **not** be used to „disinfect dirt“ – appropriate pre-treatment, if needed
Conclusions (2)

- Biocides must be used targeted to risk areas and places to achieve infection prevention
- Appropriate biocide use does not promote biocide resistance
- Appropriate biocide use does not promote antibiotic resistance
- Biocides play a crucial role in infection prevention in the „post-antibiotic era“
THANK YOU