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Antimicrobial Stewardship in the Diabetic Foot - How to get it right

Edgar J.G. Peters, MD, PhD

Financial disclores

- No relevant financial disclosures
- Member guideline committee diabetic foot
  - IWGDF
  - IDSA
  - Dutch NIV guidelines
- Research funding:
  - Fonds NutsOhra
  - Diabetes Fonds

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If Finland were your home instead of Netherlands you would...

- be **17.57% more** likely to be unemployed — more info
- use **2.3 times more** electricity
- have **17.17% less** free time
- be **2.4 times more** likely to be murdered
- make **17.09% less** money
- consume **34.95% less** oil
- be **26.67% less** likely to be in prison
- spend **26.23% less** money on health care
- experience **13.27% less** of a class divide
- die **1.43 years** sooner
- be **8.2% less** likely to die in infancy
- be **50% less** likely to have HIV/AIDS
- have **4.43% fewer** babies

www.ifitweremyhome.com

Goals and take home message

- Antimicrobial stewardship in the diabetic foot
  - Only treat infected wounds
  - Apply proper culture techniques
  - Only treat the pathogen
  - Use oral antibiotics when possible
  - Do not overuse antibiotics
  - Do not overuse antiseptics

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Antibiotic stewardship principles

- Use guidelines for antibiotic treatment
  - Make local antibiotic guidelines, based on national guidelines
- Take cultures before starting treatment
- Switch from empiric antibiotics to pathogen-directed therapy as soon as possible
- Switch from iv to oral therapy within 48-72 hours
- Consider the use of inflammatory biomarkers to decide continuation of therapy

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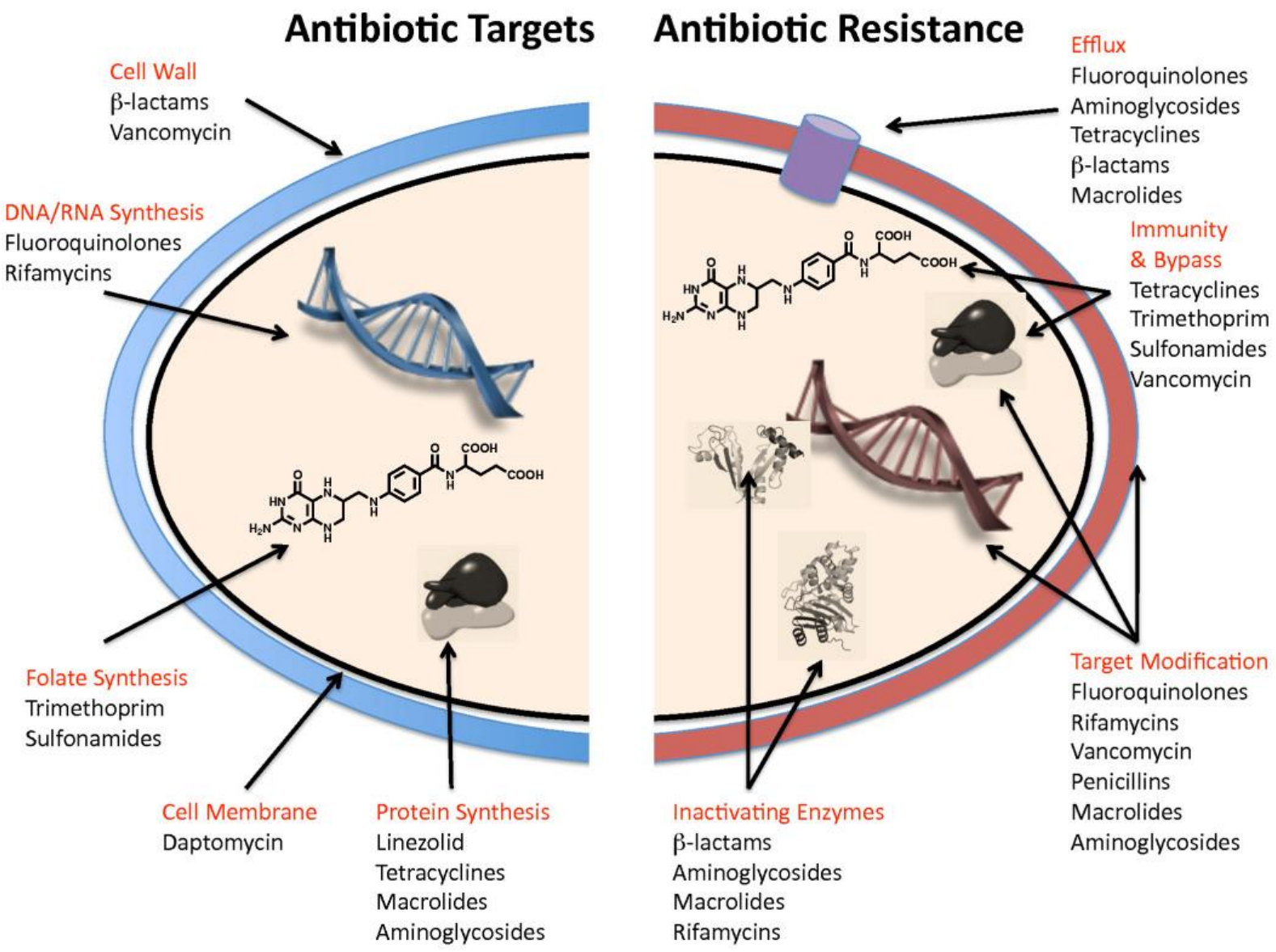
EU Guidelines for the prudent use of antimicrobials in human health (European Commission, 2017)
SWAB Dutch Guidelines for Antimicrobial Stewardship, 2016
Barlam *et al. Clinical Infectious Diseases* 2016;62(10):e51–e77



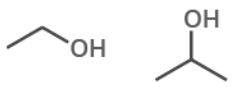
http://www.clinicaleducation.org/wp-content/uploads/Antibiotics-resistance-and-effects.jpg

A BRIEF SUMMARY OF DISINFECTANTS & ANTISEPTICS

Key: USED FOR ANTISEPSIS | USED TO DISINFECT SURFACES | USED FOR STERILISATION (E.G. MEDICAL INSTRUMENTS) | USED FOR PRESERVATION

ALCOHOLS

USED IN ALCOHOL-BASED SANITARY HAND GELS PRESENT IN HOSPITALS

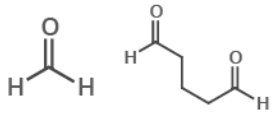


ETHANOL ISOPROPANOL

Kill many bacteria and fungi, and some viruses, when used at suitably high concentrations (usually 60-90% solution). Slow-acting, and evaporate easily, so lack residual action. Can't be used to sterilise.

ALDEHYDES

MAINLY USED FOR DISINFECTION & STERILISATION OF MEDICAL INSTRUMENTS

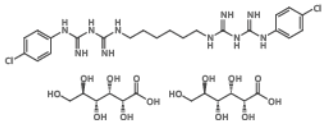


FORMALDEHYDE GLUTARALDEHYDE

Show broad activity against bacteria, fungi, and viruses. Not used for general antisepsis, due to their high toxicity. Due to the relatively long contact times required to disinfect, other agents are often preferred.

BIGUANIDES

USED IN CREAMS & FOR SKIN ANTISEPSIS IN SURGICAL PROCEDURES

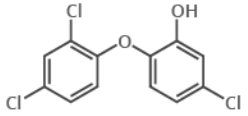


CHLORHEXIDINE DIGLUCONATE

Slow-acting, but don't evaporate easily like alcohols, so provide some residual activity. Active against most bacteria, and show some activity against fungi and viruses. Combination with alcohol increases efficacy.

BISPHENOLS

TRICLOSAN IS COMMONLY USED IN ANTISEPTIC SOAPS

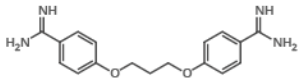


TRICLOSAN

Effective against bacteria, though more so against gram-positive bacteria. There are concerns surrounding triclosan's use in soaps due to its effects on the skin, and also due to its accumulation in the environment.

DIAMIDINES

MAINLY USED FOR THE TOPICAL TREATMENT OF WOUNDS

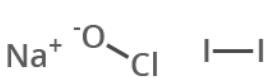


PROPAMIDINE

Less commonly used than the other featured compounds; halogenated derivatives of these compounds can also be used. Unlike some other agents, they still work in the presence of organic matter.

HALOGEN-RELEASING

MAINLY USED FOR SURFACE DISINFECTION; FOUND IN HOUSEHOLD BLEACH

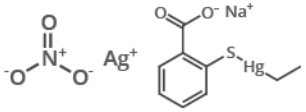


SODIUM HYPOCHLORITE IODINE

Affect bacteria, viruses, and fungi. Usually chlorine and iodine-containing compounds, with the halogens acting as oxidising agents on micro-organisms. Iodine solutions can cause irritation and staining.

METAL DERIVATIVES

RARELY USED FOR DISINFECTION, BUT CAN BE USED FOR VACCINE PRESERVATION

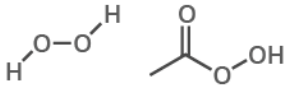


SILVER NITRATE THIOMERSAL

Silver salts are strongly bactericidal, and can be used to halt bacterial growth in burn wounds. Thiomersal is used as a preservative in some vaccines, and there are no causative links to any harmful effects.

PEROXYGENS

SUITABLE CONCENTRATIONS CAN BE USED FOR STERILISATION & ANTISEPSIS

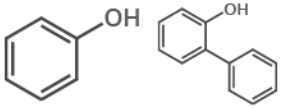


HYDROGEN PEROXIDE PERACETIC ACID

Widely used and environmentally friendly, as they decompose into safe by-products; most solutions need stabilisers to prevent decomposition. Broad spectrum of activity. Peracetic acid is the more potent.

PHENOLICS

USED FOR SURFACE DISINFECTION IN HOSPITALS AND LABORATORIES

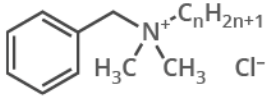


PHENOL *o*-PHENYLPHENOL

Phenol is no longer used as it is corrosive and carcinogenic. A number of derivatives are widely used, often for sterilising surfaces. They're partly responsible for the characteristic smell of hospitals.

QUATERNARY AMMONIUM SALTS

USED IN MANY ANTISEPTIC CREAMS AND KITCHEN SURFACE CLEANERS



BENZALKONIUM CHLORIDE

Low toxicity, so can be used to disinfect surfaces in food-handling areas. Work against gram positive bacteria and gram negative bacteria, though gram negative bacteria growth in solutions is possible.

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http://www.compoundchem.com/wp-content/uploads/2016/03/Guide-to-Disinfectants-Antiseptics.png

Antiseptic and antibiotic resistance

- Links between chlorohexidine tolerance and antibiotic resistance
  - Colistin[1]
  - Vancomycin[2]
- FDA bans antiseptic use in soap[3]
  - Not effective in preventing infection
  - Possible harm through antibacterial resistance

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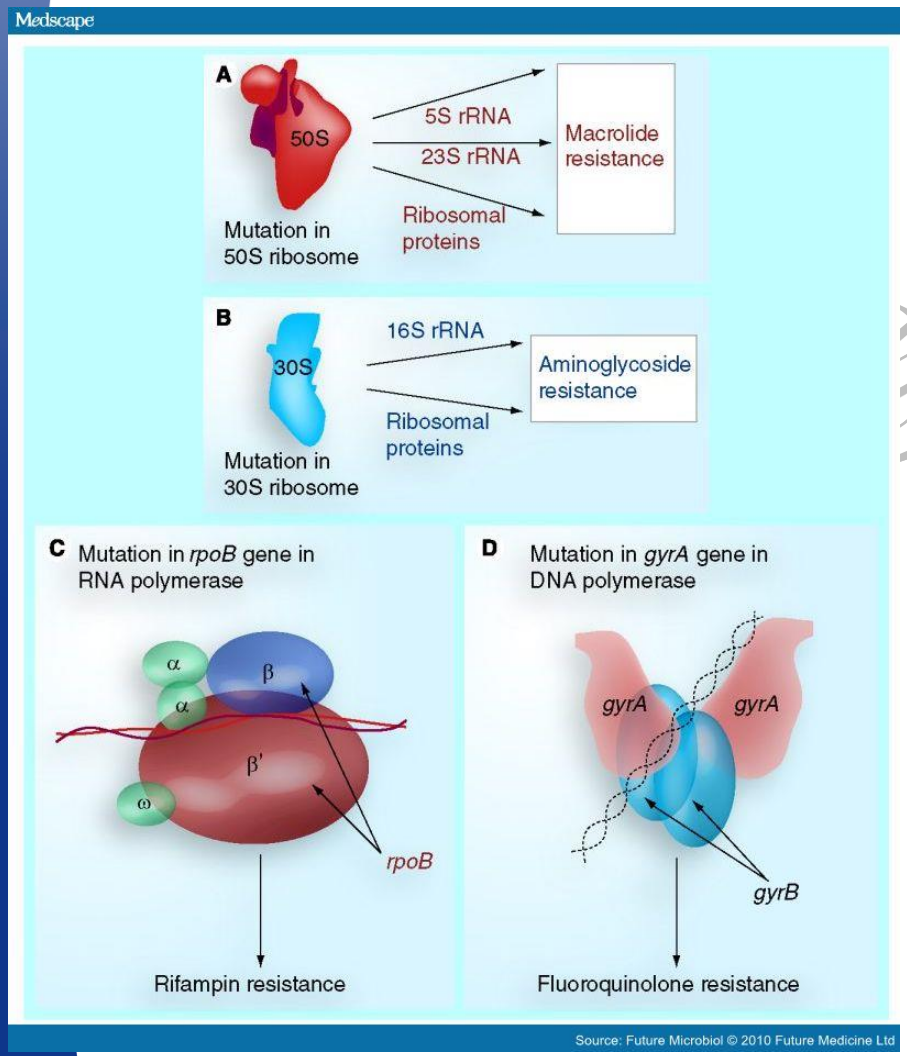
1. Wand, *Antimicrob. Agents Chemother. 2016 , 60, e01162–e01216*
2. Bhardwaj, *Antimicrob. Agents Chemother. 2016, 60, 2209–2221*
3. Giuliano, *Pharmacotherapy: J. Hum. Pharmacol. Drug Ther*, 2015. 35, 328–33

Resistance due to single mutations



http://img.medscape.com/article/734/138/734138-fig2.jpg

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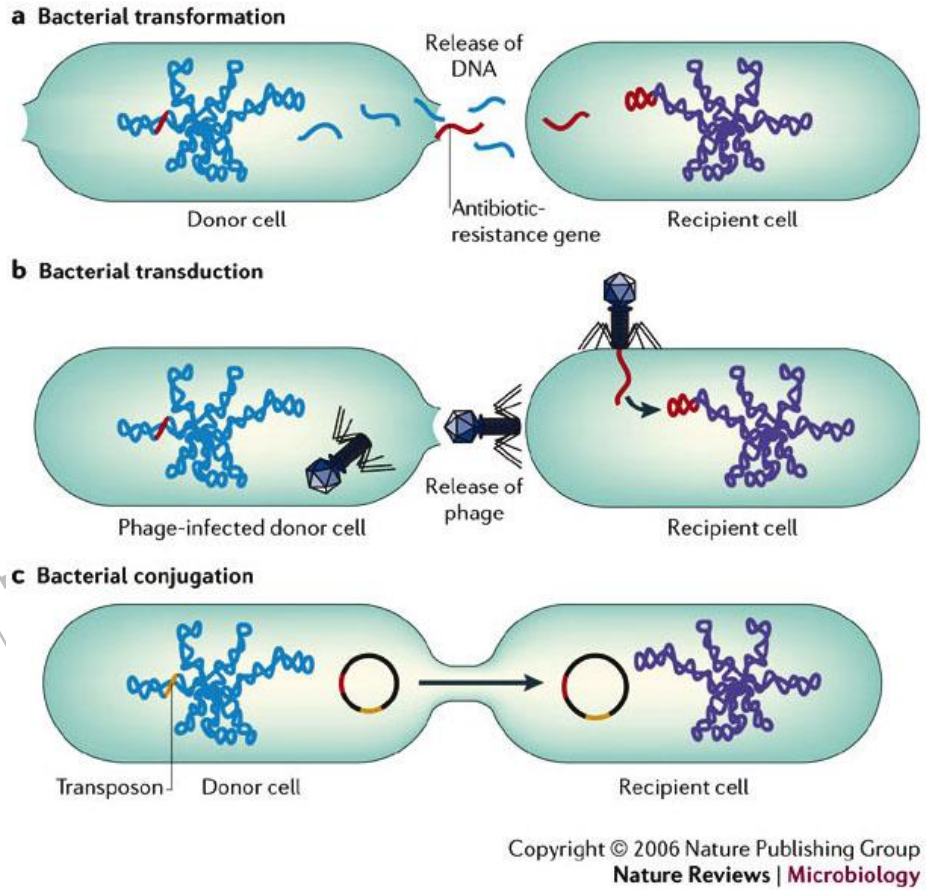
Resistance due to transfer of genes



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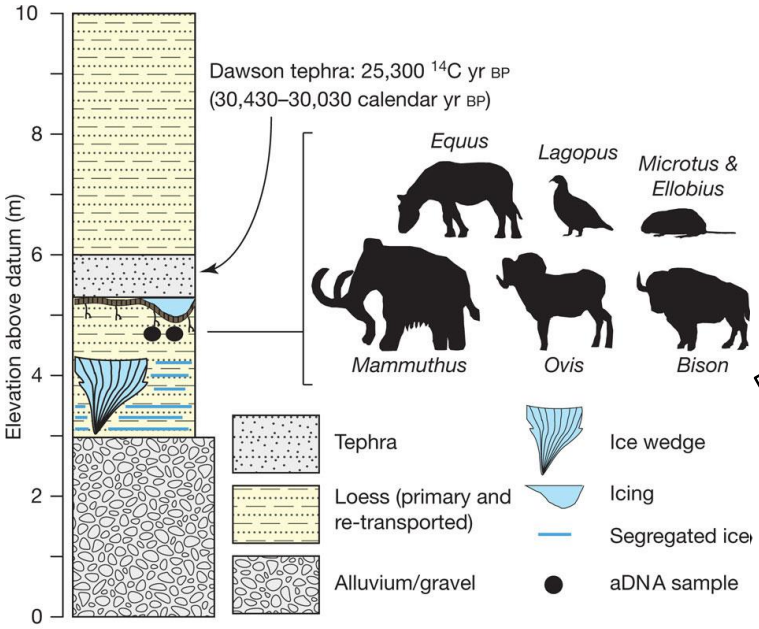
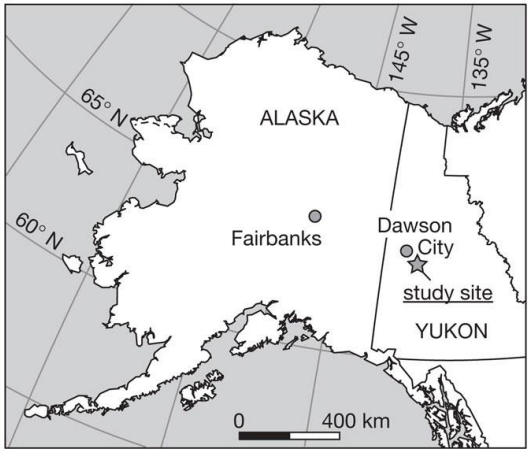
Resistance is ancient

Stratigraphic profile and location of Bear Creek site





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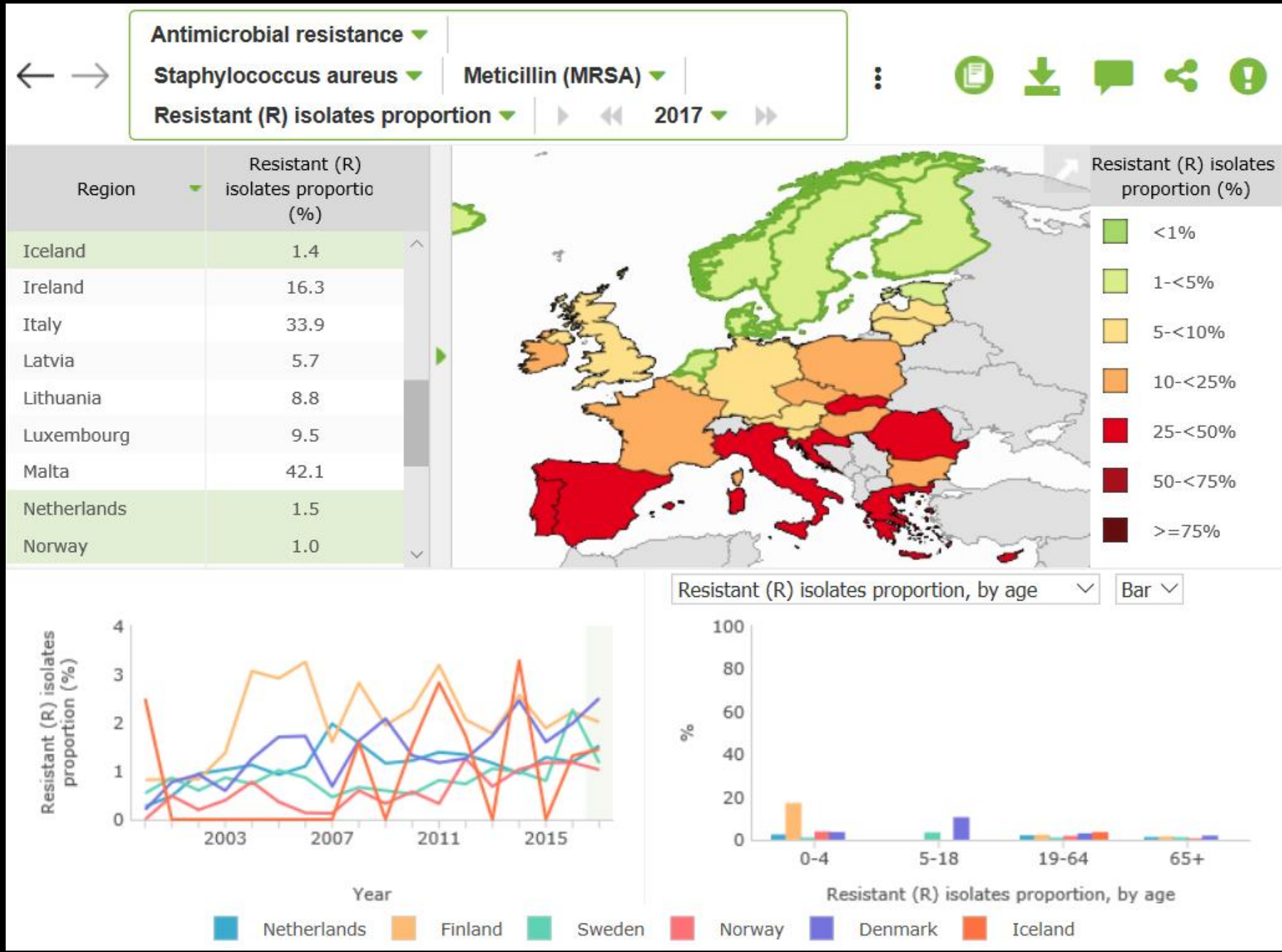
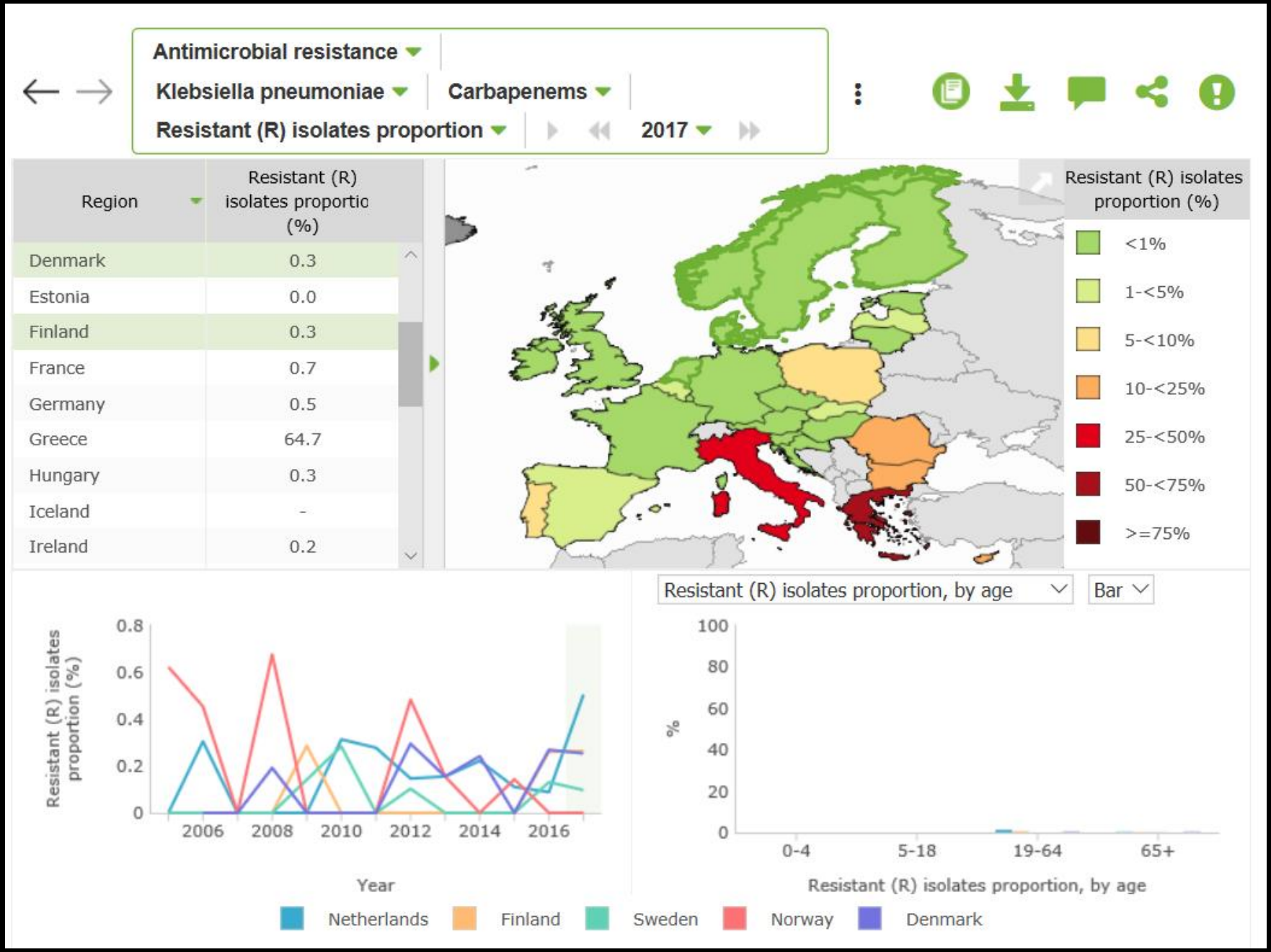
Elevation is given in metres above base of exposure. Permafrost samples from below Dawson tephra were dated to about 30 kyr bp. Preservation of the ice below and above the sample indicates that the sediments have not thawed since deposition. Silhouettes represent mammals and birds identified from ancient DNA sequences that are typical of the regional Late Pleistocene environment. aDNA, ancient DNA

nature

VM D'Costa *et al*. *Nature* **000**, 1-5 (2011) doi:10.1038/nature10388



http://ecdc.europa.eu/en/data-tools/atlas/Pages/atlas.aspx



http://ecdc.europa.eu/en/data-tools/atlas/Pages/atlas.aspx

30,000 deaths per year by MDR organisms in Europe

Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis

*Alessandro Cassini, Liselotte Diaz Högberg, Diamantis Plachouras, Annalisa Quattrocchi, Ana Hoxha, Gunnar Skov Simonsen, Mélanie Colomb-Cotinat, Mirjam E Kretzschmar, Brecht Devleesschauwer, Michele Cecchini, Driss Ait Ouakrim, Tiago Cravo Oliveira, Marc J Struelens, Carl Suetens, Dominique L Monnet, and the Burden of AMR Collaborative Group**

Summary

Background Infections due to antibiotic-resistant bacteria are threatening modern health care. However, estimating their incidence, complications, and attributable mortality is challenging. We aimed to estimate the burden of infections caused by antibiotic-resistant bacteria of public health concern in countries of the EU and European Economic Area (EEA) in 2015, measured in number of cases, attributable deaths, and disability-adjusted life-years (DALYs).

Lancet Infect Dis 2018

Published Online
November 5, 2018
http://dx.doi.org/10.1016/S1473-3099(18)30605-4

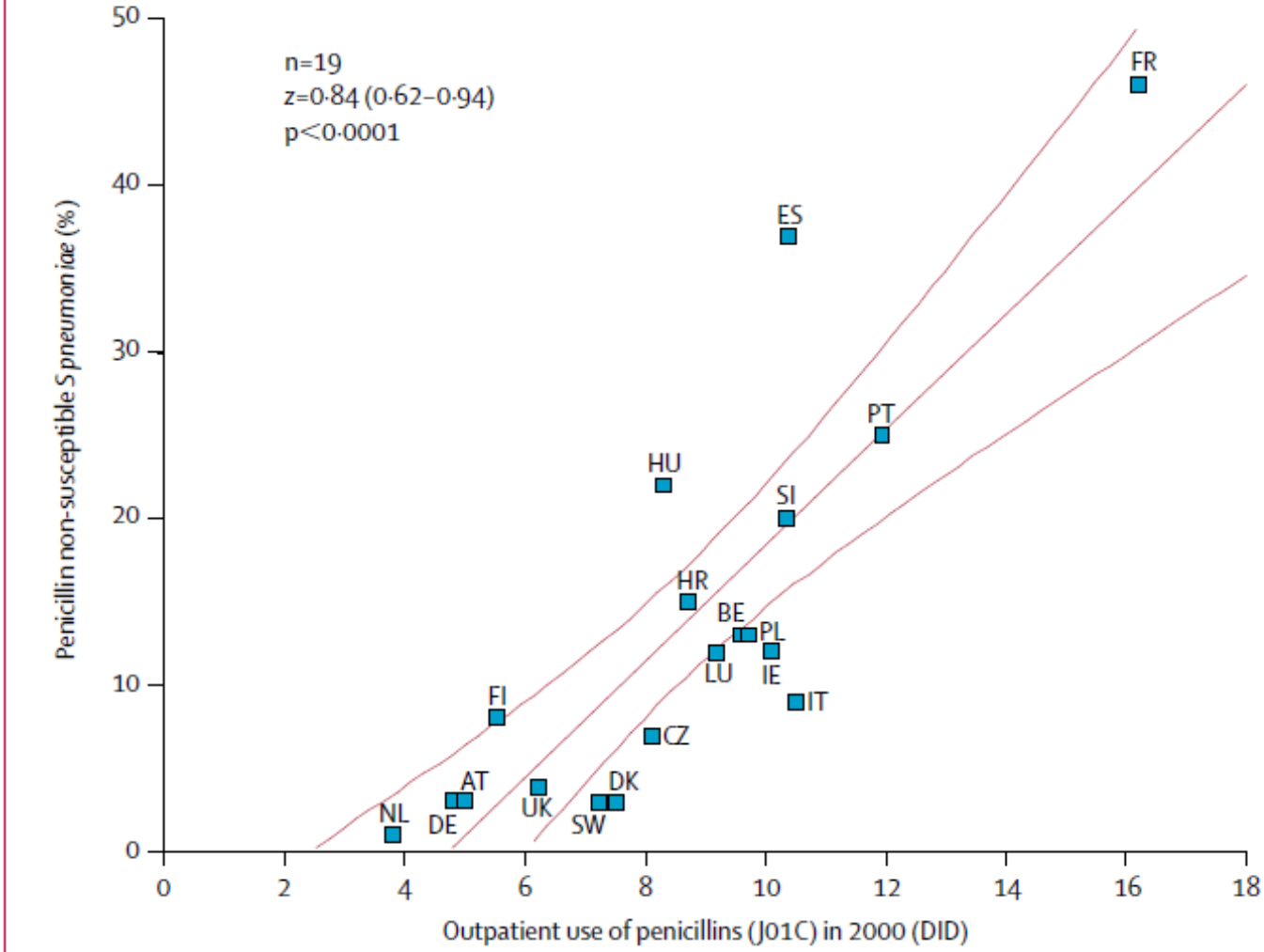


Figure 6: **Correlation between penicillin use and prevalence of penicillin non-susceptible *S pneumoniae***
AT, Austria; BE, Belgium; HR, Croatia; CZ, Czech Republic; DK, Denmark; FI, Finland; FR, France; DE, Germany; HU, Hungary; IE, Ireland; IT, Italy; LU, Luxembourg; NL, The Netherlands; PL, Poland; PT, Portugal; SI, Slovenia; ES, Spain; UK, England only.

Goossens, *Lancet*, 2005

Systematic review diabetic foot infection

- 13,365 titles reviewed
- 40 studies identified
- 15 studies to systemic antibiotics
  - 11 in osteomyelitis

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Peters, *Diabet Metab Res Rev,* IWGDF 2016

Systematic review diabetic foot infection

- Globally no differences in outcome among antibiotic regimens/route of administration
- Used duration of antibiotics
  - Skin soft tissue infection (SSTI) 6-28 days
  - SSTI and osteomyelitis 6-28 days
- Clinical cure rates
  - SSTI 48-90%
  - SSTI and osteomyelitis 61-94%

Peters, *Diabet Metab Res Rev,* IWGDF 2016

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Table 9. Suggested empirical antibiotic regimens, based on clinical severity, for diabetic foot infections.

Route and agent(s)	Mild	Moderate/ Severe	Comments
	Oral for most	Oral or Parenteral [$]	
Dicloxacillin	Yes		Requires QID dosing; inexpensive
Clindamycin*	Yes		Usually active against community-associated MRSA, but check macrolide sensitivity and consider ordering a "D-test" before using for MRSA. A protein synthesis inhibitor against some bacterial toxins
Cephalexin*	Yes		Requires QID dosing; inexpensive
Trimethoprim-sulfamethoxazole	Yes		Active against community-associated MRSA; uncertain activity against streptococci
Amoxicillin/ clavulanate*	Yes		Relatively broad-spectrum oral agent (including anaerobes)
Levofloxacin*	Yes	Yes	Once daily dosing; suboptimal *S. aureus* activity
Cefoxitin*	---	Yes	Cephalosporin that covers most anaerobes
Ceftriaxone	---	Yes	Once daily dosing
Ampicillin/ sulbactam *	---	Yes	Adequate if low suspicion of *Pseudomonas aeruginosa*
Linezolid [a]	---	Yes	Expensive; increased risk of toxicities when used > 2 weeks Only FDA approved oral agent for cSSSI caused by MRSA
Daptomycin* [a]	---	Yes	Once daily dosing. Requires serial monitoring of creatinine kinase
Vancomycin [a]*		Yes	Vancomycin MIC "creep" for MRSA may be of concern
Moxifloxacin*	---	Yes	Once daily oral dosing. Relatively broad-spectrum, including most obligate anaerobes
Ertapenem*		Yes	Once daily dosing. Relatively broad-spectrum (including anaerobes) but not active against *Pseudomonas aeruginosa*
Tigecycline*	---	Yes	Active against MRSA. Spectrum may be excessively broad. High rates of nausea and vomiting, increased mortality warning. Non-equivalent to ertapenem +/- vancomycin in 1 RCT
Piperacillin/ tazobactam*	---	Yes	TID/QID dosing—may need infusion pump for out-of-hospital use. Useful for broad-spectrum coverage, including *Pseudomonas aeruginosa,* when appropriate
Levofloxacin or ciprofloxacin with clindamycin*	---	Yes	Limited evidence supporting clindamycin for severe *S. aureus* infections; PO and IV formulations available for all 3 agents
Imipenem-cilastatin *	---	Yes	Broad-spectrum coverage; use only when this is required Consider when suspect ESBL-producing organism.

Lipsky, *CID*, IDSA guideline 2012

Do not treat clinically uninfected wounds

- Uninfected diabetic foot ulcers
  - Amoxicillin/clavulanate and ceftriaxone not effective [1,2]
- Uninfected venous leg ulcers
  - Antibiotics not useful for heavily contaminated, clinically uninfected ulcers [3]

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1. Chantelau, *Diabet Med,* 1996;13:156-9
2. Hirschl *Chemotherapy* 1992;38:275-80
3. O'Meara S, *Cochrane Database Syst Rev* 2014;1:CD003557

Biomarkers for follow up of DFO

Table 3 Inflammatory markers at baseline and during follow-up

	Baseline ($n = 35$)	3 weeks ($n = 30$)	6 weeks ($n = 32$)	P*	P†
CRP (mg/dl)					
DFO group, mean ± SD	10·08 ± 8·62	0·46 ± 0·34	0·9 ± 1·02	0·0002	0·021
NDFO group, mean ± SD	5·44 ± 7·88	1·23 ± 1·58	0·92 ± 0·94	0·096	
ESR (mm/hours)					
DFO group, mean ± SD	78·33 ± 35·93	47·48 ± 33·18	45·23 ± 28·83	<0·0001	0·017
NDFO group, mean ± SD	58·9 ± 40·25	61·38 ± 44·31	55·5 ± 40·83	0·375	
PCT (ng/ml)					
DFO group, mean ± SD	0·26 ± 0·45	0·06 ± 0·06	0·06 ± 0·06	0·048	0·179
NDFO group, mean ± SD	0·07 ± 0·07	0·06 ± 0·04	0·05 ± 0·03	0·292	
IL-6 (pg/ml)					
DFO group, mean ± SD	14·54 ± 12·98	6·23 ± 9·36	4·35 ± 5·21	0·004	0·755
NDFO group, mean ± SD	20·91 ± 21·27	5·98 ± 7·02	8·13 ± 9·5	0·099	
IL-8 (pg/ml)					
DFO group, mean ± SD	10·15 ± 4·64	52·57 ± 201·78	15·78 ± 29·18	0·347	0·526
NDFO group, mean ± SD	9·16 ± 4·42	8·53 ± 4·71	9·34 ± 3·68	0·525	
MCP-1 (pg/ml)					
DFO group, mean ± SD	45·89 ± 27·19	52·39 ± 27·71	63·40 ± 26·22	0·002	0·092
NDFO group, mean ± SD	50·28 ± 22·49	41·10 ± 26·04	78·48 ± 70·63	0·078	

Association with outcome??

Van Asten, *Int Wound J*, 2015

Antibiotics: how and how long?

Table 4. IDSA recommendations for antibiotic route and duration [9].

Site, by severity or extent, of infection	Route of administration	Duration of therapy
Soft-tissue only		
Mild		1 – 2 weeks; may extend up to 4 weeks if slow to resolve
Moderate	Oral (or initial parenteral)	2 – 4 weeks
Severe	Initial parenteral, switch to oral when possible	2 – 4 weeks
Bone or joint		
No residual infected tissue (e.g., post-amputation)	Parenteral or oral	2 – 5 days
Residual infected soft tissue, but not bone	Parenteral or oral	2 – 4 weeks
Residual infected but viable bone	Initial parenteral, then consider oral switch	4 – 6 weeks
No surgery, or residual dead bone postoperatively	Initial parenteral, then consider oral switch	>3 months

Lipsky, *Clin Infect Dis, 2012*

Lipsky, *Diab Metab Res Rev,* 2016

Wound swabs

- Easier to perform
- Non-invasive

- Identifying anaerobes (and gram-negatives)??

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Lipsky, *Diabet Metab Res Rev*, 2016

Tissue samples

- More time-consuming
- Risk of injury to surrounding tissues

- Safe in large cohorts
- More accurate microbiological diagnosis of DFI

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Lipsky, *Diabet Metab Res Rev*, 2016

Table 3. Proportion of pathogens isolated from cultures of bone biopsy and/or swab samples obtained from 69 patients with diabetes with suspected foot osteomyelitis.

Pathogen	No. of instances in which culture yielded the specified pathogen				Concordance,[a] %
	Total	From bone biopsy sample only	From swab sample only	From both bone biopsy and swab samples	
Staphylococcus aureus	49	13	15	21	42.8
CNS	35	30	4	1	2.8
Streptococci[b]	31	11	12	8	25.8
Enterococci	15	9	5	1	6.67
Corynebacteria	10	2	8	0	0
Gram-negative bacilli	42	12	18	12	28.5
Anaerobes	9	6	3	0	0
Total	191	79	65	43	22.5

Senneville, 2006, *Clin Infect Dis*

Outcome of diabetic foot osteomyelitis

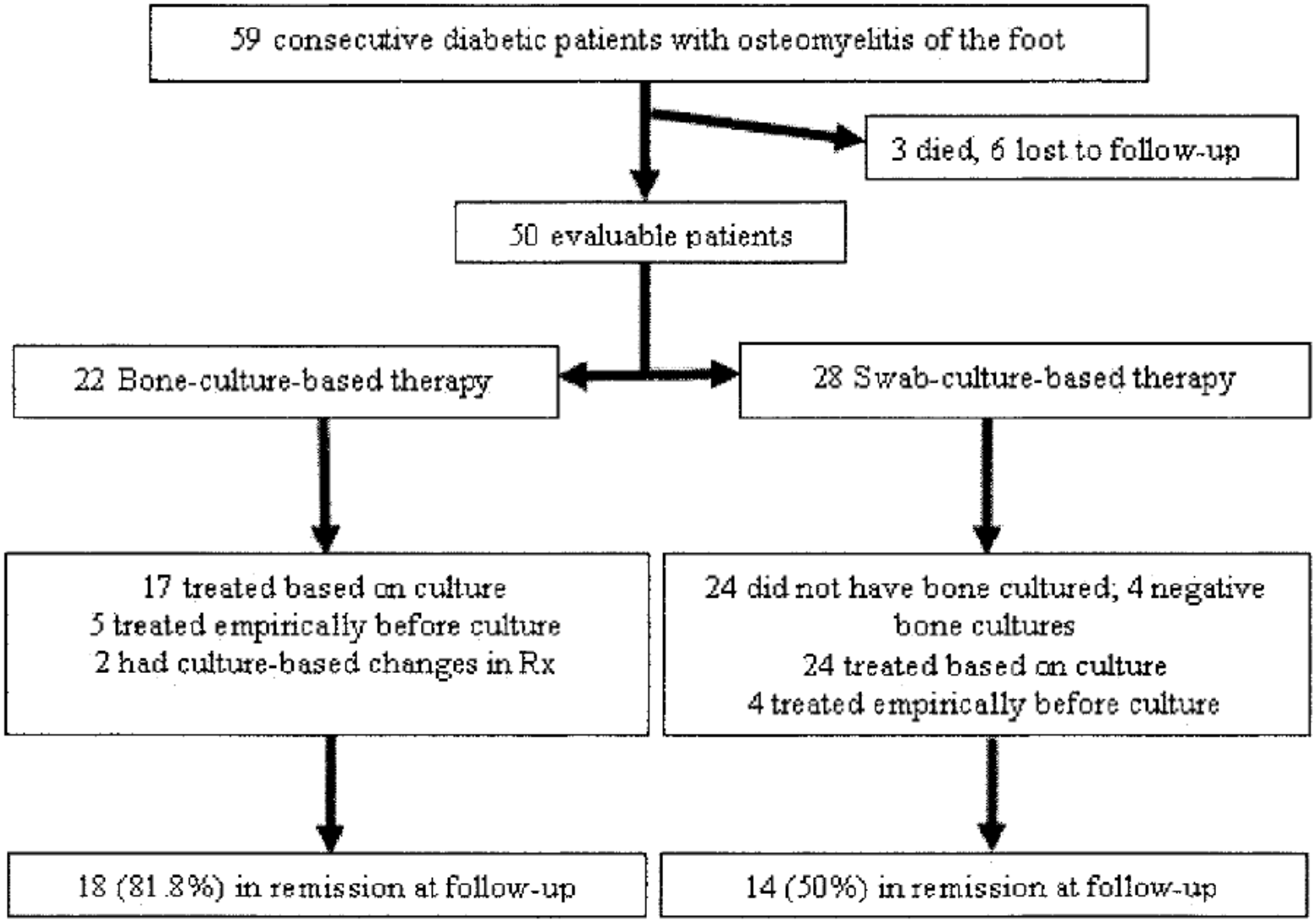

Figure 1—*Summarized data for patients' outcome.*

Senneville *CID 2008*

Treatment: myths

Do not:

- Treat uninfected ulcers to promote healing
- Treat infected ulcers until the ulcer is healed
- Treat all the organisms isolated from the microbiological specimens
- Hospitalise all infections
- Give lots of intravenous therapy

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Lipsky 2016 Diabet Metab Res Rev

Take home message

- Antimicrobial stewardship in the diabetic foot
  - Only treat infected wounds
  - Apply proper culture techniques
  - Only treat the pathogen
  - Use oral antibiotics when possible
  - Do not overuse antibiotics
  - Do not overuse antiseptics

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8th international symposium on the diabetic foot
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