Treatment of diabetic foot infections : state of the art

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FACULTE DE MEDECINE

Zurich Balgrist Nov. 2

Disclosures E. Senneville

- Has received honoraria, travel expenses and hospitality for serving as speaker and on advisory boards for Pfizer, MSD, Novartis-Pharma, Bayer, Cepheid, Diaxonhit, Shionogi, AdvanzPharma, and Menarini

- Chair of the IWGDF/IDSA subgroup on Infection (2023 guidelines)

Approach to Treating Diabetic Foot Infections : the Plan

1. Diagnose infection (clinical diagnosis ++)
   - Presence; severity; tissues involved
   - Vascular status of foot

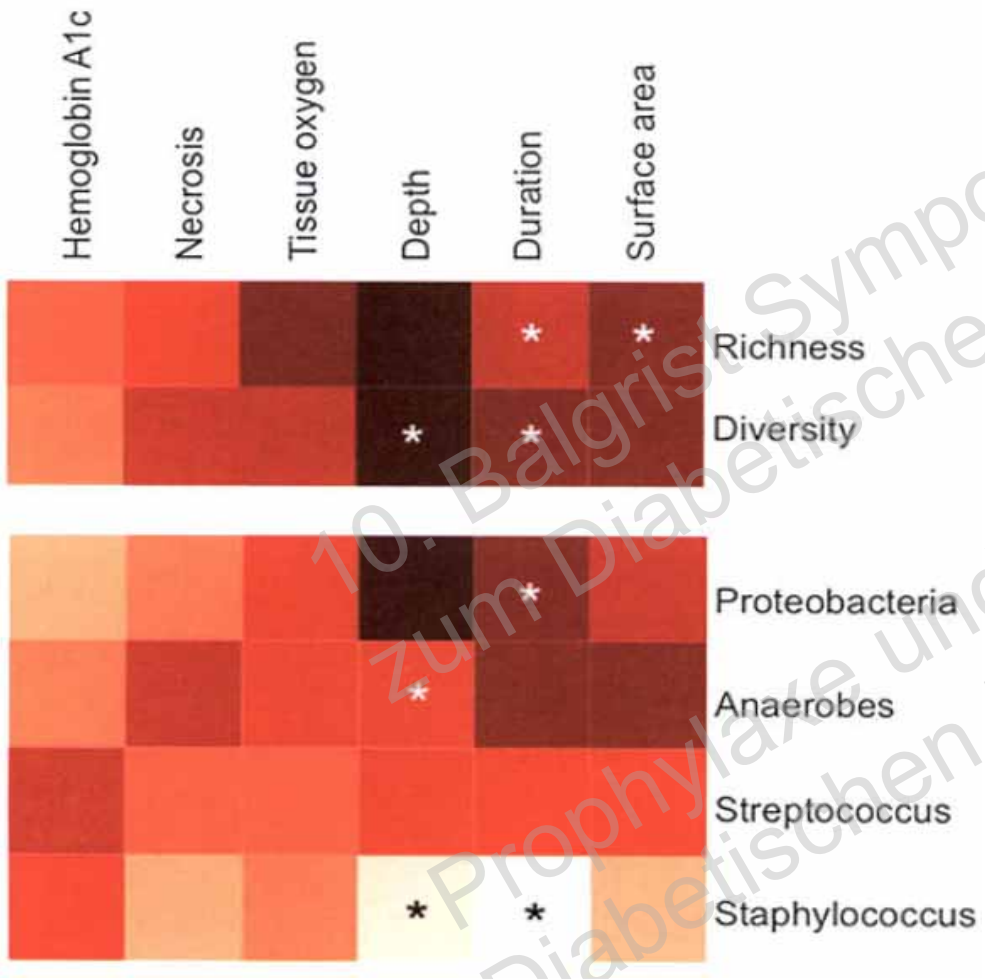
2. Obtain appropriate cultures
   - Tissue preferred
   - Bone for osteomyelitis

3. Consider need for surgery
   - Debridement; drainage; bone resection
   - Revascularization

4. Select antibiotic therapy
   - Initial, empiric
   - Definitive (culture-based)

- … and the foot ulcer (off-loading, wound nursing) ++

Neuropathic DFUs microbiome and clinical factors



Shallow and short duration:

- ↑ *S. aureus*
- ↑ streptococci
- ↓ *Anaerobes*

Deep and long duration:

- ↑ Bacterial Diversity
- ↑ Anaerobes
- ↑ *Proteobacteria*

≠

Poor Glycemic Control:

- ↑ *Staphylococcus*
- ↑ *Streptococcus*

Gardner, *Diabetes* 2013

Early surgery in severe DFIs with and without DFOs

= within 72 hours of presentation
Patients hospitalized for a severe DFI, with or without osteomyelitis

Early versus late surgery :

- less major amputation
- lower length of hospitalisation
- reduced duration of Abx
- lower death rates

Zhou S et al. Open Forum Infect Dis 2021, Lin CW et al. BMC Fam Pract 202

Antibiotic treatment options from RCTs

- Penicillins; cephalosporins; carbapenems; metronidazole (in combination with other antibiotic[s]); clindamycin; linezolid; daptomycin; fluoroquinolones; vancomycin
- Tigecycline not a preferred option

2023 IWGDF guidelines on infection

Antibiotic therapy for ST-DFIs

Tigecyline versus ertapenem

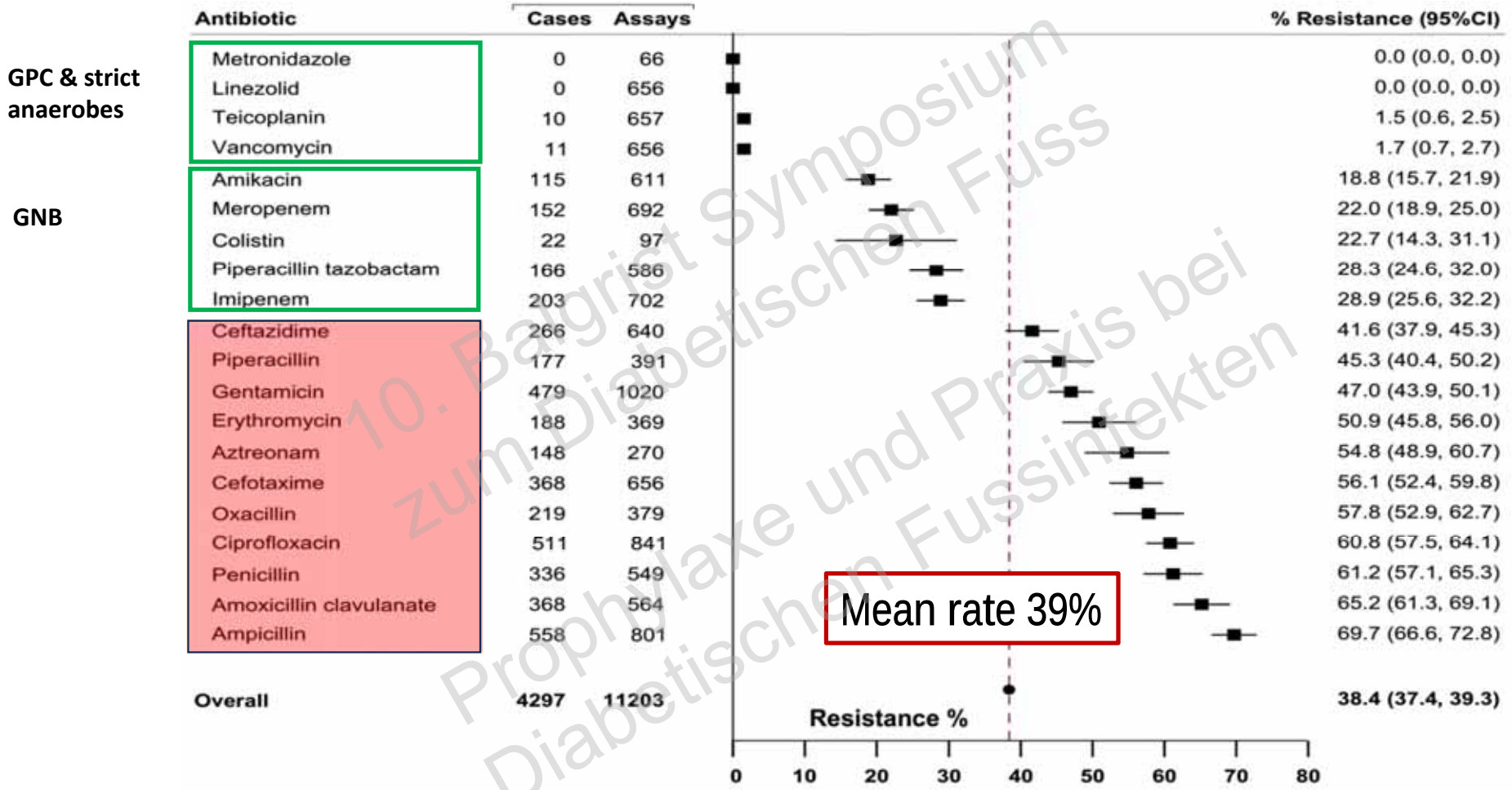
- Inferiority of tigecycline to ertapenem with or without vancomycin ST-DFIs and higher adverse events [1]

Ertapenem versus piperacillin-tazobactam

- Similar results in one RCT (SIDESTEP) study (patients admitted with moderate to severe DFIs)[2]
- Inferiority of ertapenem to piperacillin-tazobactam in patients with severe ST-DFI[3]

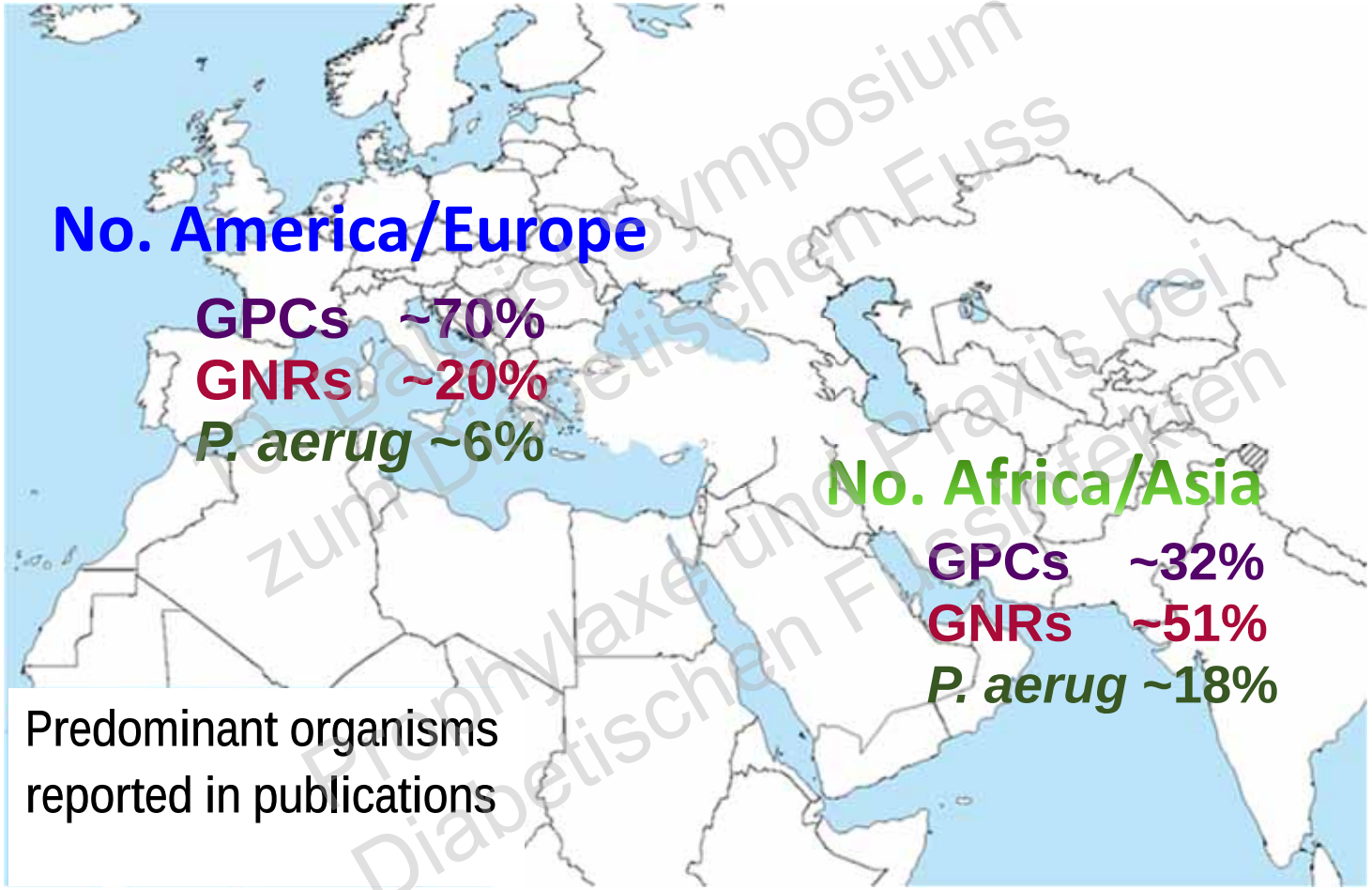
[1]Lauf L *et al.* Diagn Microbiol Infect Dis 2014; [2] Lipsky BA *et al.* Lancet 2005; [3]Xu ZR *et al*. J Antimicrob Chemother 2016

Antibiotic Resistance to DFI Pathogens: 765 Episodes in 462 Patients



Pitocco et al, *Eur Rev Med Pharmacol Sci* 2019

Microbiology of DFI in Different *Continents*



Which antibiotic for empirical Abx of ST-DFI?

	Antibiotics	Infection severity IDSA (IWGDF)	Route	Spectrum
Out patient	Flucloxacillin	Mild (2)	Oral	GPC*
	Clindamycin	Mild (2)	Oral	GPC*
	Cephalexin	Mild (2)	Oral	GPC*
In patient	Amoxicillin-clavulanic acid	Severe (3+4)	Parenteral	Gram + / -
	Piperacillin-tazobactam	Severe (3+4)	Parenteral	Gram + / -
	Pip-taz/glycopeptide +/- AG	Severe (3+4)	Parenteral	Gram + / -

- *S. aureus*; βH streptococci
- AG : aminoglycoside

Anti-Pseudomonas empirical Abx?

- PsA DFI is uncommon (9%)
- Empiric anti-Pseudomonas antibiotics in 88% of patients admitted for DFI

Veve MP *et al*. OFID 2022

In favor of empirical anti *P. aeruginosa* Abx:

- infection severity
- failing previous Abx
- immunosuppression
- local epidemiology (including warm climate countries)
- local signs ? (Uçkay I et *al.* Endocrinol Diabetes Metab 2021)

Duration antibiotic therapy for ST-DFIs

2020 systematic review : soft-tissue DFI need not be treated for longer than 2 weeks

2 retrospective cohort studies
Patients hospitalized with moderate to severe DFIs
and
Surgical debridement (81%) including amputation in 59%

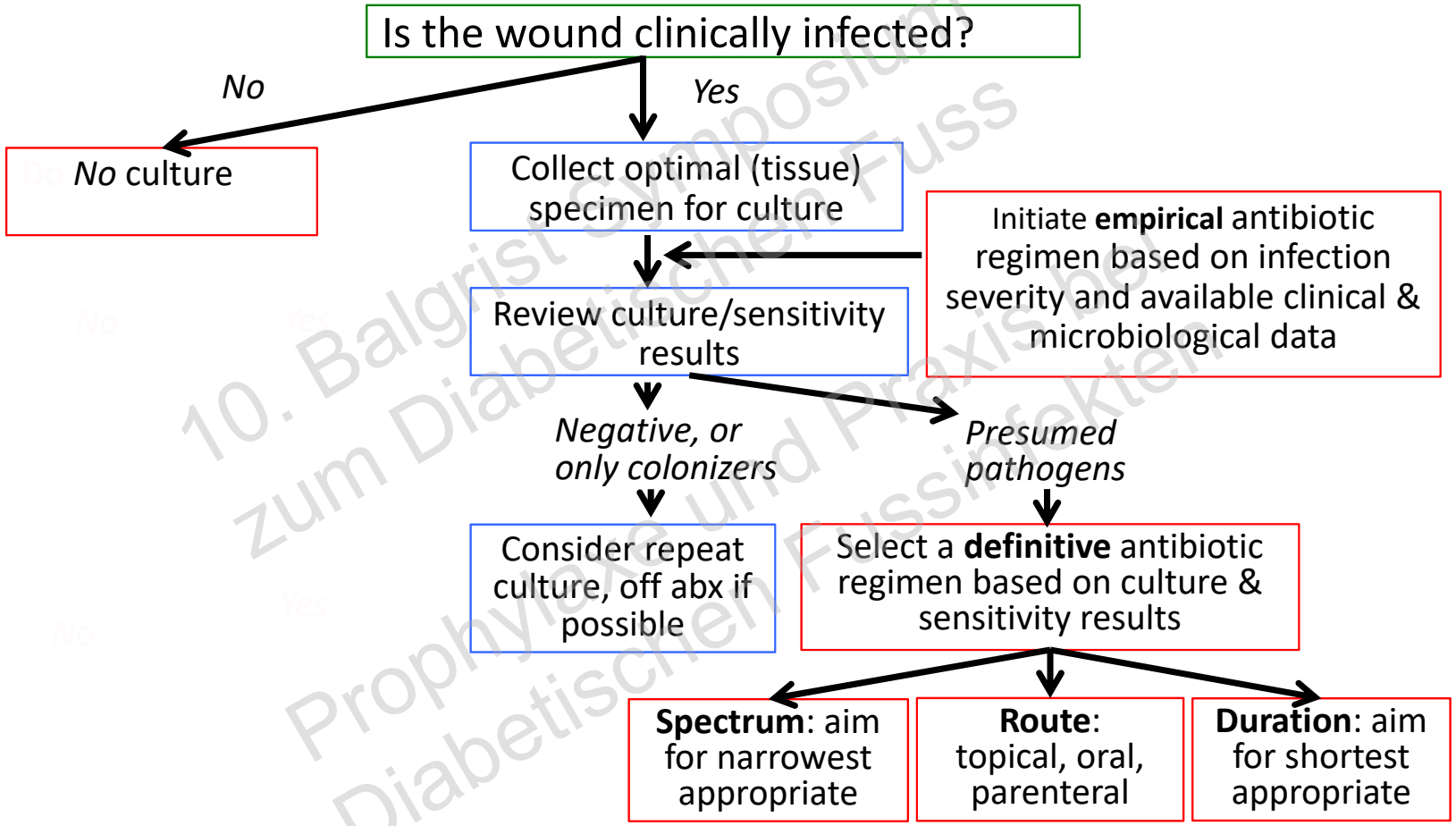
- No effect of the duration of Abx on the risk of recurrence (HR 1.0, 95% CI 0.99-1.01) with or without DFO

Prospective randomized-controlled trial (preliminary data)
Patients hospitalized with moderate or severe ST-DFIs treated *with* surgical debridement
10 vs. 20 days of Abx

- Similar results in both group (non-inferiority margin of 25%)

Gariani K et al. Diabetes Obes Metab 2019; Haug F et al. Int J Infect Dis 2022; Pham TT et al. Ann Surg 2022

Simplified Approach to Antibiotic Therapy for DFIs



Modified from Lipsky B oral com ISD, The Hague 2023

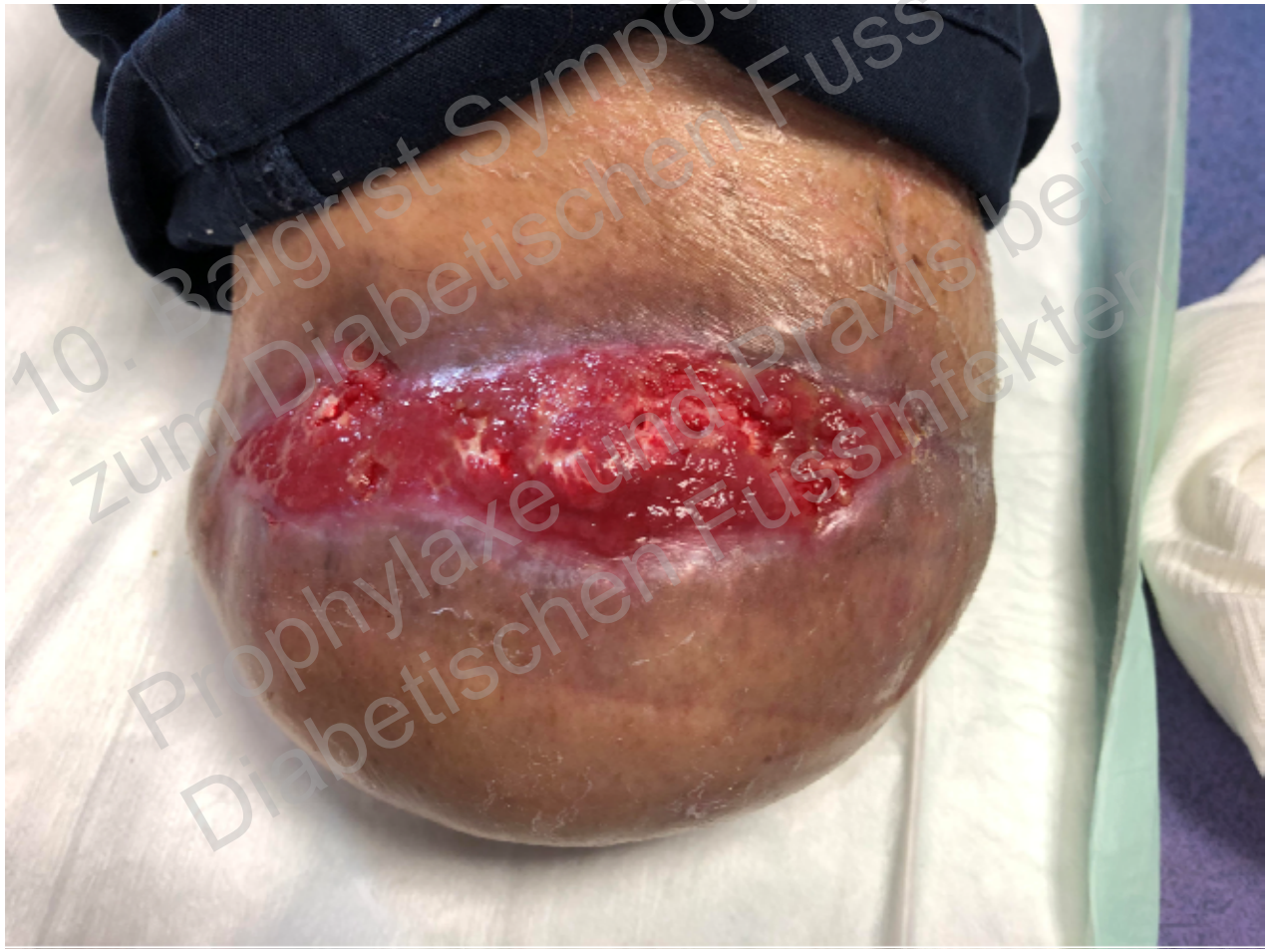
Primarily Surgical vs Medical Treatment for DF Osteomyelitis: Criteria of Choice

Medical	Surgical
▪ Pt too unstable for surgery	• Substantial bone necrosis
▪ Bad post-op mechanics likely	• Fxnly non-salvageable foot
▪ No other need for surgery	• Pt is non-ambulatory
▪ Small, forefoot lesion	• ⇧ risks antibiotic problems
▪ No skilled surgeon available	• No available active antibiotic
▪ Surgery costs prohibitive	• Uncorrectable foot ischemia
▪ Patient preference	• Patient preference

Lipsky BA. *Diabetes Care* 2014

Much easier to treat

- An osteomyelitis… without any infected bone

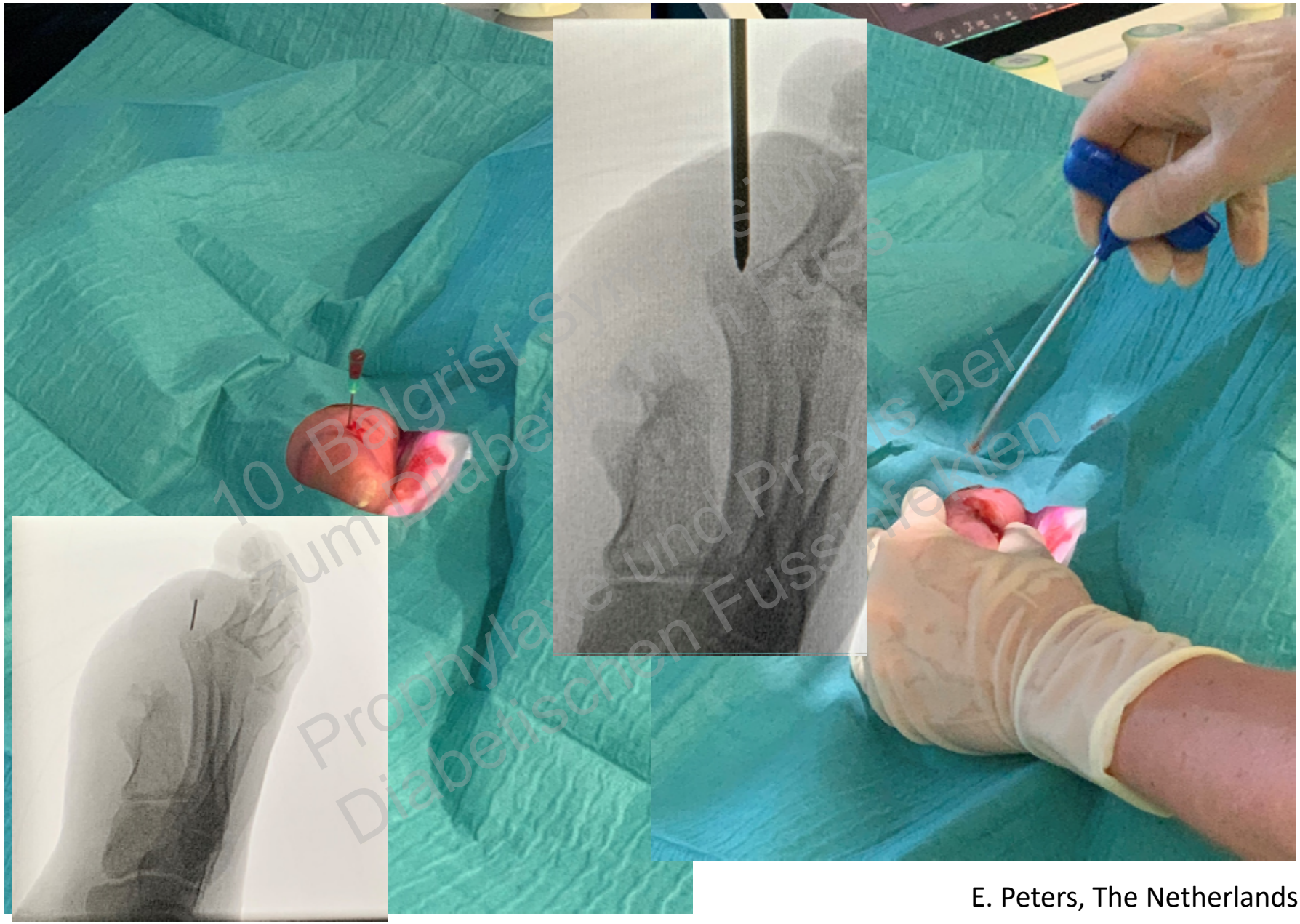


Comparison of culture results for DF Osteomyelitis

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				
	Total	From bone biopsy sample only	From swab sample only	From both bone biopsy and swab samples	Concordance,[a] %
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, *Clin Infect Dis* 2006



E. Peters, The Netherlands

Medical treatment of DF Osteomyelitis

References	N° of patients	Antibiotic therapy	Duration of treatment (weeks)	Remission (%)	Follow-up (months)
Bamberger (1987)	51	Miscellaneous	≥ 10	22 (52)	19±2
Nix (1987)	24	Ciprofloxacin	18±18	7 (29)	≤12

11 studies

424 patients

Remission rate : 29-77% (9 out of 11 studies > 60%)

		23/50 pts)			
Lazaro-Martinez (2014)	24	Miscellaneous	12	18 (75)	3 (after healing)
Tone (2015)	40	(Rifampin combinations in 26/40 pts)	6 versus 12	26 (66)	≥ 12 after the EOT
Zeun (2016)	85 (including 29 amputations)	Miscelaneous (mostly BL, cipro and metronidazole)	10	54 (63.5)	≥ 12 after the EOT

Management of a patient with osteomyelitis of the foot

- Selecting an antimicrobial agent

IDSA GUIDELINES

2012 Infectious Diseases Society of America Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infections[a]

"***No data support the superiority*** *of any specific antibiotic agent or treatment strategy, route, or duration of therapy*."

IWGDF/IDSA guidelines on the diagnosis and treatment of diabetes-related foot infections (IWGDF/IDSA 2023)

"When prescribing antibiotic therapy for DFO, the clinician must consider several issues, in particular achieving a high enough serum level to ensure ***penetration to bone****. It is particularly important to consider the* ***bioavailability for oral agents*** *(i.e., absorption from the gastrointestinal tract into the bloodstream) if that route of therapy is selected."*

Microbiology of DF Osteomyelitis

Variables	Present study	Senneville *et al.* [14]	Aragon-Sanchez *et al.* [11]
Number of samples	80	76	176
Number of isolates	129	125	204
Mean number of isolates per sample	1.6 ± 1	1.54	–
Number of culture negative samples (%)	2 (2.5%)	2[a]	20 (11%)
Number (%) of isolates, by pathogen			
Gram-positive			
Staphylococci	61 (47%)	65 (52%)	117 (57%)
Staphylococcus aureus	43 (33%)	33 (26%)	95 (47%)
MRSA	24 (19%)	12 (10%)	35 (17%)
Coagulase-negative staphylococci	18 (14%)	32 (26%)	22 (11%)
Streptococci	12 (9%)	15 (12%)	7 (3%)
Enterococci	15 (12%)	10 (8%)	2 (1%)
Corynebacteriae	5 (4%)	3 (2%)	–
Gram-negative bacilli	26 (20%)	23 (18%)	59 (29%)
Pseudomonas aeruginosa	10 (8%)	3 (2%)	18 (9%)
Anaerobes	5 (4%)	6 (5%)	–

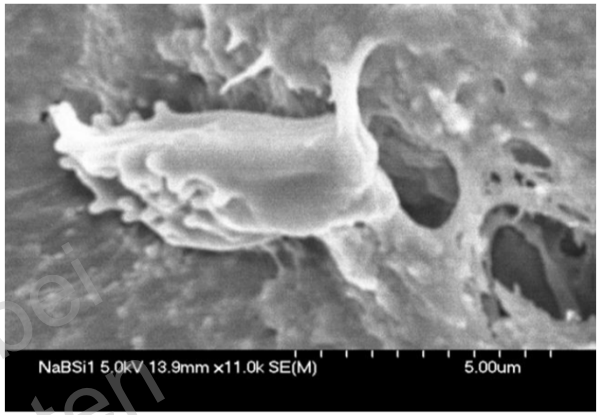
Dq| edfwhulgo vshflhv

Lesens O *et al.* CMI 2012

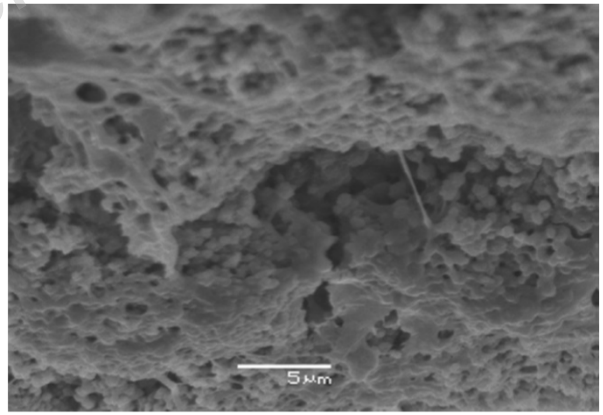
Most DF Osteomyelitis are biofilm-related infections

Presence of biofilm in bone samples taken from patients with DFOs in ≈ 75% of cases

- Bacteria present in bone tissue and the intracellular position (osteoblasts-osteocytes)
- Reduced bacterial metabolism intracellular in the biofilm
- Glycoprotein matrix
- Local immunosuppression
- Specific environment (pH, PpO2, protein concentration, ...)



Baudoux F *et al.* Diab & Metabol 2012



Johani K *et al.* Clin Microb Inf 2018

Antibiotics for DF Osteomyelitis treatment medically

Widely available

- Aminoglycoside
- beta-lactams,
- fusidic acid,
- glycopeptide,
- lincosamides,
- macrolides,
- nitro-imidazole,
- oxazolidinones,
- polymyxin,
- quinolones,
- rifamycins,
- sulfonamides,
- tetracyclines

High oral bioavailability

- Aminoglycoside
- beta-lactams,
- fusidic acid,
- glycopeptide,
- lincosamides,
- macrolides,
- nitro-imidazole,
- oxazolidinones,
- polymyxin,
- quinolones,
- rifamycins,
- sulfonamides,
- tetracyclines

High bone diffusion

- Aminoglycoside
- beta-lactams,
- fusidic acid,
- glycopeptide,
- lincosamides,
- macrolides,
- nitro-imidazole,
- oxazolidinones,
- polymyxin,
- quinolones,
- rifamycins,
- sulfonamides,
- tetracyclines

Efficacy in biofilm

- Aminoglycoside
- beta-lactams,
- fusidic acid,
- glycopeptide,
- lincosamides,
- macrolides,
- metronidazole,
- oxazolidinones,
- polymyxin,
- quinolones,
- rifamycins,
- sulfonamides,
- tetracyclines

Fosfomycin IV
Daptomycin
Oritavancin
Dalbavancin?

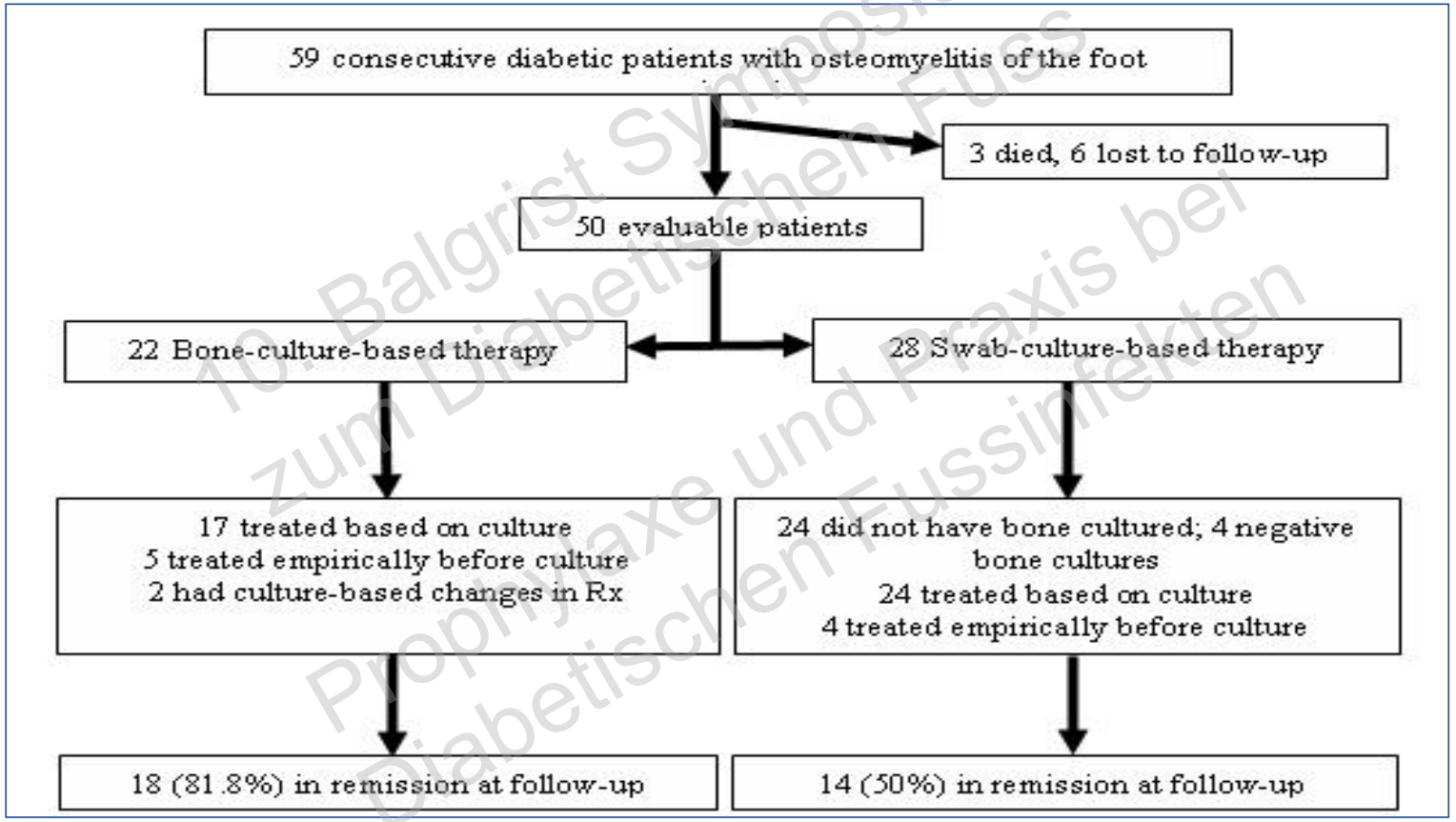
Antibiotic therapy of chronic osteomyelitis

Table 1 Antibiotic treatment of chronic implant-free osteomyelitis (concomitant to surgery if no surgical removal *in toto*; personal suggestions)

Parenteral treatment				Oral treatment		
	Antibiotic	Alternatives	Duration	Antibiotic	Alternatives	Duration[p]
Methicillin-resistant staphylococci	Vancomycin[a]	Teicoplanin[c]	0–2 weeks	Fusidic acid[g] + rifampin[b]	Ciprofloxacin[h] + rifampin[b]	6–12 weeks
		Daptomycin[n]	0–2 weeks		Levofloxacin[i] + rifampin[b]	6–12 weeks
		Tigecycline[d]	0–2 weeks		Doxycyclin[k] + rifampin[b]	6–12 weeks
		Linezolid[e]	0–2 weeks		Minocyclin[l] + rifampin[b]	6–12 weeks
		Ceftobripole[f]	0–2 weeks		Cotrimoxazol[m] + rifampin[b]	6–12 weeks
Methicillin-sensitive staphylococci and other Gram-positives	Cephalosporins of 1st or 2nd generation,	Vancomycin[a]	0–2 weeks	Clindamycine[p]	Ciprofloxacin[h] + rifampin[b]	6–12 weeks
		Daptomycin[n]	0–2 weeks		Levofloxacin[i] (+ rifampin[b])	6–12 weeks
		Penicillins	0–2 weeks		Cotrimoxazole[m] + rifampin[b]	6–12 weeks
Gram-negatives	Ceftriaxon	Ceftriaxone	0–2 weeks		Ciprofloxacin[h]	6–12 weeks
		Ceftazidime	0–2 weeks		Levofloxacin[i]	6–12 weeks
		Cefepime	0–2 weeks			
Anaerobes	Amoxicillin-clavulanate	Carbapenems	0–2 weeks	Metronidazole[q]	Clindamycine[p]	6–12 weeks

Uckay I *et al*. Curr Infect Dis Resp 2012

Bone culture-based Abx using Rifampin or F-quinolone combinations: impact on the outcome



Senneville E *et al*. Diabetes Care 2008

Gramberg *et al. Trials* (2021) 22:517
https://doi.org/10.1186/s13063-021-05472-6

Trials

STUDY PROTOCOL Open Access

Using a BonE BiOPsy (BeBoP) to determine the causative agent in persons with diabetes and foot osteomyelitis: study protocol for a multicentre, randomised controlled trial

Outcomes of patients treated with and without adjunctive rifampicin (RIF) for DFO

- 463#sdwlhqw#wuhdwhg#zlwk#UII#yv1#9377#zlwkrxw#UII#
- Orz hu#hyhq w#udwhv#lq#wkh#UII#jurxs#591<(#yv#6:15(#*S*@135,
- UII#sdwlhqw##
  - |rxqjhu#phdq#djh/#9515#yv#971<#|hduv,
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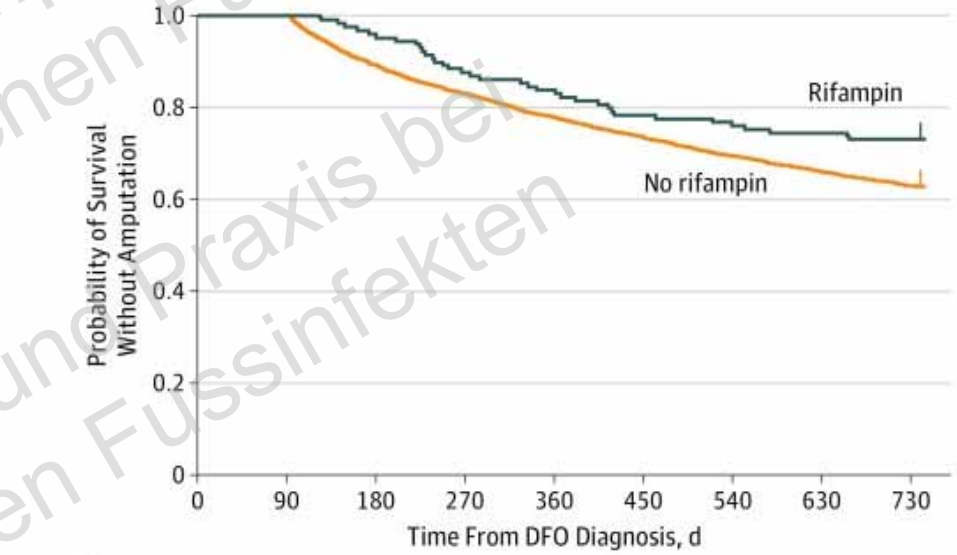
  - pruh#G#vshfldo|#frqvxowdwlrqv#7;18(#yv#6517(,
  - pruh#riwq#kdg *V#dxuhxv* +7516(#yv#5<13(,
- Orjlwdf#uhjuhvvlrq#vljqlilfdqw#dvvrfldwlrq#ri#uldp slq#+rggv#udwlr/#3198#<8(#FL/3176031<9>*S*@137,



Wilson BM *et al.* JAMA Netw Open 2019

Bessesen *et al. BMC Infectious Diseases* (2020) 20:23
https://doi.org/10.1186/s12879-019-4751-3

BMC Infectious Diseases

STUDY PROTOCOL Open Access

A multicenter randomized placebo controlled trial of rifampin to reduce pedal amputations for osteomyelitis in veterans with diabetes (VA INTREPID)

Mary T. Bessesen[1,2], Gheorghe Doros[3,4], Adam M. Henrie[5], Kelly M. Harrington[3,6], John A. Hermos[3,7], Robert A. Bonomo[8,9], Ryan E. Ferguson[3,10], Grant D. Huang[11] and Sheldon T. Brown[12,13*]

Investigation of Rifampin to Reduce Pedal Amputations for Osteomyelitis in Diabetics (VA INTREPID)
ClinicalTrials.gov NCT03012529

Which route?

Oviva study

Li et al. Trials (2015) 16:583
DOI 10.1186/s13063-015-1098-y

Trials

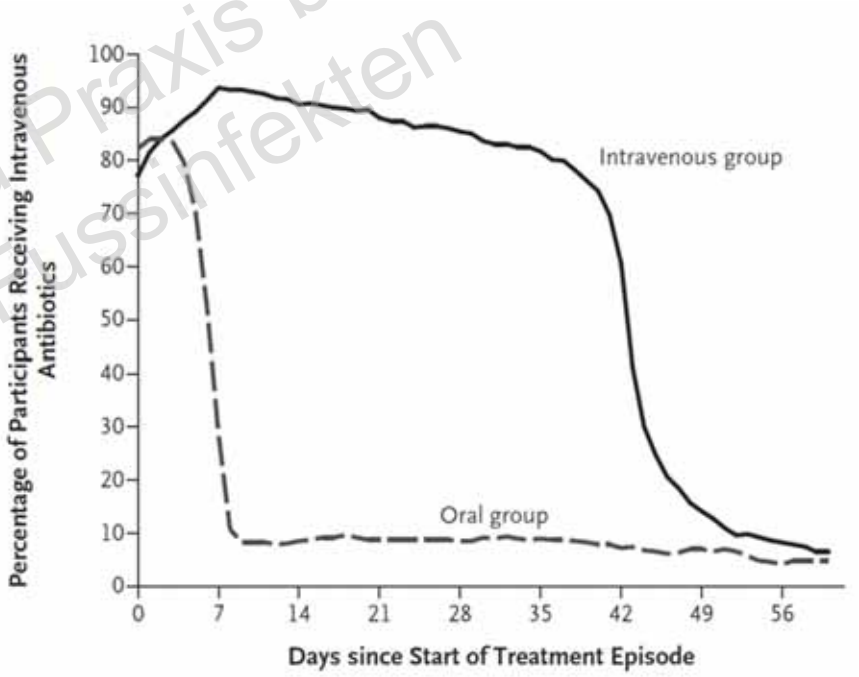
STUDY PROTOCOL Open Access

Oral versus intravenous antibiotic treatment for bone and joint infections (OVIVA): study protocol for a randomised controlled trial

Ho Kwong Li[1*], Matthew Scarborough[2], Rhea Zambellas[3], Cushla Cooper[3], Ines Rombach[3], A. Sarah Walker[4], Benjamin A. Lipsky[5], Andrew Briggs[6], Andrew Seaton[7], Bridget Atkins[2], Andrew Woodhouse[8], Anthony Berendt[2], Ivor Byren[2], Brian Angus[1], Hemant Pandit[2], David Stubbs[2], Martin McNally[2], Guy Thwaites[9] and Philip Bejon[10]

Results:
1054 randomized participants (527/arm)
Endpoint achieved for 1015 (96.30%)
Failures = 141/1015 (13.89%):
- 74/506 (14.62%) intravenous
- 67/509 (13.16%) oral

ITT analysis: risk of failure attributed to IV/PO difference = −1.38% (90% CI: −4.94, 2.19), non-inferiority criterion achieved (95%CI <7.5%)



Li HK *et al*. N Engl J Med 2019

Intravenous antibiotic therapy for DF Osteomyelitis

- Retrospective cohort of 1018 DFI episodes in 482 patients including 392 episodes of DFO
- Total population : surgical debridement for 824 episodes (81%), of which 596 (59%) required amputation
- Patients with total amputations were excluded
- Median follow-up of 3 years

	Osteomyelitis Single episode n = 304	P*	n = 392 Subsequent episodes n = 88
Lower extremity amputation: partial, n (%)	240 (79)	0.001	53 (60%)
Median duration intravenous antibiotic therapy, days	4	0.998	4 days
>7 days compared with ≤7 days, n (%)	185 (61)	0.637	56 (64%)

Gariani K *et al.* Diabetes Obes Metab 2018

Which route?

Six-Week Versus Twelve-Week Antibiotic Therapy for Nonsurgically Treated Diabetic Foot Osteomyelitis: A Multicenter Open-Label Controlled Randomized Study

Alina Tone,[1] Sophie Nguyen,[1] Fabrice Devemy,[2] Hélène Topolinski,[3] Michel Valette,[1] Marie Cazaubiel,[4] Armelle Fayard,[5] Éric Beltrand,[6] Christine Lemaire,[3] and Éric Senneville[1]

Diabetes Care 2015;38:302–307 | DOI: 10.2337/dc14-1514

- Antibiotics were administered **either orally for the entire treatment period or intravenously for a short period (5 to 7 days)** followed by a long course of oral antimicrobial therapy
- We did not identify any significant parameters associated with patient outcome.

Tone A *et al.* Diab Care 2016

IV or Oral Abx for DF Osteomyelitis ?

Regimen	Number of episodes of osteomyelitis (%)					
	Total	Remission	Healing†	Static	Relapse	Amputation
Oral alone	64	53*	5	1	2	3
Oral + intravenous*	29	22**	1	0	0	6
Total	93 (100%)	75 (80.5%)	6 (6.5%)	1 (1%)	2 (2%)	9 (10%)

* (82.3%)

**(75.7%)

Embil J *et al.* Foot & Ankle Int 2006

Duration of antibiotic therapy for DFO after bone resection

3 versus 6 weeks of systemic Abx (prospective, randomized, non-inferiority, pilot trial)
median number of surgical debridement = 1

- similar remission rates and Abx-related adverse events

DFIs including DFO after amputation (retrospective study)
entire intravenous antibiotic course vs. oral or discontinued immediately after the intervention
Failure rates:

- no effect of the total duration of post-amputation Abx
- similar results in case of an immediate postoperative discontinuation of Abx

Gariani K *et al.* Clin Infect Dis 2021; Gill AS et al. J Foot Ankle Surg 2022

Duration Antibiotic Therapy By Clinical Situation

Infection Severity (skin & soft tissues)	Route	Duration
- Class 2: Mild	Oral	1-2 weeks*
- Class 3 / 4: Moderate / Severe	Oral / Initially IV	2-4 weeks
Bone/joint	**Route**	**Duration**
- Resected	Oral / Initially IV	2-5 days
- Debrided (soft tissue infection)	Oral / Initially IV	1-2 weeks
- Culture + bone margin after resection	Oral / Initially IV	3 weeks
- No surgery, or dead bone	Oral / Initially IV	6 weeks

*10 days following surgical debridement

Senneville et al. IWGDF Infection Guideline 2023; DMMR 2023; CID 2023

Intra-Osseus Local Antimicrobial

- Carriers : polymethylmethacrylate, calcium sulfate/hydroxyapatite
- Beads, spacers or cement, powder application
- Aims :
  - treat bone infection
  - fill dead space
  - prevent recurrent infection
- Requirements :
  - be biocompatible and thermoresistant
  - minimal toxicity (osteointegration)
  - prolonged (local) drug release
  - antibiotic agents : gentamicin, tobramycin, or vancomycin
- Efficacy
  - overall : little high-quality evidence (resolution and prevention of recurrence)

Evaluating Antibiotic Therapy for Treating DFIs

- Retrospective cohort study DFI patients in Indonesia
- 113 subjects assessed; 54% received “appropriate” antibiotic therapy
- Main outcome: clinical improvement infection after 1-2 wks therapy
- Appropriate (vs inappropriate) therapy group:
  - Higher proportion clinically improved (61% vs 42%, p=0.08)
  - Multivariate analysis: 2.6 X more likely to clinically improve (p=0.03)

Aviatin *et al.* Infect Chemother 2023

Treatment of DFI/DFO?

- Infection is a clinical diagnosis
- Culture and Gram stain
  - Do not diagnose infection by positive culture
  - Send tissue to the lab, not swabs
  - Know your local resistance profile
- Do not treat uninfected ulcers with (local or systemic) antibiotics
- Do not *systematically* use broad-spectrum antibiotics
- **Do not neglect (urgent) surgery (debridement, revascularisation)**
- Urgent surgery does not mean AMPUTATION !!!

Special thanks to and respect for:

Pr Benjamin Lipsky (Seattle, USA)

Dr Anthony Berendt (Oxford, UK)

Thank you!