

Diabetic foot infections

Antibiotic treatment - knowledge and open questions

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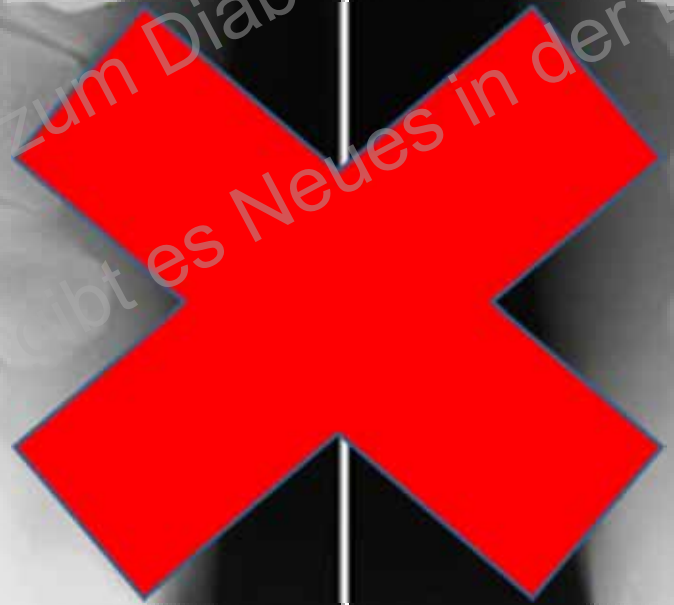
8. Balgrist Symposium
zum Diabetischen Fuss:
Was gibt es Neues in der Behandlung?

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8. Baltzrist Symposium

zum Diabetischen Fuss:
Was gibt es Neues in der Behandlung?





Non-surgical treatment of diabetic foot osteomyelitis

Mesut Mutluoglu, Benjamin A Lipsky

Lancet Diabetes Endocrinol 2017; 5: 668

A 68-year-old man with well controlled type 2 diabetes presented to the GATA Haydarpasa Teaching Hospital suggestive of relapse of infection and CRP concentration (4.2 mg/L) and ESR (8 mm/h) were normal.

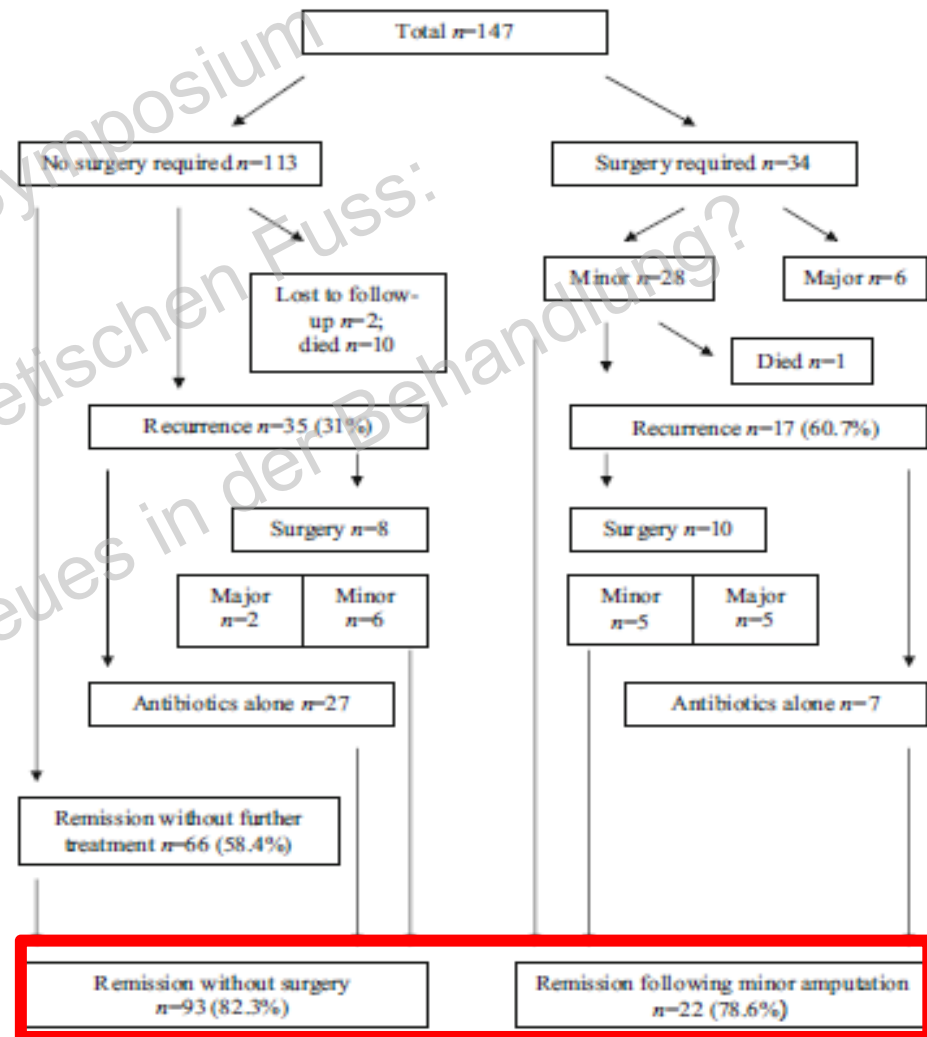


Example from Geneva – 1 year patience



Primarily non-surgical management of osteomyelitis of the foot in diabetes

E. L. Game · W. J. Jeffcoate





Antibiotics Versus Conservative Surgery for Treating Diabetic Foot Osteomyelitis: A Randomized Comparative Trial

José Luis Lázaro-Martínez,¹ Javier Aragón-Sánchez,² and Esther García-Morales¹

RESULTS

Eighteen patients (75%) achieved primary healing in the AG, and 19 (86.3%) in the SG ($P = 0.33$). The median time to healing was 7 weeks (quartile [Q] 1 to Q5, Q3–Q8) in the AG and 6 weeks (Q1–Q3, Q3–Q9) in the SG ($P = 0.72$). The conditions of four patients from the AG worsened (16.6%), and they underwent surgery.

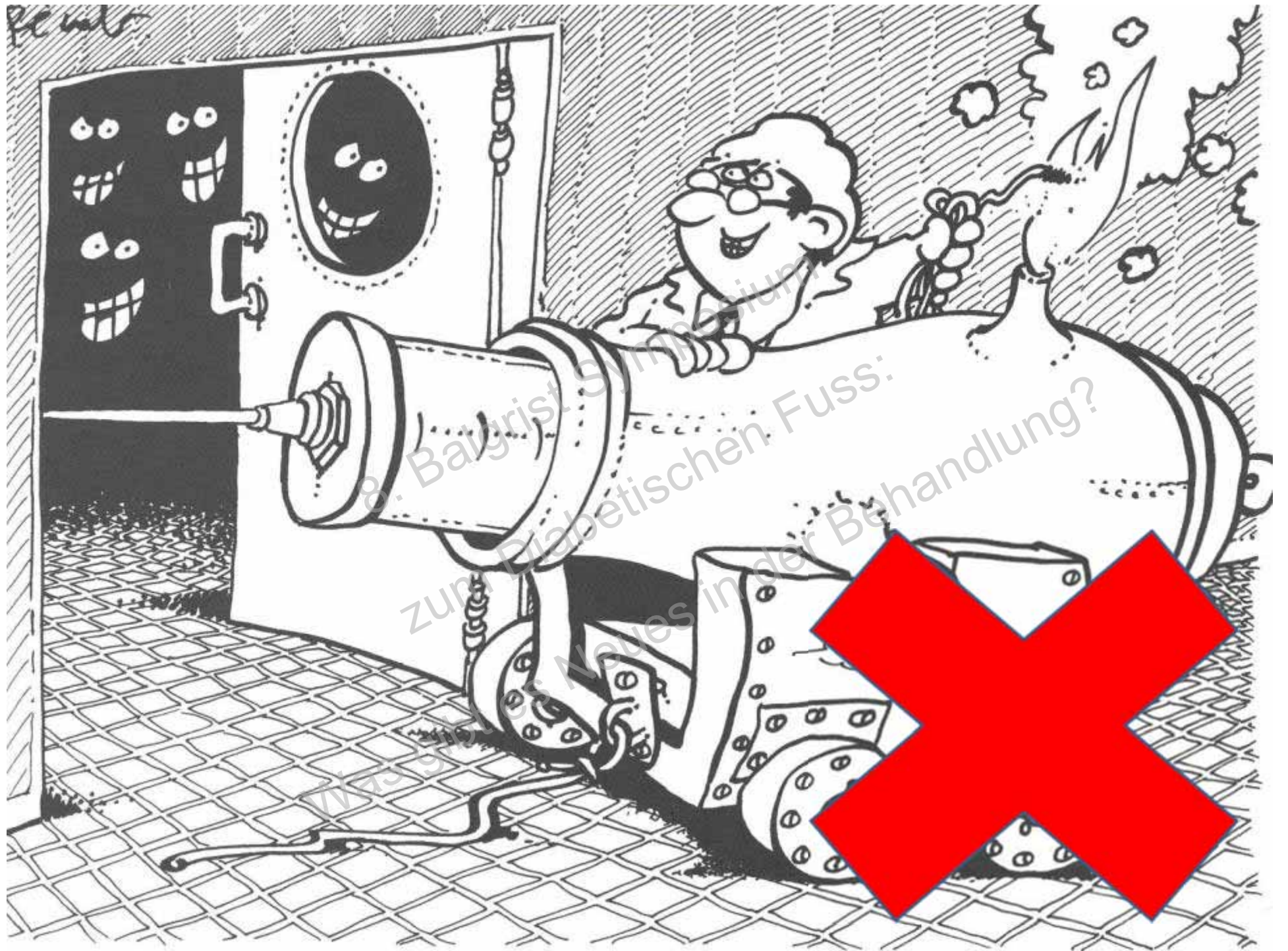
Three patients from the SG required reoperation. No difference was found between the two groups regarding minor amputations ($P = 0.336$).

- Antibiotic therapy –
what we know



Table 7. Studies of Antibiotic Therapy for Diabetic Foot Infections Published Since 2004 (and Not Included in Previous Version of This Guideline)

Antibiotic Agent(s) (Route)	Patients Treated, No.	Study Design	Patient Group	Type/Severity of Infection	Reference
Metronidazole + ceftriaxone vs ticarcillin/clavulanate (IV)	70	Prospective open label	H	Older men, Wagner grades 1–3	Clay 2004 [150]
Ceftobiprole vs vancomycin + ceftazidime (IV)	828	RCDBT DFI subgroup	H	cSSSI	Deresinski 2008 [147]
Piperacillin/tazobactam vs ampicillin/sulbactam (IV)	314	Prospective open label	H	Moderate/severe infected DFU	Harkless 2005 [149]
Daptomycin vs vancomycin or Semisynthetic penicillin (IV)	133	RCSBT DFI subgroup	H	Gram + DFI	Lipsky 2005 [155]
Ertapenem vs piperacillin/tazobactam (IV)	586	RCDBT	H	Moderate/severe DFI	Lipsky 2005 [120]
Moxifloxacin (IV to PO) vs piperacillin/tazobactam (IV) to amoxicillin/clavulanate (PO)	78	RCDBT DFI subgroup	H	cSSSI, including DFI (not classified)	Lipsky 2007 [148]
Pexiganan (topical) vs ofloxacin (PO)	835	2 RCDBTs	O	Mildly infected DFU	Lipsky 2008 [114]
Ceftriaxone vs fluoroquinolone (IV)	180	Prospective open label	H	“Severe limb-threatening” DFI	Lobmann 2004 [151]
Moxifloxacin vs amoxicillin/clavulanate (IV to PO)	804	Prospective open label	H	cSSSI, including DFI	Vick-Fragoso 2009 [152]
Tigecycline vs ertapenem (IV)	944	RDBCT	H	Qualifying DFI± osteomyelitis	Clinicaltrials.gov 2010 [158]
Piperacillin/tazobactam vs imipenem/cilastatin (IV)	62	RCT open-label	H	Severe DFI, including osteomyelitis	Saltoglu 2010 [157]



Antibiotic therapy – what we know

IDSA GUIDELINES

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

Benjamin A. Lipsky,¹ Anthony R. Berendt,² Paul B. Cornia,³ James C. Pile,⁴ Edgar J. G. Peters,⁵ David G. Armstrong,⁶
H. Gunner Deery,⁷ John M. Embil,⁸ Warren S. Joseph,⁹ Adolf W. Karchmer,¹⁰ Michael S. Pinzur,¹¹ and Eric Senneville¹²

¹Department of Medicine, University of Washington, Veterans Affairs Puget Sound Health Care System, Seattle; ²Bone Infection Unit, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Trust, Oxford; ³Department of Medicine, University of Washington, Veteran Affairs Puget Sound Health Care System, Seattle; ⁴Divisions of Hospital Medicine and Infectious Diseases, MetroHealth Medical Center, Cleveland, Ohio; ⁵Department of Internal Medicine, VU University Medical Center, Amsterdam, The Netherlands; ⁶Southern Arizona Limb Salvage Alliance, Department of Surgery, University of Arizona, Tucson; ⁷Northern Michigan Infectious Diseases, Petoskey; ⁸Department of Medicine, University of Manitoba, Winnipeg, Canada; ⁹Division of Podiatric Surgery, Department of Surgery, Roxborough Memorial Hospital, Philadelphia, Pennsylvania; ¹⁰Department of Medicine, Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; ¹¹Department of Orthopaedic Surgery and Rehabilitation, Loyola University Medical Center, Maywood, Illinois; and ¹²Department of Infectious Diseases, Dron Hospital, Tourcoing, France

Clinical Infectious Diseases 2012;54(12):132–173

Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2012.

DOI: 10.1093/cid/cis346

Table 8. Suggested empirical antibiotic regimens, based on clinical severity, for diabetic foot infections.

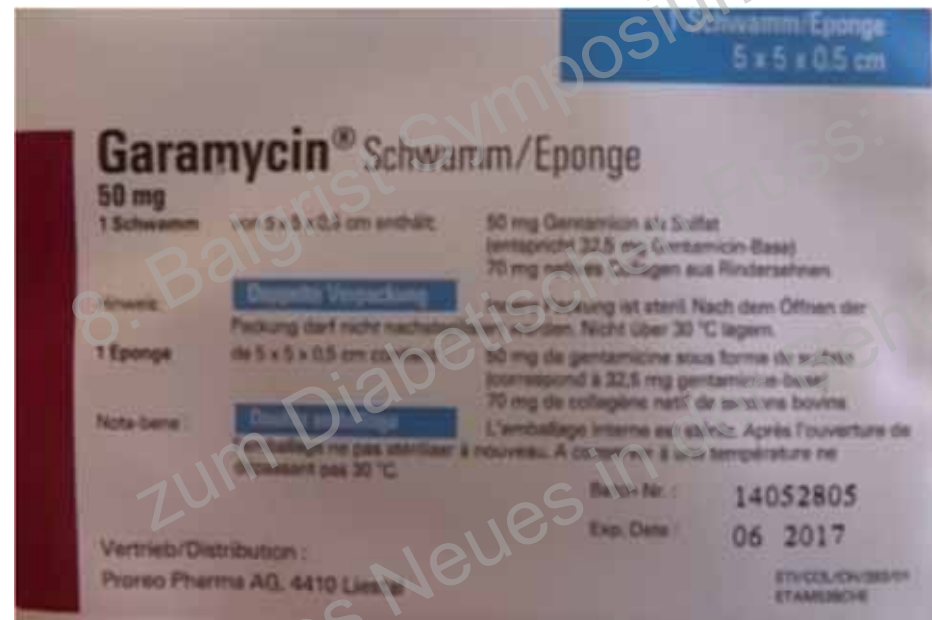
Route and agent(s)	Mild	Moderate	Severe
Advised route	Oral for most	Oral or parenteral, based on clinical situation and agent(s) selected	Intravenous, at least initially
Dicloxacillin	Yes
Clindamycin	Yes
Cephalexin	Yes
Trimethoprim-sulfamethoxazole	Yes	Yes	...
Amoxicillin/clavulanate	Yes	Yes	...
Levofloxacin	Yes	Yes	...
Cefoxitin	...	Yes	...
Ceftriaxone	...	Yes	...
Ampicillin/sulbactam	...	Yes	...
Linezolid ^a (with or without aztreonam)	...	Yes	...
Daptomycin ^a (with or without aztreonam)	...	Yes	...
Ertapenem	...	Yes	...
Cefuroxime with or without metronidazole	...	Yes	...
Ticarcillin/clavulanate	...	Yes	...
Piperacillin/tazobactam	...	Yes	Yes
Levofloxacin or ciprofloxacin with clindamycin	...	Yes	Yes
Imipenem-cilastatin	Yes
Vancomycin ^a and ceftazidime (with or without metronidazole)



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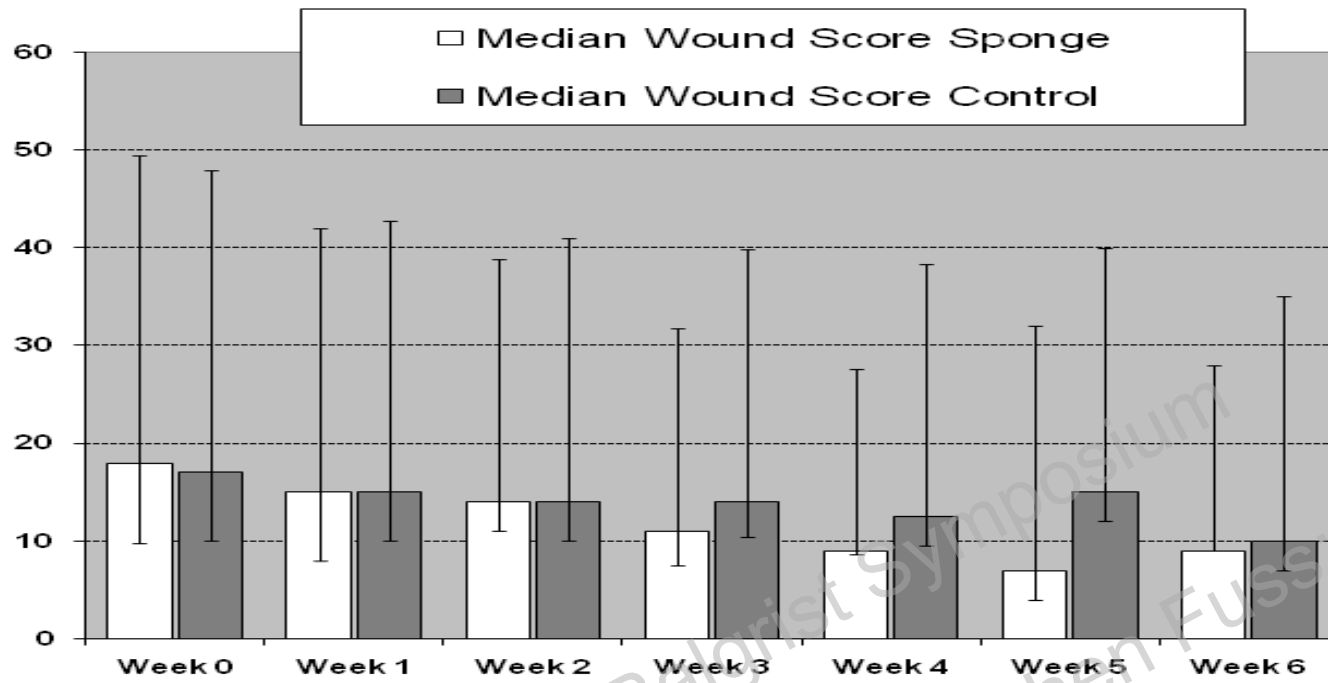
Putting the sponge on the wound

Efficacy and Safety of a Topical Gentamicin-Collagen Sponge (GCS) in Combination with Systemic Antibiotic Therapy for Moderate or Severe Diabetic Foot Ulcer Infection (DFUI): A Randomized, Controlled Study



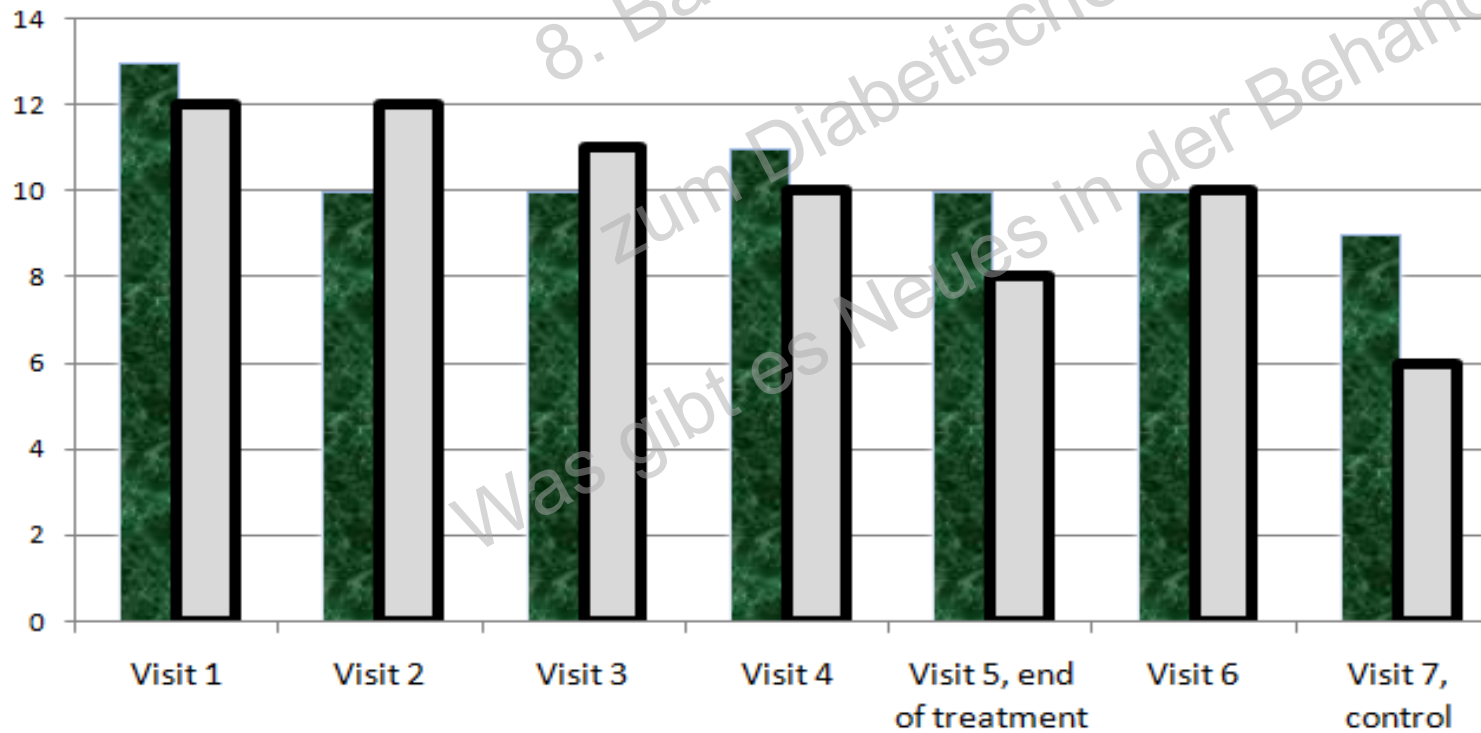
Ilker Uçkay, Benjamin Kressmann, Sarah Malacarne, Anna Toumanova, Jaafar Jaafar, Daniel Lew, Benjamin A. Lipsky

ClinicalTrials.gov (NCT01951768)



Above:
With systemic antibiotics

Beneath:
Without systemic antibiotics



■ Gentamicin sponge

□ no sponge

Article: Clinical Practice

Does osteomyelitis in the feet of patients with diabetes really recur after surgical treatment? Natural history of a surgical series

J. Aragón-Sánchez¹, J.L. Lázaro-Martínez², C. Hernández-Herrero³, N. Campillo-Vilorio⁴, Y. Quintana-Marrero¹, E. García-Morales² and M.J. Hernández-Herrero¹

¹Diabetic Foot Unit, La Paloma Hospital, Las Palmas de Gran Canaria, ²Diabetic Foot Unit, Complutense University Clinic, Madrid ³Endocrinology Department, University Macarena Hospital, Seville, Spain and ⁴Diabetic Foot Unit, Diabetology Department, Plaza de la Salud General Hospital, Dominican Republic

64 patients: median duration of follow-up was 101.8 weeks

- Recurrence 4.6%
- Re-ulceration 43.0%
- New osteomyelitis 16.9%



Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Are antibiotic-resistant pathogens more common in subsequent episodes of diabetic foot infection?



Dan Lebowitz^{a,b,1}, Karim Gariani^{b,c,1}, Benjamin Kressmann^{b,d}, Elodie von Dach^e, Benedikt Huttner^{b,e}, Placido Bartolone^d, Nam Lê^d, Morad Mohammad^d, Benjamin A. Lipsky^{b,f}, Ilker Uçkay^{b,d,e,*}

Table 1

Rates of antibiotic resistance according to the increasing number of episodes of diabetic foot infection.

All pathogens causing DFI, by episode			p-Value ^a
Episode 1	Episode 2	Episode 3	
49%	23%	14%	0.21
53%	25%	11%	0.08
54%	23%	8%	0.38
46%	23%	17%	0.27

DFI, diabetic foot infection.

^a p-Value for trend.

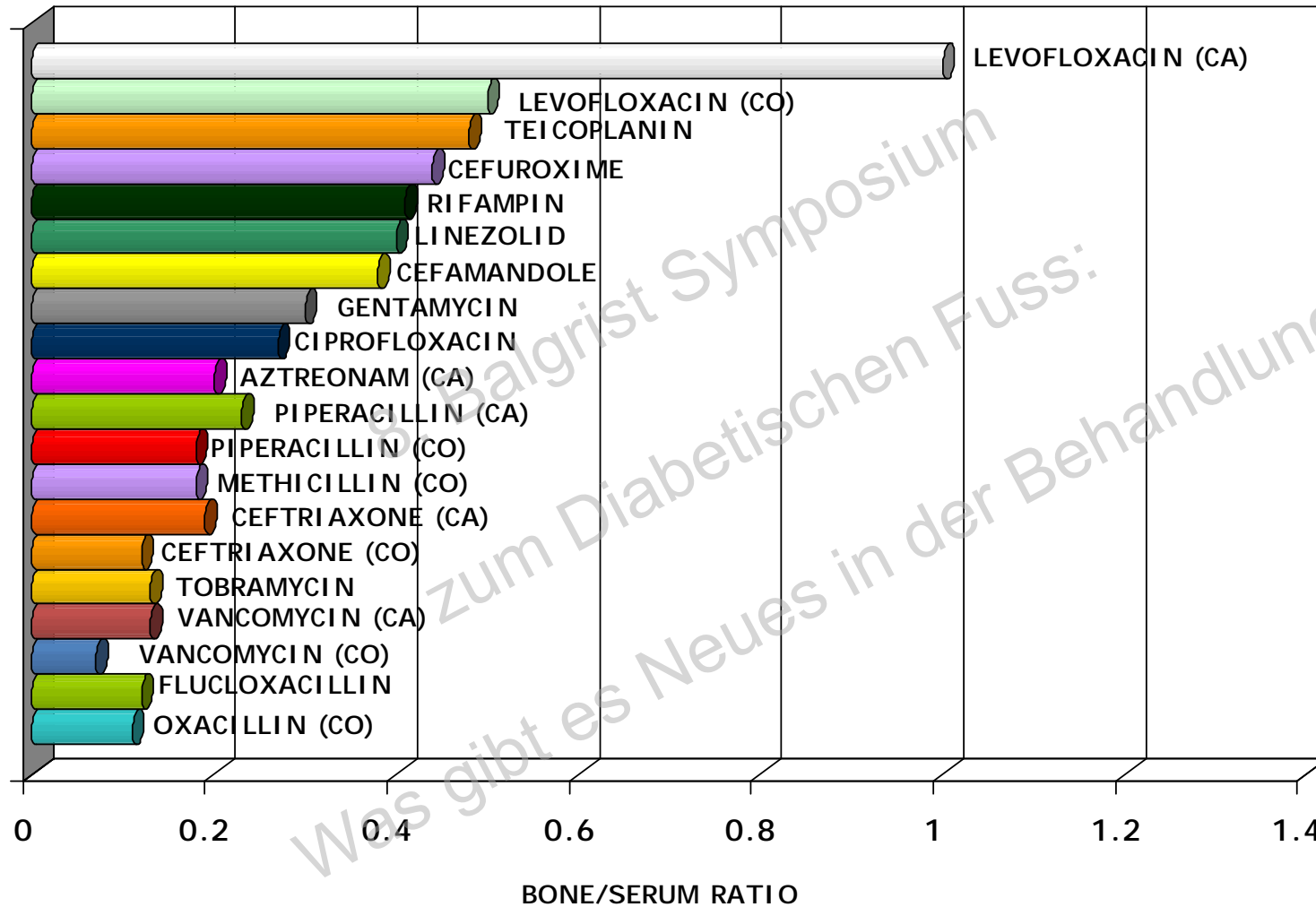
Parenteral antibiotics ?



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ANTIBIOTICS AND BONE PENETRATION

Landersdorfer CB et al. *Clin Pharmacokinet* 2009;48:89-124



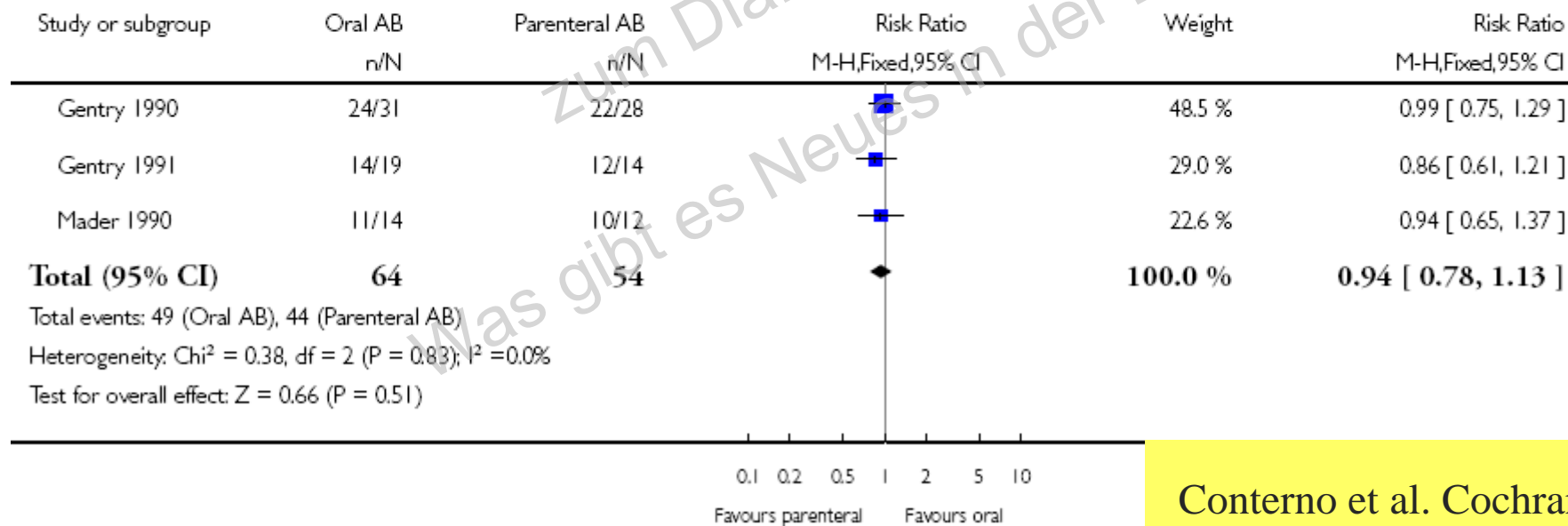


Analysis 1.2. Comparison 1 Oral antibiotic versus parenteral antibiotic (AB), Outcome 2 Remission at least 12 months after the end of treatment.

Review: Antibiotics for treating chronic osteomyelitis in adults

Comparison: 1 Oral antibiotic versus parenteral antibiotic (AB)

Outcome: 2 Remission at least 12 months after the end of treatment

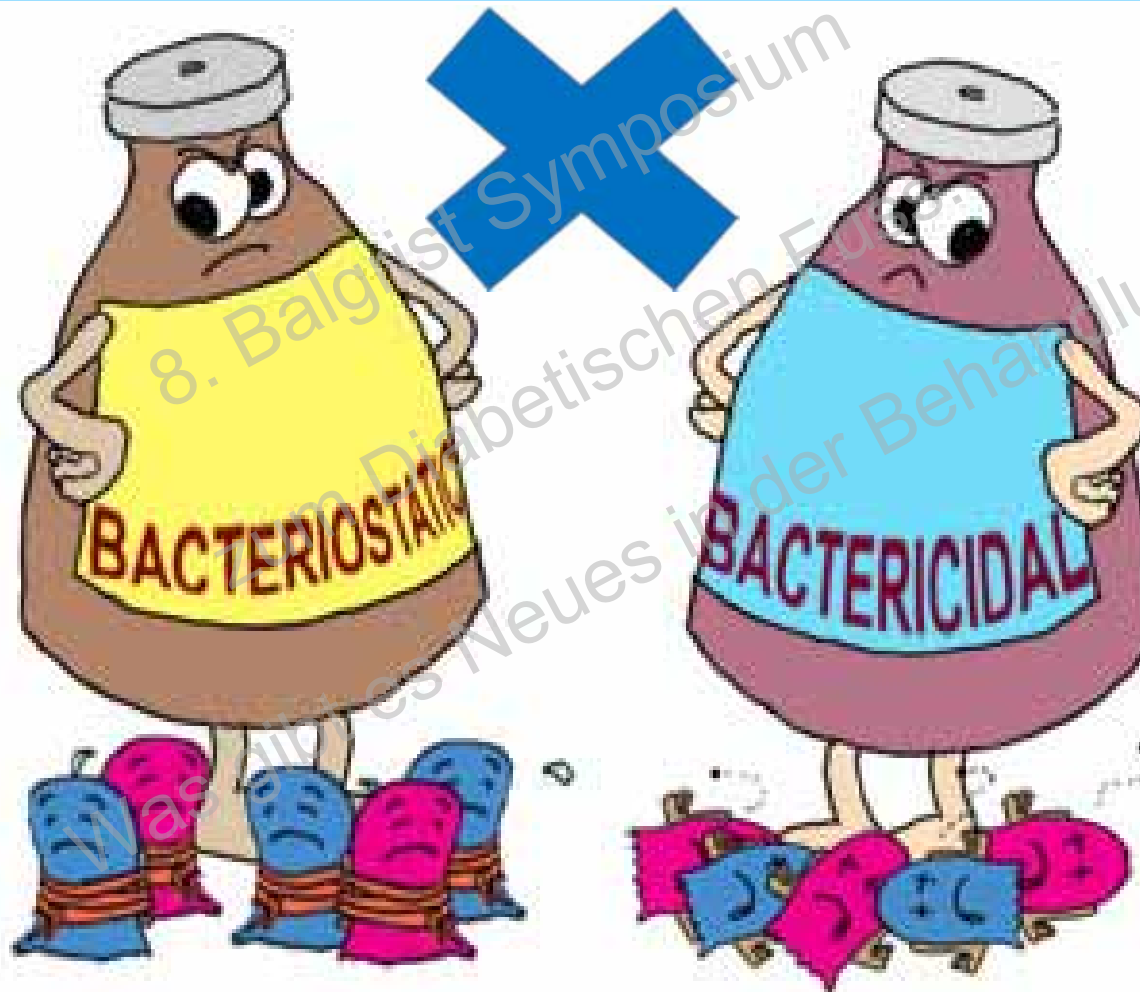


Conterno et al. Cochrane 2008

Bacteriostatic vs. bactericidal agents for osteoarticular infections

B. Kressmann, I. Uçkay, C. Landelle, M. Betz, D. Lew, BA. Lipsky

EXAMPLES:
Chloramphenicol
Erythromycin
Clindamycin
Sulfonamides
Trimethoprim
Tetracyclines



EXAMPLES:
Aminoglycosides
Beta-lactams
Vancomycin
Quinolones
Rifampin
Metronidazole

Amoxicillin / Clavulanate



Author	Year	Study type	No. of diabetic foot infections	Proportion treated with a oral β -lactam antibiotic	Proportion reported in remission	Remarks
Lipsky et al. ¹⁷	1997	RCT	108 (26 with osteomyelitis)	60%	83%	No difference when compared to oral quinolone
Embil et al. ⁵	2006	Retro	93 with osteomyelitis	100% (amoxiclav)	75 (80.5%)	followup duration was 50 +/- 50 weeks
Lazaro-Martinez et al. ⁴⁰	2014	RCT	24 with osteomyelitis	100% (amoxiclav)	75%	Daily dose: 1000 mg bid

Courtesy of Prof. P. Sendi

BRIEF REPORT

Oral amoxicillin-clavulanate for treating diabetic foot infections

Karim Gariani MD^{1,2} | Dan Lebowitz RN^{1,3} | Benjamin Kressmann RN¹ |
Elodie von Dach RN¹ | Parham Sendi MD^{4,5} | Felix Waibel MD⁶ | Martin Berli MD⁶ |
Tanja Huber PhD⁷ | Benjamin A. Lipsky MD^{1,8} | Ilker Uçkay MD^{1,9}

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⁴Department of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland

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⁶Orthopaedic Surgery, Balgrist University Hospital, Zurich, Switzerland

⁷Pharmacology, Balgrist University Hospital, Zurich, Switzerland

Aim: To assess amoxicillin-clavulanate (AMC) for the oral therapy of diabetic foot infections (DFIs), especially for diabetic foot osteomyelitis (DFO).

Methods: We performed a retrospective cohort analysis among 794 DFI episodes, including 339 DFO cases.

Results: The median duration of antibiotic therapy after surgical debridement (including partial amputation) was 30 days (DFO, 30 days). Oral AMC was prescribed for a median of 20 days (interquartile range, 12-30 days). The median ratio of oral AMC among the entire antibiotic treatment was 0.9 (interquartile range, 0.7-1.0). After a median follow-up of 3.3 years, 178 DFIs (22%) overall recurred (DFO, 75; 22%). Overall, oral AMC led to 74% remission compared with 79% with other regimens (χ^2 -test; $P = 0.15$). In multivariate analyses and stratified subgroup analyses, oral AMC resulted in similar clinical outcomes to other antimicrobial regimens, when used orally from the start, after an initial parenteral therapy, or when prescribed for DFO.

Conclusions: Oral AMC is a reasonable option when treating patients with DFIs and DFOs.

- **Antibiotic therapy – what we don't know**



Table 8. Suggested empirical antibiotic regimens, based on clinical severity, for diabetic foot infections.

Route and agent(s)	Mild	Moderate	Severe
Advised route	Oral for most	Oral or parenteral, based on clinical situation and agent(s) selected	Intravenous, at least initially
Dicloxacillin	Yes
Clindamycin	Yes
Cephalexin	Yes
Trimethoprim-sulfamethoxazole	Yes	Yes	...
Amoxicillin/clavulanate	Yes	Yes	...
Levofloxacin	Yes	Yes	...
Cefoxitin	...	Yes	...
Ceftriaxone	...	Yes	...
Ampicillin/sulbactam	...	Yes	...
Linezolid ^a (with or without aztreonam)	...	Yes	...
Daptomycin ^a (with or without aztreonam)	...	Yes	...
Ertapenem	...	Yes	...
Cefuroxime with or without metronidazole	...	Yes	...
Ticarcillin/clavulanate	...	Yes	...
Piperacillin/tazobactam	...	Yes	Yes
Levofloxacin or ciprofloxacin with clindamycin	...	Yes	Yes
Imipenem-cilastatin	Yes
Vancomycin ^a and ceftazidime (with or without metronidazole)

Table 1. Results of selected reports from around the world over the past decade of the microbiology of diabetic foot wounds.

First author [Reference]	Country	Year	Types of wounds	No. of patients	Percentage of isolates from wound culture					
					Staphylococci	Streptococci	Gram- positive	Gram- negative	<i>Ps. aeruginosa</i>	Anaerobes
Carvalho [109]	Brazil	2003	Infections	141	20	4	29	59	7	12
Candel [110]	Spain	2003	Infections	27	49	15	78	22	1	2
Anandi [111]	India	2004	Infections	107	14	—	—	—	—	4
Unachukwu [112]	Nigeria	2005	Gangrene	60	56	—	—	—	—	—
Senneville [113]	France	2005	Bone	76	52	12	—	18	2	5
Abdulrazak [114]	Kuwait	2005	Infections	86	38	17	74	26	18	11
Shankar [115]	India	2005	Infections	77	—	3	42	58	30	6
Yoga [116]	Malaysia	2006	Infections	44	20	—	—	—	14	—
Gadepalli [72]	India	2006	Ulcers	80	20	0	33	51	10	15
Sharma [117]	Nepal	2006	Ulcers	—	38	—	—	—	18	—
Örmen [118]	Turkey	2007	Bone	50	—	—	40	60	—	—
Raja [119]	Malaysia	2007	Infections	194	44	25	45	52	25	—
Çetin [120]	Turkey	2007	Infections	65	18	6	59	41	8	3
Dowd [121]	USA	2008	Ulcers	40	8	37	—	—	15	18
Umadevi [122]	India	2008	Infections	105	17	0	29	71	17	0
Koharo [123]	Pakistan	2009	Infections	60	20	3	27	73	48	2
Ramakant [35]	India	2010	Ulcers	447	19	3	31	57	17	1
Zubair [124]	India	2010	Infections	60	31	0	38	62	11	0
Özgen [125]	Turkey	2010	Infections	70	17	7	33	56	10	0



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55 diabetic foot infections, surgery 84%

2 microbiological assessments:
On admission, and 1 week later.

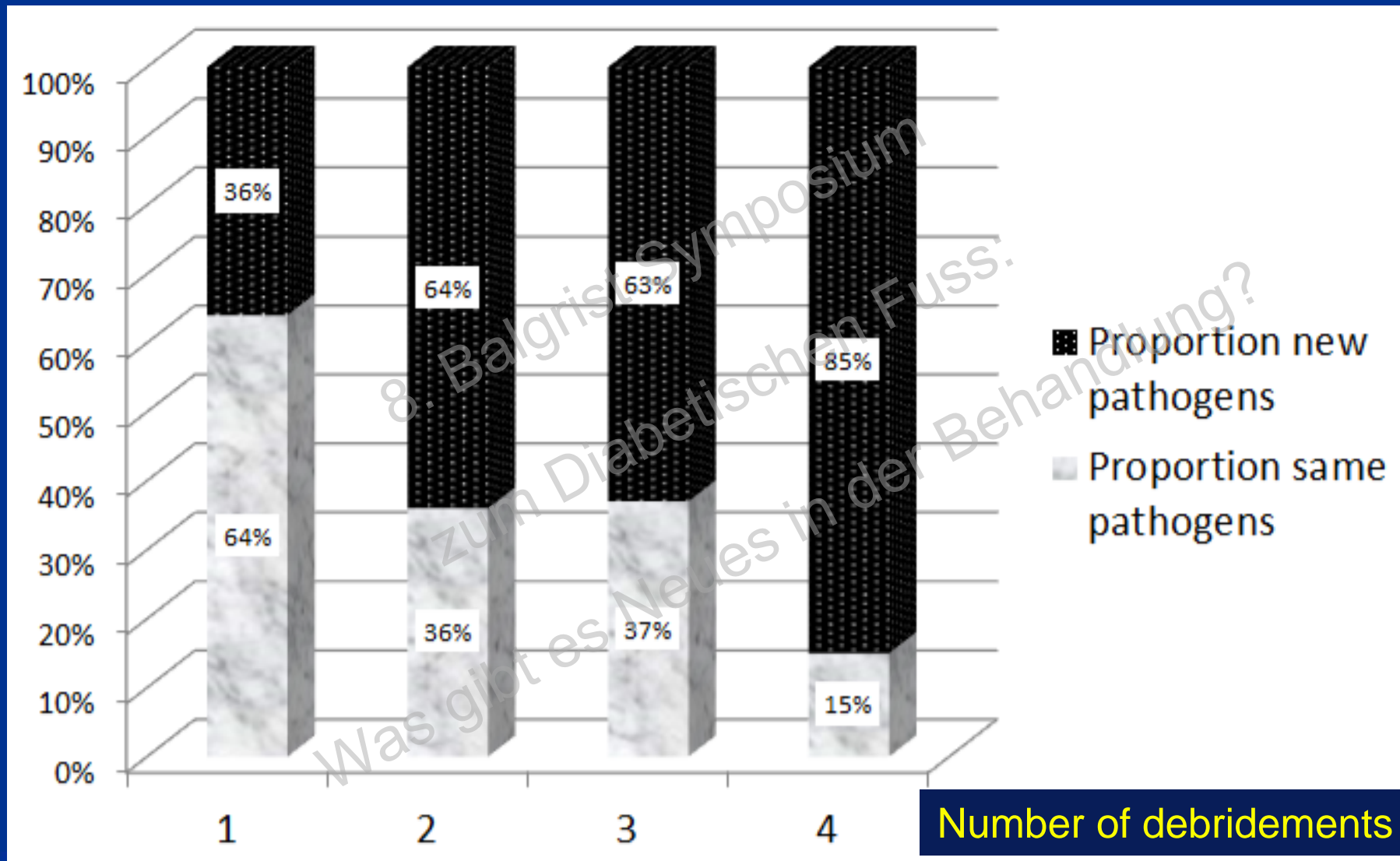
Table 1. First culture showing community acquired infections

Organisms isolated	Frequency (%) (n=55)
Klebsiella	14 (25.5)
E-coli	11 (20)
Enterococci	9 (16.4)
Proteus	4 (7.3)
Staphylococcus aureus	4 (7.3)
Enterobacter	3 (5.5)
Pseudomonas	1 (1.8)
Gram negative cocci	1 (1.8)
Non-fermenting gram neg bacilli	1 (1.8)
No growth	7 (12.7)

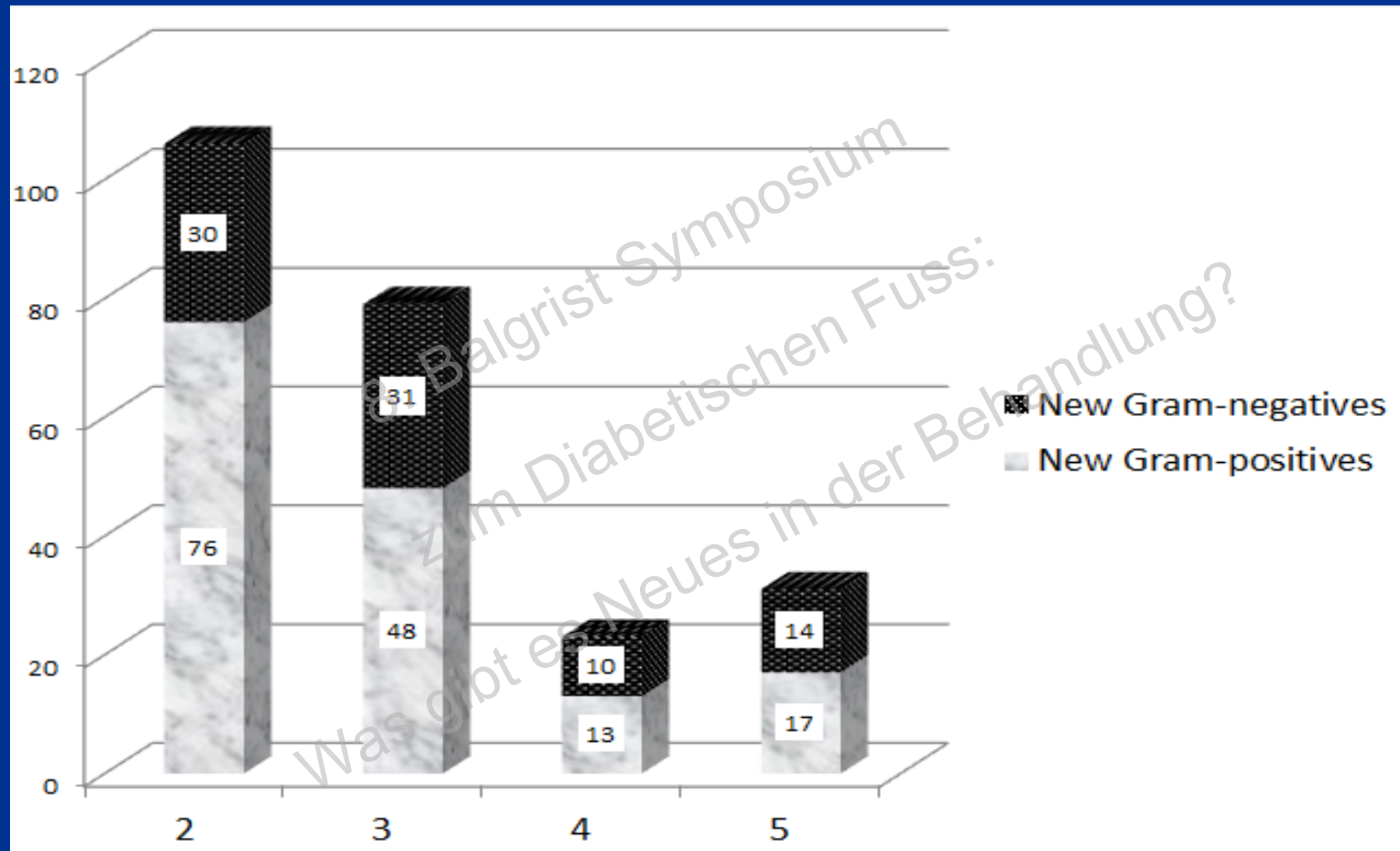
Table 3: Second culture showing hospital acquired infections.

Organism isolated	Frequency (%)
Pseudomonas	28 (50.9)
E. coli	8 (14.5)
Proteus	7 (12.7)
Gram positive cocci in pairs	4 (7.3)
Staphylococcus aureus	4 (7.3)
Non-fermenting gram negative bacilli	1 (1.8)
No growth	3 (5.5)

Proportions of « new infections »



Distribution according to the Gram coloration



Duration ?



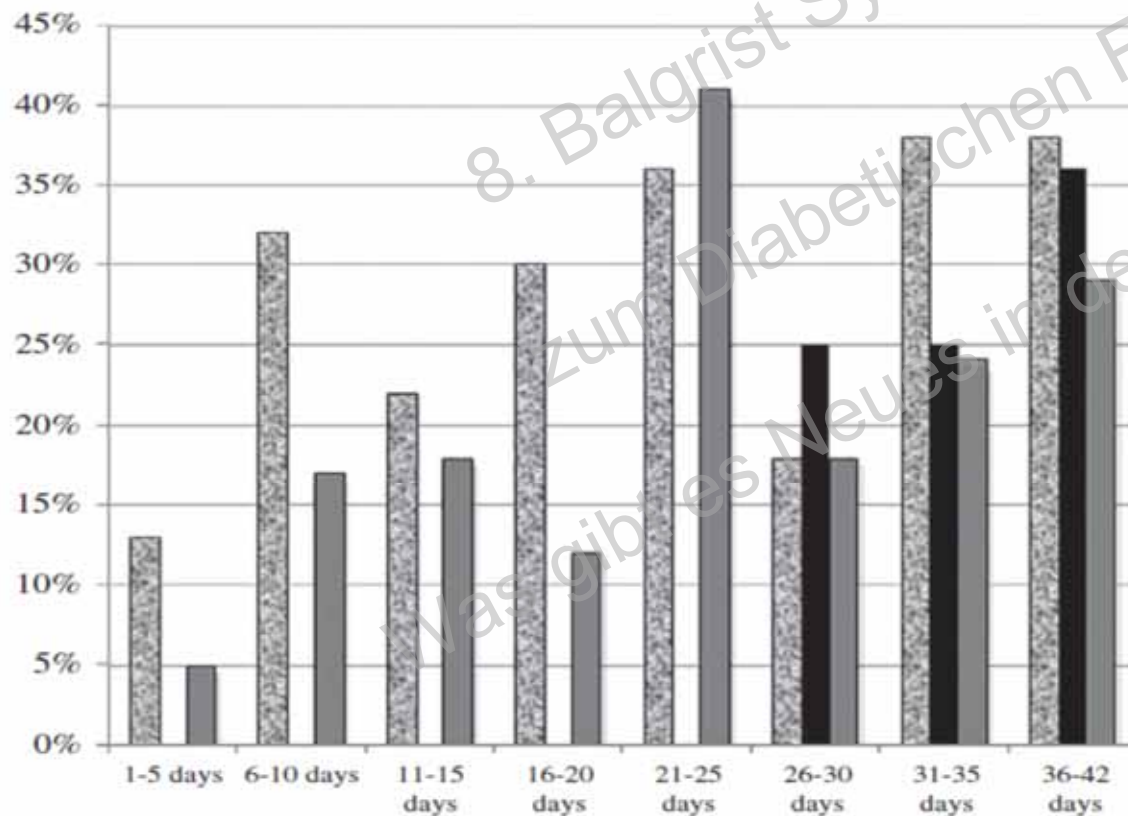
Table 11. Suggested Route, Setting, and Duration of Antibiotic Therapy, by Clinical Syndrome




Site of Infection, by Severity or Extent	Route of Administration	Setting	Duration of Therapy
Soft-tissue only			
Mild	Topical or oral	Outpatient	1–2 wk; may extend up to 4 wk if slow to resolve
Moderate	Oral (or initial parenteral)	Outpatient/ inpatient	1–3 wk
Severe	Initial parenteral, switch to oral when possible	Inpatient, then outpatient	2–4 wk
Bone or joint			
No residual infected tissue (eg, postamputation)	Parenteral or oral	...	2–5 d
Residual infected soft tissue (but not bone)	Parenteral or oral	...	1–3 wk
Residual infected (but viable) bone	Initial parenteral, then consider oral switch	...	4–6 wk

Remission in diabetic foot infections: Duration of antibiotic therapy and other possible associated factors

Karim Gariani MD^{1,2} | Dan Lebowitz MD¹ | Elodie von Dach RN³ |

Benjamin Kressmann RN¹ | Benjamin A. Lipsky MD^{1,4} | Ilker Uçkay MD^{1,3} 



-  Clinical recurrence soft tissue infections only
-  Clinical recurrence non-amputated osteomyelitis
-  Clinical recurrence all post-amputation

1018 DFI episodes



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

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

Alina Tone,¹ Sophie Nguyen,¹
Fabrice Devemy,² Hélène Topolinski,³
Michel Valette,¹ Marie Cazaubiel,⁴
Armelle Fayard,⁵ Éric Beltrand,⁵
Christine Lemaire,³ and Éric Senneville¹

Table 4—Clinical outcome of 40 diabetic patients with osteomyelitis of the foot treated nonsurgically according to the duration of antibiotic therapy

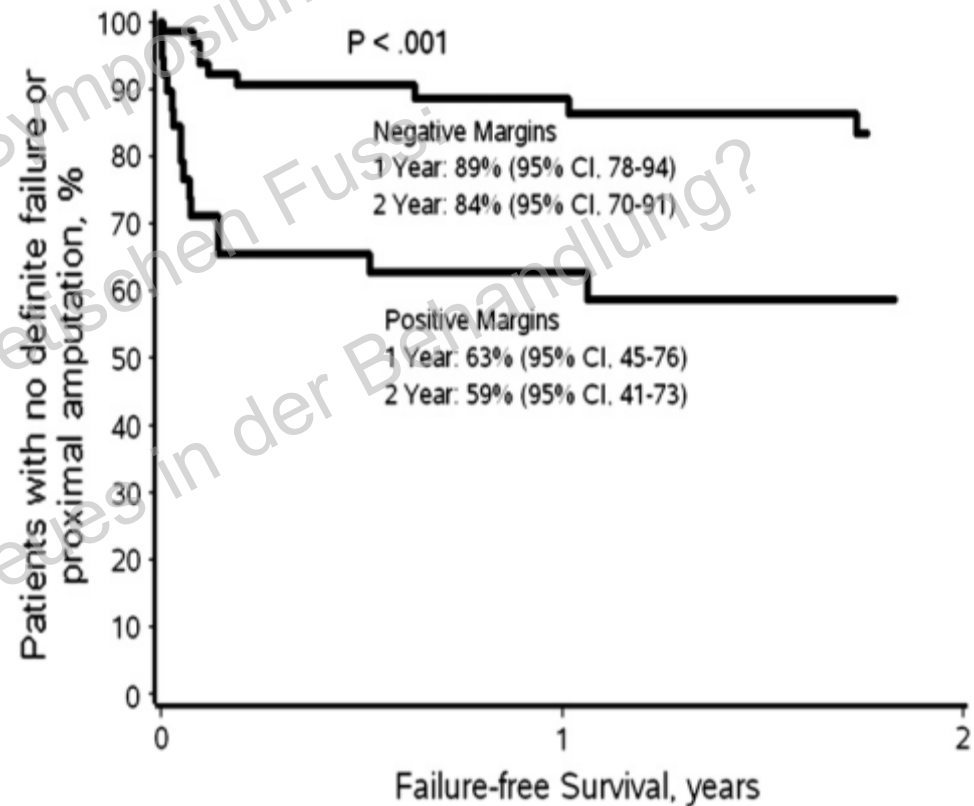
Patient outcome	6 weeks n = 20	12 weeks n = 20	P
Overall remission	12 (60)	14 (70)	0.50
Complete healing ^a	18 (90)	16 (80)	0.38
Time to complete healing (weeks ± SD)	13.1 ± 12.2	16.8 ± 17.4	0.44
Overall failure	8 (40)	6 (30)	0.50
Noncomplete healing	2 (10)	4 (20)	0.37
Relapsing osteomyelitis	2 (10)	3 (15)	1
Worsening radiological bone abnormalities	6 (30)	4 (20)	0.46
Bone resection	2 (10)	2 (10)	1
Spread of osteomyelitis to contiguous sites	4 (20)	2 (10)	0.37
Major amputation	2 (10)	2 (10)	1

Table 3—Antibiotic-related gastrointestinal adverse events reported in 40 diabetic patients with DFO treated nonsurgically according to the duration of antibiotic therapy

Antibiotic-related adverse events	6 weeks n = 20	12 weeks n = 20
Nausea	1 (5)	2 (10)
Vomiting	1 (5)	2 (10)
Diarrhea	0	2 (10)
Hepatic cytolysis/cholestasis	1 (5)	3 (15)
Total	3 (15)	9 (45) ^a

Data are number of patients (%). ^aP = 0.04.

Post-amputation, residual osteitis ?



Kowalski et al. J Foot Ankle Surg 2011

Swiss Working Group (2019)

Diabetic Foot Infection: Treatment

Issue	Action
4. Antibiotics 2	<ul style="list-style-type: none">- Duration of treatment<ul style="list-style-type: none">A. Soft tissue infection<ul style="list-style-type: none">• Mild: 5-7 days or dependent on clinical course• Moderate: 7-14 days or dependent on clinical course• Severe: 12-20 days or dependent on clinical courseB. Osteomyelitis<ul style="list-style-type: none">• 4-6 weeks if no resection of infected bone• 2-6 weeks if residual infected (but viable) bone after resection• 0-1 week if no residual infected tissue after resection (eg postamputation)

Der Balgrist

Study design:	<p>Unblinded randomized prospective trial</p> <ul style="list-style-type: none">- Postoperative randomization 1:1 concerning duration of systemic antibiotics:<ul style="list-style-type: none">- 1 vs. 4 days for eventual residual soft tissue infection- 1 vs. 3 weeks for eventual residual stump osteitis- Stop of all antibiotics if no intraoperative bacterial growth at Day 4 or according to randomization arm. Choice of antibiotics according to international guidelines. Oral antibiotics possible.
Inclusion / Exclusion criteria:	<p>Inclusion criteria:</p> <ul style="list-style-type: none">• Age \geq 18 years• Diabetic foot infections or ischemia/necrosis with surgical amputation/disarticulation level in vicinity of MRI signs of infection• At least two months of follow-up from hospitalization• Patient signing to participate, including acceptance of local wound care, off-loading and arterial re-vascularization (if clinically indicated). <p>Exclusion criteria:</p> <ul style="list-style-type: none">• At least 5 cm of distance between amputation level and infection.• Any concomitant infection requiring more than 5 days of systemic antibiotic therapy• Eventual osteosynthesis material not removed



Principles and practice of antibiotic stewardship in the management of diabetic foot infections

Ilker Uçkay^{a,b}, Martin Berli^b, Parham Sendi^{c,d}, and Benjamin A. Lipsky^{e,f}

Purpose of review

Systemic antibiotic therapy in persons with a diabetic foot infection (DFI) is frequent, increasing the risk of promoting resistance to common pathogens. Applying principles of antibiotic stewardship may help avoid this problem.

Recent findings

We performed a systematic review of the literature, especially seeking recently published studies, for data on the role and value of antibiotic stewardship (especially reducing the spectrum and duration of antibiotic therapy) in community and hospital populations of persons with a DFI.

Table 1. Summary of possible measures to promote antibiotic stewardship in diabetic foot infections (authors' selection)

Setting	Group action	Individual action	Difficulties	Reference
Community	Statewide policies		No specific governmental initiatives found	–
	Treatment guidelines	Less antibiotic use	None	Lipsky [2]
	Diabetic foot centers		No published proof of antibiotic prescribing	–
	Outcome benchmarking		Varied case-mix clouds interpretation	Milne [32]
Healthcare institutions	Stewardship programs	Less antibiotic use	Resource-consuming	Lipsky [18]
	Withhold antibiotics before sampling		Reluctance to withdrawal antibiotics	Al-Mayahi [38]
	Guidelines for microbiological sampling		None	Sotto [41]
	Restriction of selected antibiotics		Difficult to gain accepted by clinicians	Lipsky [18]
	Cycling of antibiotic agents		No published data for diabetic foot infections	–
	Clinical pathway		Targets mostly amputations and ulcer care	Martinez [39]
	Link doctors/nurses (dedicated staff)		Not explored in the literature	–
	Feedback of results		Benefit not specifically reported in the literature	Lipsky [18]
	Professional wound care		None	Lipsky [2]
	Bacteriophage therapy		Minimal published evidence of clinical efficacy	Chibber [31]
		Topical antiseptics	No benefit if combined with systemic antibiotics	Abbas [29]
		Infectiology consultant		Availability of ID consultant
	New diagnostic tools		Unclear influence on antibiotic prescribing	Lavigne [42]



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Thank you very much !!!

