

A Pragmatic Approach to Diabetic Foot Infections in the UK

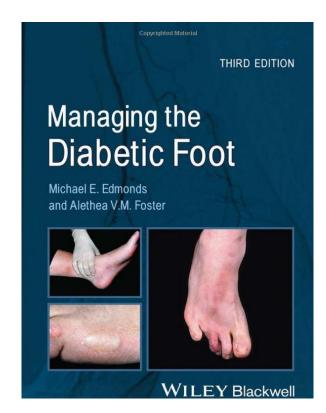
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A Quote

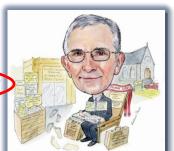
"The microbiology of the diabetic foot is unique"



Edmonds ME et al. Managing the Diabetic Foot. 3rd Ed. Blackwell Publishing 2014

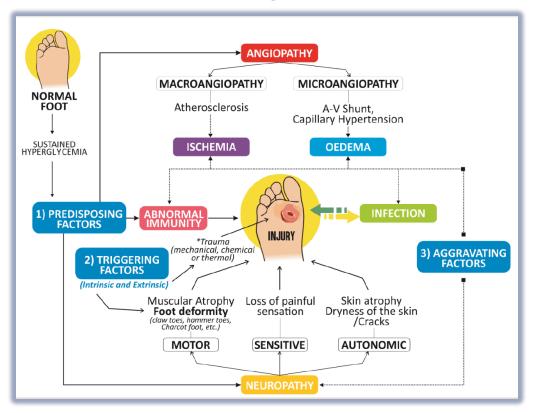
The 10 Foot Commandments

- 1. I am thy foot forever. Take good care of me, for thou shalt have no foot other than me
- 2. Thou shalt regularly debride me, when I develop callosities and ulcers
- 3. Thou shalt fit me with casts and insoles to offload my high pressure areas
- 4. Thou shalt carefully look for early signs of infection in me and treat it aggressively
- 5. Thou shalt diagnose ischaemia without delay and revascularise me
- 6. Thou shalt educate all patients how to examine me and take care of me
- 7. Thou shalt carefully inspect the shoes that I have to wear and encourage the use of appropriate footwear
- 8. Thou shalt continuously aim to achieve tighter blood glucose control for me
- 9. Thou shalt not commit amputation on me, unless there is a compelling reason
- 10. Thou shalt not covet thy neighbour's amputation rates, but try to improve yours





So Many Things to Consider



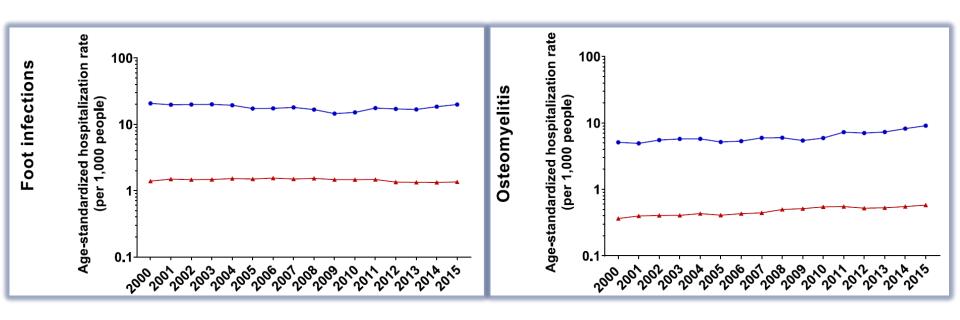
Hospitalisation for Infection – 2007 & 2016 – DM vs No DM

Infection type	All ages		20-44 years		45-64 years		65-74 years		≥75 years	
	2007	2016	2007	2016	2007	2016	2007	2016	2007	2016
Pneumonia										
Men				26/20 46			404550	454640	10/10/10	
Rate ratio (95% CI) ^a p value for trend Women	1.5 (1.5, 1.6) <0.001	1.3 (1.3, 1.4)	6.2 (4.5, 8.4) 0.015	3.6 (2.8, 4.6)	2.7 (2.5, 3.0) 0.003	2.1 (2.0, 2.3)	1.8 (1.7, 2.0) 0.081	1.7 (1.6, 1.8)	1.3 (1.3, 1.4) <0.001	1.2 (1.1, 1.2)
Rate ratio (95% CI) ^a	1.5 (1.5, 1.6)	1.4 (1.3, 1.4)	7.6 (5.1, 10.9)	2.8 (2.0, 3.9)	2.3 (2.0, 2.8)	1.8 (1.6, 2.0)	2.5 (2.2, 2.7)	1.8 (1.7, 2.0)	1.4 (1.3, 1.4)	1.3 (1.3, 1.3)
p value for trend	0.016	1.4 (1.5, 1.4)	0.004	2.0 (2.0, 5.7)	0.008	1.0 (1.0, 2.0)	0.014	1.0 (1.7, 2.0)	0.452	1.5 (1.5, 1.5)
Influenza	0.010		0.004		0.000		0.014		0.432	
Men										
Rate ratio (95% CI) ^a	2.1 (1.8, 2.4)	1.7 (1.6, 1.9)	_	_	_	_	_	_	_	_
p value for trend	0.029	(,,	_		_		_		_	
Women										
Rate ratio (95% CI) ^a	1.7 (1.5, 2.0)	1.6 (1.4, 1.7)	_	_	_	_	_	_	_	_
p value for trend	0.063		_		_		_		_	
Tuberculosis										
Men										
Rate ratio (95% CI) ^a	2.2 (2.0, 2.4)	1.8 (1.7, 2.0)	8.5 (6.0, 11.6)	7.0 (4.8, 9.9)	4.3 (3.7, 4.9)	3.3 (2.8, 3.8)	2.1 (1.8, 2.5)	1.9 (1.6, 2.2)	1.1 (1.0, 1.3)	1.0 (0.9, 1.2)
p value for trend	0.076		0.903		0.008		0.821		0.950	
Women										
Rate ratio (95% CI) ^a	2.1 (1.8, 2.4)	2.2 (1.9, 2.5)	3.3 (1.6, 6.1)	7.5 (4.8, 11.2)	2.7 (2.0, 3.6)	3.3 (2.6, 4.2)	2.8 (2.1, 3.8)	1.2 (0.8, 1.7)	1.5 (1.2, 1.8)	1.7 (1.4, 2.2)
p value for trend	0.093		0.158		0.028		0.199		0.284	
Kidney infection										
Men										
Rate ratio (95% CI) ^a	2.5 (1.7, 3.5)	4.9 (3.9, 6.2)	_	_	_	_	_	_	_	_
p value for trend	0.031		_		_		_		_	
Women Rate ratio (95% CI) ^a	21(17.27)	22(28.27)								
p value for trend	2.1 (1.7, 2.7) 0.145	3.2 (2.8, 3.7)	_	_	_	_	_	_	_	_
Sepsis	0.143		_		_		_		_	
Men										
Rate ratio (95% CI) ^a	2.3 (2.1, 2.5)	2.1 (2.0, 2.2)	8.3 (4.0, 15.1)	11.2 (7.1, 16.9)	4.8 (3.9, 5.8)	3.8 (3.3, 4.4)	2.5 (2.1, 3.0)	2.6 (2.3, 2.9)	1.9 (1.7, 2.1)	1.7 (1.6, 1.8)
p value for trend	0.430	2.1 (2.0, 2.2)	0.682	11.2 (7.1, 10.7)	0.266	2.0 (3.3, 1.7)	0.649	2.0 (2.3, 2.7)	0.238	(1.0, 1.0)
Women	0.150		0.002		5,200		5.017		0.200	
Rate ratio (95% CI) ^a	2.3 (2.1, 2.5)	2.3 (2.2, 2.4)	4.3 (1.3, 10.3)	6.3 (3.4, 10.7)	5.8 (4.5, 7.5)	5.6 (4.7, 6.6)	4.4 (3.6, 5.3)	3.3 (2.8, 3.8)	1.9 (1.7, 2.0)	2.0 (1.8, 2.1)
p value for trend	0.220	(, _/ 1)	0.215	(,/)	0.242	(, =)	0.078	(=,)	0.904	(, =

Luk AO et al Diabeteologia 2021;64(1):109-118



Admission for Foot Infections



- Diabetes
- No Diabetes

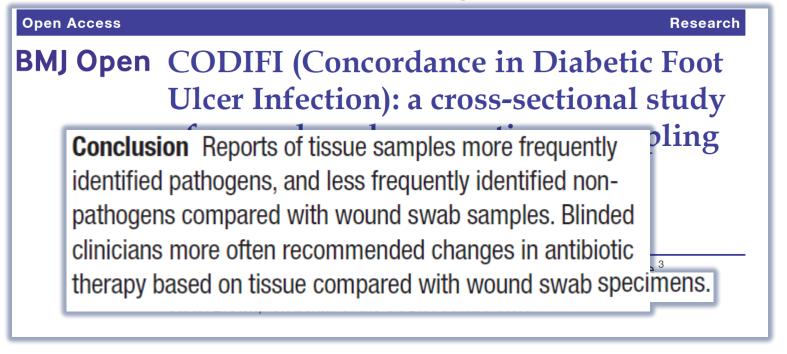
Harding JL et al Diabetes Care 2020;43(1):106-116

What Are the Challenges?

- Empirical vs targeted
- Covering the most common organisms
- Local resistance patterns ('stewardship')
- Local microbiologists
- C. difficile risks
- Osteomyelitis

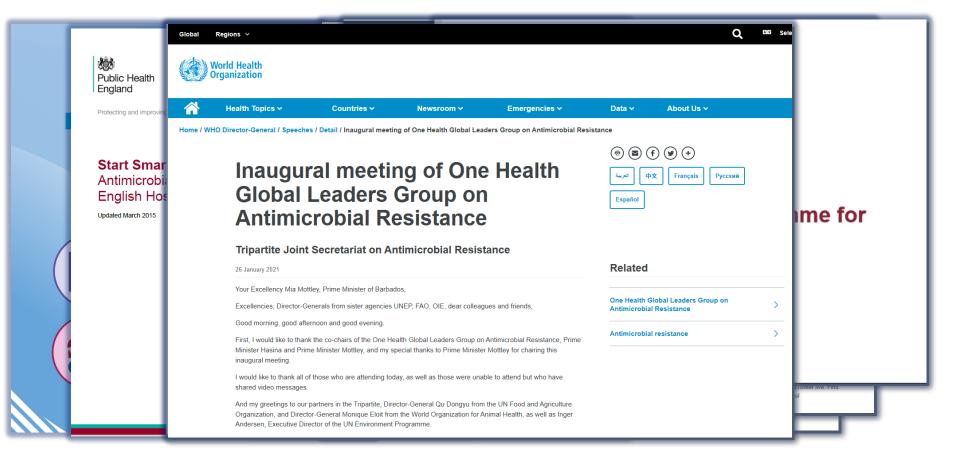
- Costs
- Alternatives for penicillin allergic patients
- Colonisation vs infection
- Compliance with a multi drug regimen
- Patient choice
- Sampling

Sampling?





Directives and Initiatives





International Examples – Choosing Wisely



https://www.choosingwisely.org.au/resources/health-professionals/antibiotic-resources-for-clinicians https://choosingwiselycanada.org/campaign/antibiotics/ https://www.choosingwisely.org/wp-content/uploads/2017/07/APMA-Choosing-Wisely-List.pdf

What is Already Used?

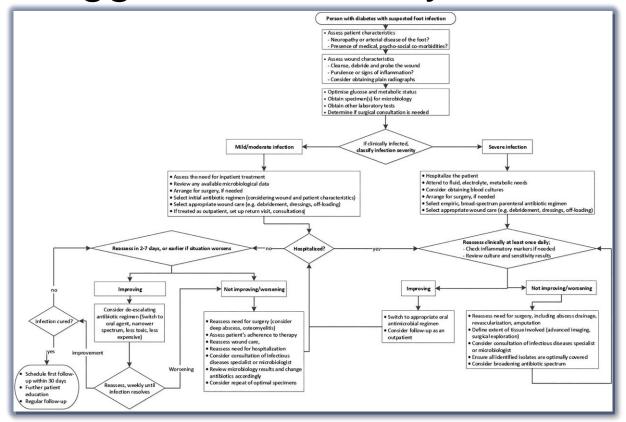
- IDSA / IWGDF
- Wagner
- University of Texas
- S(AD)/SAD / SINBAD (Site, Ischemia, Neuropathy, Bacterial Infection, Depth)
- Ulcer Severity Index
- Diabetic Ulcer Severity Score
- DEPA (Depth, Extent, Phase, Aetiology)

What is Already Used?

 But these are all wound classification / scoring systems and most do not advice on treatment



A Suggested Pathway - IWGDF



IDSA 2012

- Don't treat a clinically uninfected wound
- Use an antibiotic in addition to appropriate wound care for infected wounds
- For mild to moderate infections in treatment naïve patients cover aerobic GPC
- For moderate infections use a broad spectrum agent pending culture results

IDSA 2012

- Treat MRSA empirically if there is history of prior infection / high prevalence of colonisation / severe infection
- Route of administration depends on severity of infection
- Treat until the resolution of infection, not wound healing



IDSA 2012 – Treatment Options

Infection Severity	Probable Pathogen(s)	Antibiotic Agent
Mild	Staphylococcus aureus (MSSA); Streptococcus spp	Dicloxacillin, Clindamycin, Cephalexin, Levofloxacin, Amoxicillin-clavulanate Clarythromycin, Metronidazole
	Methicillin-resistant S. aureus (MRSA)	Doxycycline, Trimethoprim, Rifampicin
Moderate or severe	MSSA; Streptococcus spp; Enterobacteriaceae; obligate anaerobes	Levofloxacin, Cefoxitin, Ceftriaxone, Ampicillin- sulbactam, Moxifloxacin, <i>Ertapenem</i> , Tigecycline, Levofloxacin or ciprofloxacin with clindamycin, <i>Imipenem-</i> cilastatin, Metronidazole, Teicoplanin,
	MRSA	Linezolid, Daptomycin, Vancomycin
	Pseudomonas aeruginosa	Piperacillin-tazobactam
	MRSA, Enterobacteriacae, Pseudomonas, and obligate anaerobes	Vancomycin plus one of the following: ceftazidime, cefepime, piperacillin-tazobactam, aztreonam or a carbapenem

BOLD = most commonly used in trials

Italics = FDA approved for diabetic foot infections

Lipsky BA et al Clin Infect Dis 2012;54:e132-173



What's Available in the UK

Infection Severity	Probable Pathogen(s)	Antibiotic Agent
Mild	Staphylococcus aureus (MSSA); Streptococcus spp	Dicloxacillin, Clindamycin, Cephalexin, Levofloxacin, Amoxicillin-clavulanate Clarythromycin, Metronidazole
	Methicillin-resistant S. aureus (MRSA)	Doxycycline, Trimethoprim, Rifampicin
Moderate or severe	MSSA; Streptococcus spp; Enterobacteriaceae; obligate anaerobes	Levofloxacin, Cefoxitin, Ceftriaxone, Moxifloxacin, <i>Ertapenem,</i> Tigecycline, Levofloxacin or ciprofloxacin with clindamycin, <i>Imipenem-cilastatin</i>
	MRSA	Linezolid, Daptomycin, Vancomycin
	Pseudomonas aeruginosa	Piperacillin-tazobactam
BOLD = most commonly	MRSA, Enterobacteriacae, Pseudomonas, and obligate anaerobes used in trials	Vancomycin plus one of the following: ceftazidime, cefepime, piperacillin-tazobactam, aztreonam or a carbapenem

Italics = FDA approved for diabetic foot infections



What's Cheap?

		•		
Infection Severity	Probable Pathogen(s)	Antibiotic Agent		
Mild	Staphylococcus aureus (MSSA); Streptococcus spp	Claydromyon Metronidazole		
	Methicillin-resistant S. aureus (MRSA)	Doxycycline, Trimethoprim, Rifampicin		
Moderate or severe	MSSA; Streptococcus spp; Enterobacteriaceae; obligate anaerobes	Levofloxacin, Ceftriaxone, Moxifloxacin, Ceftriaxone, Cef		
	MRSA	Linezolid, Daptomycin, Vancomycin		
	Pseudomonas aeruginosa	Piperacillin-tazobactam		
BOLD = most commonly (MRSA, Enterobacteriacae, Pseudomonas, and obligate anaerobes used in trials	Vancomycin plus one of the following: ceftazidime, cefepime, piperacillin-tazobactam, aztreonam or a carbapenem		

Italics = FDA approved for diabetic foot infections

Are There any Limitations to the Available Guidelines?

- There is very little RCT data to make decisions on
- Most of the drugs that have regulatory approval for treating diabetic foot infections are new (read "expensive")
- Almost nothing is mentioned about admissions avoidance

IDSA / IWGDF Classification

Clinical Description	IDSA	IWGDF
No symptoms or signs of infection	Uninfected	1
Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below). If erythema, must be >0.5 cm to ≤2 cm around the ulcer.	Mild	2
Local infection (as described above) with erythema > 2 cm, or involving structures deeper than skin and subcutaneous tissues (e.g., abscess, osteomyelitis, septic arthritis, fasciitis), and no systemic inflammatory response signs (as described below)	Moderate	3
Local infection (as described above) with the signs of SIRS, as manifested by ≥2 of the following: • Temperature >38°C or <36°C • Heart rate >90 beats/min • Respiratory rate >20 breaths/min or PaCO2 <32 mm Hg • White blood cell count >12 000 or <4000 cells/μL or ≥10% immature (band) forms	Severe	4

Admissions Avoidance

Clinical Description	IDSA	IWGDF
No symptoms or signs of infection	Uninfected	1
Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below). If erythema, must be >0.5 cm to ≤ 2 cm around the ulcer.	Mild	2
Local infection (as described above) with erythema > 2 cm, or involving structures deeper than skin and subcutaneous tissues (e.g., abscess, osteomyelitis, septic arthritis, fasciitis), and no systemic inflammatory response signs (as described below)	Moderate	3
Cellulitis > 2 cm around the ulcer associated with lymphangitis or foot failing to respond to oral antibiotics alone and not systemically unwell	Moderate infection borderline admission	
Local infection (as described above) with the signs of SIRS, as manifested by ≥2 of the following: • Temperature >38°C or <36°C • Heart rate >90 beats/min • Respiratory rate >20 breaths/min or PaCO2 <32 mm Hg • White blood cell count >12 000 or <4000 cells/μL or ≥10% immature (band) forms	Severe	4



Norwich Protocol

Infection Severity	Probable Pathogen(s)	Antibiotic Agent
Mild	Staphylococcus aureus (MSSA); Streptococcus spp	Clindamycin, Caphalexin Levolloxacin Amoxicillin-clavulanate Clarythromycin, Metronidazole, flucolaxilllin
	Methicillin-resistant S. aureus (MRSA)	Doxycycline, Trimethoprim, Rifampicin
Moderate or severe	MSSA; Streptococcus spp; Enterobacteriaceae; obligate anaerobes	Levolloxacin, Celoxiin, Ceftriaxone, Ampicillingulla de la companyacine de la companyacin
	MRSA	Linezolid, Daptomycin, Vancomycin
	Pseudomonas aeruginosa	Piperacillin-tazobactam
	MRSA, Enterobacteriacae, Pseudomonas, and obligate anaerobes	Vancomycin plus one of the following: ceftazidime, cefepime, piperacillin-tazobactam aztreonam or a carbapenem
BOLD = most commonly used in trials Italics = FDA approved for diabetic foot infections		Gooday C et al Diabetic Medicine 2013;30(5):581-589

IDSA Modification?

Table 2. Infectious Diseases Society of America and International Working Group on the D Foot Infection	iabetic Foot Classifica	ations of Diabetic
Clinical Manifestation of Infection	PEDIS Grade	IDSA Infection Severity
No symptoms or signs of infection	1	Uninfected
Infection present, as defined by the presence of at least 2 of the following items:		
 Local swelling or induration Erythema Local tenderness or pain Local warmth Purulent discharge (thick, opaque to white or sanguineous secretion) 		
Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below). If erythema, must be >0.5 cm to ≤2 cm around the ulcer. Exclude other causes of an inflammatory response of the skin (eg, trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis).	2	Mild
Local infection (as described above) with erythema > 2 cm, or involving structures deeper than skin and subcutaneous tissues (eg, abscess, osteomyelitis, septic arthritis, fasciitis), and No systemic inflammatory response signs (as described below)	3	Moderate
Local infection (as described above) with the signs of SIRS, as manifested by ≥2 of the following:	4	Severe ^a
 Temperature >38°C or <36°C Heart rate >90 beats/min Respiratory rate >20 breaths/min or PaCO₂ <32 mm Hg White blood cell count >12 000 or <4000 cells/µL or ≥10% immature (band) forms 		

Table 3. Revised Infectious Diseases Society of America Diabetic Foot Infection Classification Diabetic foot ulceration without any manifestation of No infection The infection is limited to skin or superficial subcutaneous tissues without local complication or systemic >2 Manifestations of: Mild Soft Tissue Local swelling or induration Infection Erythema (Any extending ≤2cm around the ulceration) Local tenderness or pain · Local warmth Purulent discharge Either systemically stable or unstable patient with ≥1 of the following: erythema extending >2 cm from the ulceration, lymphangitis, spread beneath fascia, deep tissue abscess, gangrene. Can involve muscle, tendon, and joint, but does not involve bone. This includes patients who meet criteria for moderate or Moderate/Severe Soft Tissue severe infections. Infection Temperature >38°C or <36°C Heart rate >90 beats/min · Respiratory rate >20 breaths/min or PaCO, <32 mm Hg White blood cell count >12 000 or <4000 cells/µL or ≥10% immature (band) forms Any bone infection of the foot. This includes patients who meet criteria for moderate or severe infections as noted above including systemic Moderate/ • Temperature >38°C or <36°C Severe Foot • Heart rate >90 beats/min Osteomyelitis • Respiratory rate >20 breaths/min or PaCO, <32 mm Hg White blood cell count >12 000 or <4000 cells/µL or ≥10% immature (band) forms Abbreviation: PaCO,, partial pressure of carbon dioxide.

Lipsky BA et al Clin Infect Dis 2012;54:e132-173 Lavery LA et al Clin Infect Dis 2020;70(8):1573-1579

Co-Amoxiclav?

Oral amoxicillin-clavulanate for treating diabetic foot infections

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Karim Gariani MD^{1,2} | Dan Lebowitz RN^{1,3} | Benjamin Kressmann RN^1 | Elodie von Dach RN^1 | Parham Sendi MD^{4,5} | Felix Waibel MD^6 | Martin Berli MD^6 | Tanja Huber PhD^7 | Benjamin A. Lipsky MD^{1,8} | Ilker Uçkay MD^{1,9} \bigcirc
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Conclusions: Oral AMC is a reasonable option when treating patients with DFIs and DFOs.

What About Osteomyelitis?

- NICE says Think about osteomyelitis if the person with diabetes has a local infection, a deep foot wound or a chronic foot wound
- If osteomyelitis is suspected in a person with diabetes but is not confirmed by initial X-ray, consider an MRI to confirm the diagnosis

Diagnosing diabetic foot osteomyelitis

Benjamin A. Lipsky² | Suzanne A.V. van Asten³ | Eric M. Senneville¹

NICE NG19

Edgar J. Peters⁴

Senneville EM et al DMRR 2020;36(Suppl 1):e3250





Original Investigation | Infectious Diseases

Adjunctive Rifampin Therapy For Diabetic Foot Osteomyelitis in the Veterans Health Administration

Brigid M. Wilson, PhD; Mary T. Bessesen, MD; Gheorghe Doros, PhD; Sheldon T. Brown, MD; Elie Saade, MD, MPH; John Hermos, MD; Federico Perez, MD, MS; Marion Skalweit, MD, PhD; Brad Spellberg, MD; Robert A. Bonomo, MD

CONCLUSIONS AND RELEVANCE In this cohort study, patients administered rifampin experienced lower rates of death and amputation than patients not treated with rifampin, which remained significant after adjustment for confounders. These results coupled with existing evidence from small clinical trials suggest the addition of rifampin to current treatment regimens may be a useful antimicrobial option in the treatment of DFO.

An Opposing View....

Systematic Review or Meta-analysis

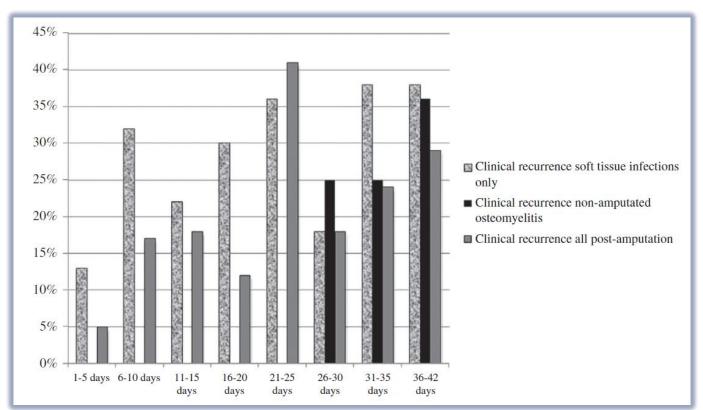
Systematic review of randomized controlled trials on antibiotic treatment for osteomyelitis in diabetes

K. Xing¹, G.Huang¹, S. Hua³, G. Xu⁴ and M. Li²

Conclusions There is no definitive evidence supporting the superiority of any particular antibiotic agent, dose, or administration duration in the treatment of osteomyelitis in diabetes. As the included studies had some flaws and limitations, further research is necessary.



Duration of Treatment?



 No idea! No differences in outcome for long or short duration

The Same Group - 3 Weeks Non-Inferior to 6 Weeks

Three versus six weeks of antibiotic therapy for diabetic foot osteomyelitis: A prospective, randomized, non-inferiority pilot trial

Karim Gariani, MD^{1*}, Truong-Thanh Pham, MD^{2,3*}, Benjamin Kressmann, RN^{2,3}, François R. Jornayvaz, MD¹, Giacomo Gastaldi, MD¹, Dimitrios Stafylakis, MD³, Jacques Philippe, MD¹, Benjamin A. Lipsky, MD^{2,4}, İlker Uçkay, MD^{2,3,5,6}

COVID

- Single centre 105 people in 2019 and 120 in 2020
- Antibiotic resistance in DFU went from 36% to 63%
- Associated with self administration / GP prescription

Highlighting the need for appropriate education and stewardship

Is CRP a Useful Guide?

No, not really

Is routine measurement of the serum C-reactive protein level helpful during antibiotic therapy for diabetic foot infection?

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Truong-Thanh Pham MD<sup>1,2</sup> | Oliver Wetzel MD<sup>3</sup> | Karim Gariani MD<sup>4</sup> | Benjamin Kressmann RN<sup>1,2</sup> | François R. Jornayvaz MD<sup>4</sup> | Benjamin A. Lipsky MD<sup>1,5</sup> | İlker Uçkay MD<sup>1,2,6</sup>
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In our prospective cohorts, a blunt iterative monitoring of CRP during DFI treatment, without correlation with clinical findings, failed to predict treatment failures.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

H.-K. Li, I. Rombach, R. Zambellas, A.S. Walker, M.A. McNally, B.L. Atkins, B.A. Lipsky, H.C. Hughes, D. Bose, M. Kümin, C. Scarborough, P.C. Matthews, A.J. Brent, J. Lomas, R. Gundle, M. Rogers, A. Taylor, B. Angus, I. Byren, A.R. Berendt, S. Warren, F.E. Fitzgerald, D.J.F. Mack, S. Hopkins, J. Folb, H.E. Reynolds, E. Moore, J. Marshall, N. Jenkins, C.E. Moran, A.F. Woodhouse, S. Stafford, R.A. Seaton, C. Vallance, C.J. Hemsley, K. Bisnauthsing, J.A.T. Sandoe, I. Aggarwal, S.C. Ellis, D.J. Bunn, R.K. Sutherland, G. Barlow, C. Cooper, C. Geue, N. McMeekin, A.H. Briggs, P. Sendi, E. Khatamzas, T. Wangrangsimakul, T.H.N. Wong, L.K. Barrett, A. Alvand, C.F. Old, J. Bostock, J. Paul, G. Cooke, G.E. Thwaites, P. Bejon, and M. Scarborough, for the OVIVA Trial Collaborators*

 Not enough people with diabetes in this cohort of 1054 people to be able to see any differences

Other Things on the Horizon

- Emerging agents
 - WF10
 - Pirfenidone
 - Deferoxamine
 - GTN
 - Biologics
 - Growth factors
 - Insulin
 - Neuropeptides
 - Cell/gene therapy
 - Amniotic membrane
 - Plant extracts

- Microbiota local & regional
- Biofilm biology
- Molecular approaches
- MDR organisms
- Phages

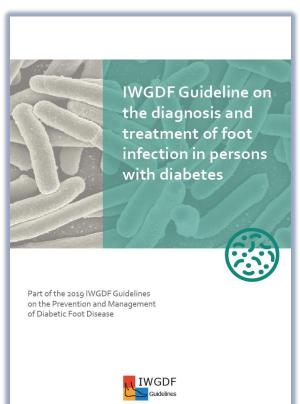
- Debridement
- Dressings
- Topical antibiotics
- Nanomedicine

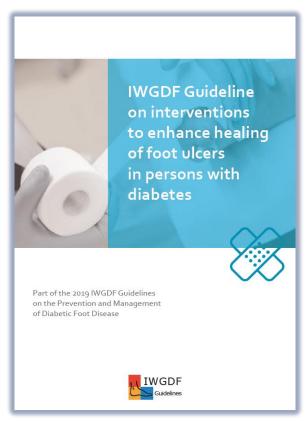
Ramirez-Acuña JM et al Antibiotics 2019, 8, 193 Dai J et al Can J Diab 2020;44(4):342-349



But is There Good Evidence?

No, not really





Conclusions - Pragmatism

- The microbiology of the diabetic foot is an ever changing challenge
- It's an active area but there is still a lot of work to do to get good quality evidence
- Talk to your friendly neighbourhood microbiologists regularly
- Think about parenteral antibiotics as a way of avoiding admissions



A Pragmatic Approach to Diabetic Foot Infections in the UK

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