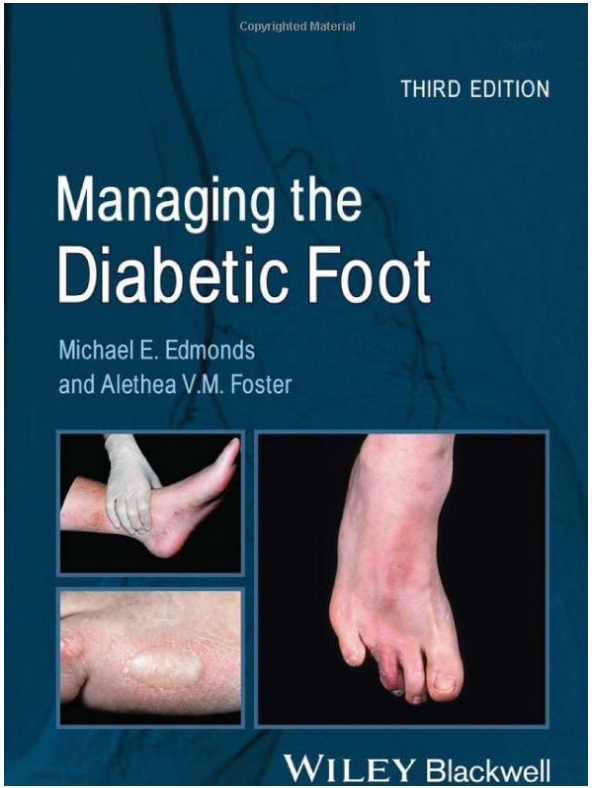
An Update on Antibiotic Management of Infection in the Diabetic Foot

Prof Ketan Dhatariya MSc MD MS FRCP PhD
Consultant in Diabetes and Endocrinology
Norfolk and Norwich University Hospitals

A Quote

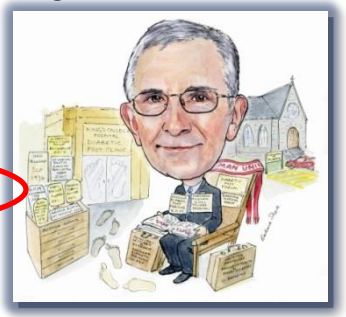
"The microbiology of the diabetic foot is unique"



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

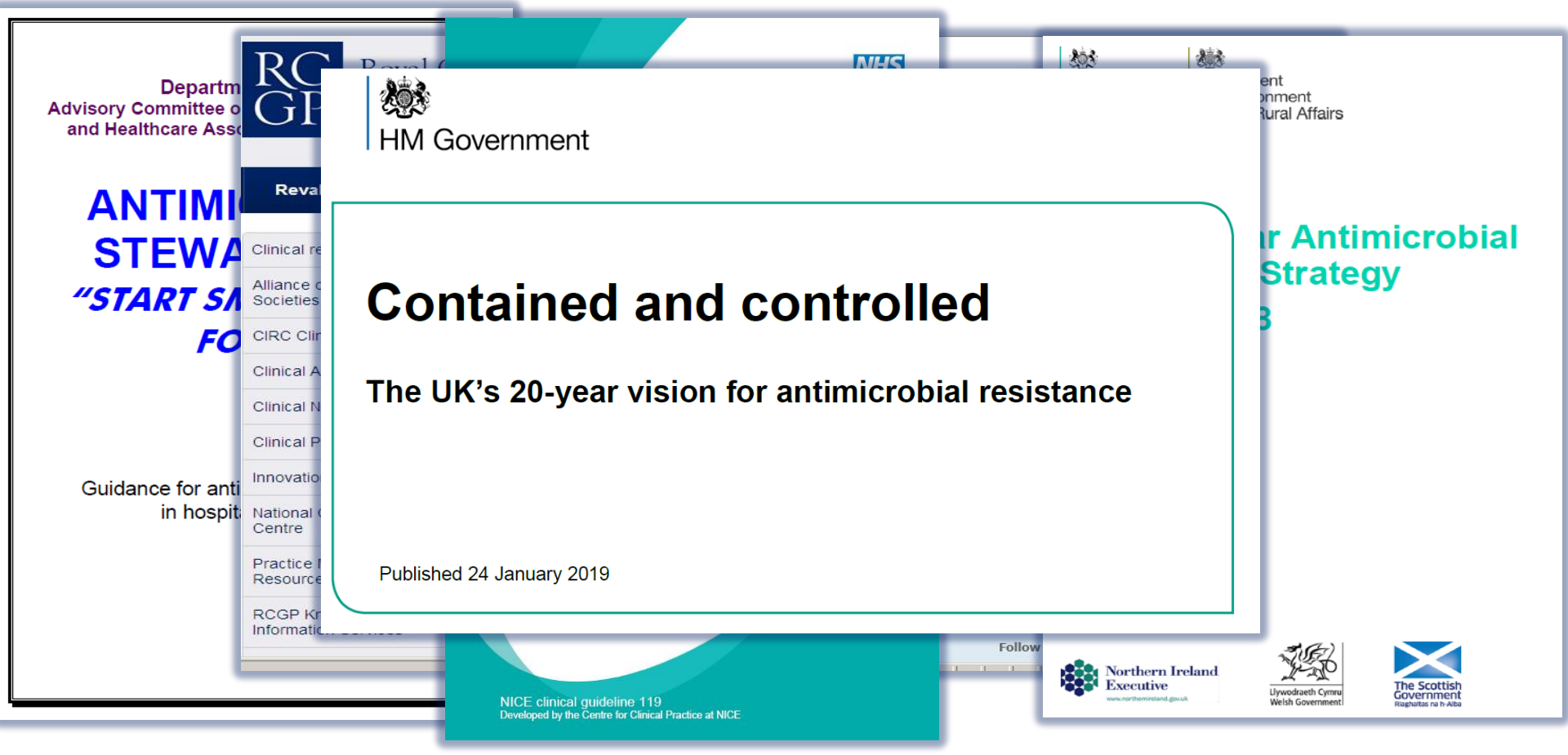


Papanas, Edmonds et al BMJ 2005;331(7531):1497

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

Government Directives



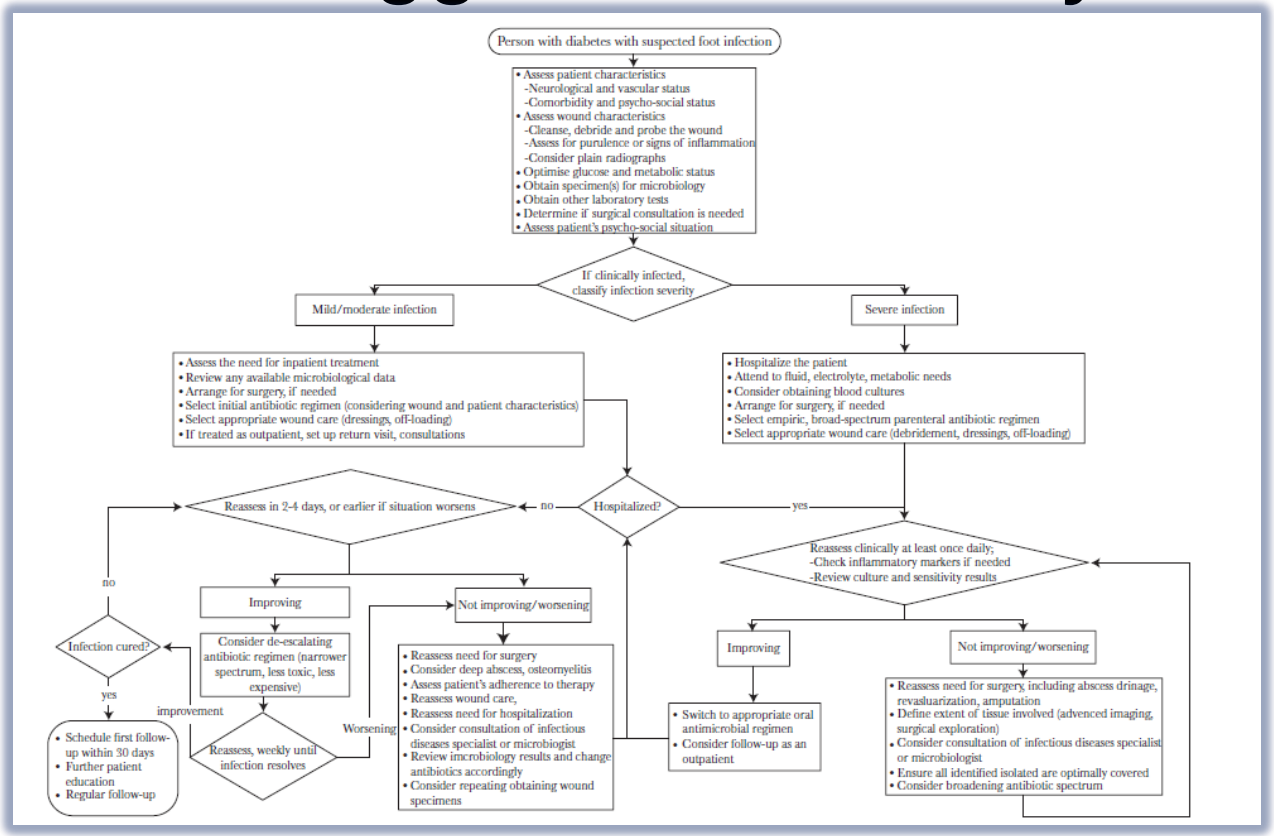
What is Available Already?

- 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 Available Already?

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

A Suggested Pathway



Lipsky BA et al Diab Metab Res Rev 2016;32(Suppl 1):S45-74

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

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

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

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

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, ***Ertapenem,*** Tigecycline, Levofloxacin or ciprofloxacin with clindamycin, **Imipenem-cilastatin**, Metronidazole, Teicoplanin, Fucidin
	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

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Lets Talk About Cost – 1 Month Supply

- Clindamycin - £46.37
- Cephalexin - £5.43
- Levofloxacin - £140.64
- Co-amoxiclav - £7.07
- Doxycycline - £3.88
- Ceftriaxone* - £287.40
- Moxifloxacin - £57.24
- Ertapenem* - £949.50
- Tigecycline* - £872.37
- Ciprofloxacin - £4.80
- Imipenem/cilastin*- £2233.80
- Linezolid - £492.72
- Daptomycin* - £1800
- Vancomycin* - £2250
- Tazocin* - £1365.30
- Ceftazidime* - £249.30
- Aztreonam* - £2256

Standard doses, generic costs using unbroken pack sizes where applicable - BNF March 2019
* Given IV (nursing and other costs not included)
Assumptions made – 80Kg, normal renal function, severe infection, antibiotic needed for the whole month

Where Does that Fit In?

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Cheaper Treatment Options

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Are There any Limitations to the Available Guidelines?

- As we have seen 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

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

Admissions Avoidance

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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

Gooday C et al Diabet Med 2013;30(5):581-589

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Norwich Protocol

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	FIRST CHOICE	PENICILLIN ALLERGY	DURATION
	PARTIAL OR FULL THICKNESS	*PARTIAL OR FULL THICKNESS*	
MILD	Co-amoxiclav 625mg tds PO	Clarithromycin 500mgs bd PO	Review after 1-2 weeks. May require an additional 1-2 weeks of treatment
MODERATE	Co-amoxiclav 625mgs tds PO If co-amoxiclav has previously been used with no success then consider using Clindamycin 150mg-300mg qds PO instead	Clindamycin 150mg - 300mg qds PO	2-4 weeks
MODERATE INFECTION BORDERLINE ADMISSION	Ceftriaxone 1-2g od IM* Ciprofloxacin 500mgs bd PO Metronidazole 400mg tds PO If MRSA positive use teicoplanin in place of ceftriaxone	Ceftriaxone 1-2g od IM* Ciprofloxacin 500mgs bd PO Metronidazole 400mg tds PO Teicoplanin IM* 400mg od Ciprofloxacin 500mg bd PO Metronidazole 400mg tds PO	2-4 weeks
SEVERE NEEDS ADMISSION	Tazocin 4.5g tds IV If polymicrobial infection suspected with MRSA then add in vancomcyin 1g bd IV to the above	Clarithromycin 500mg bd IV Metronidazole 500mg tds IV Ceftazidime 1g tds IV (2g tds IV if very severe). Substitute with Ciprofloxacin 500mg bd PO in true penicillin allergy. If polymicrobial infection suspected with MRSA then add in vancomcyin 1g bd IV to the above regimen (omitting clarithromycin)	2-4 weeks
OSTEOMYELITIS	Co-amoxiclav 625mg tds PO (+ sodium fusidate 500mg tds PO if no evidence of healing after 4 weeks and a sodium fusidate sensitive staph aureus identified). Consider ciprofloxacin 500mg bd + metronidazole 400mg tds PO if a gram negative organism identified or no evidence of improvement after 4 weeks	Clindamycin 300mg qds PO Consider ciprofloxacin 500mg bd + metronidazole 400mg tds PO if a gram negative organism identified or no evidence of improvement after 4 weeks	4-6 weeks

Gooday C et al Diabetic Medicine 2013;30(5):581-589

Co-Amoxiclav?

Oral amoxicillin-clavulanate for treating diabetic foot infections

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]

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

Gariani K et al Diabetes Obesity Metabolism 2019;21(6):1483-1486

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

NICE NG19

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Gooday C et al Diabetic Medicine 2013;30(5):581-589

Published This Month

Systematic Review or Meta-analysis

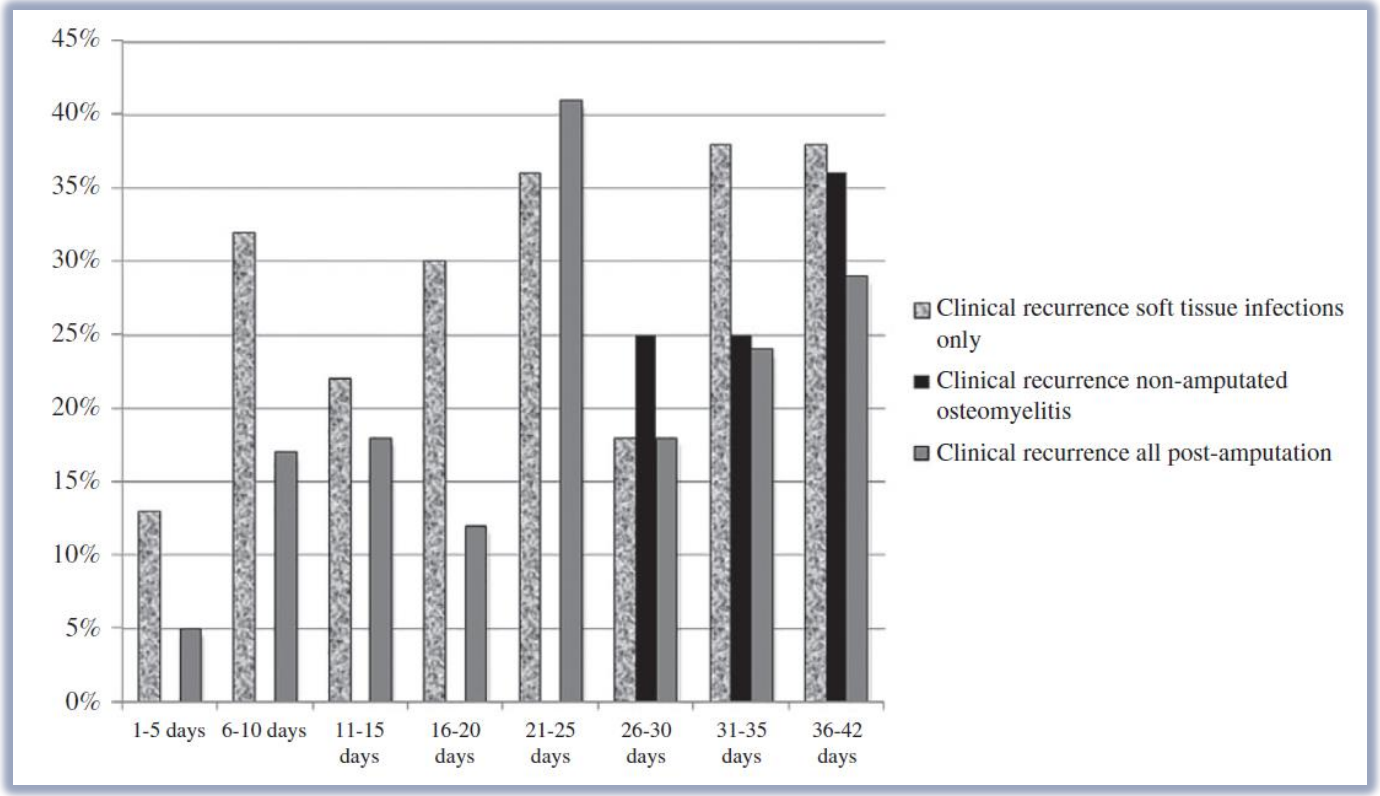
Systematic review of randomized controlled trials on antibiotic treatment for osteomyelitis in diabetes

K. Xing[1], G.Huang[1], S. Hua[3], G. Xu[4] and M. Li[2]

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.

Xing K et al Diabetic Medicine 2019;36(5):546-556

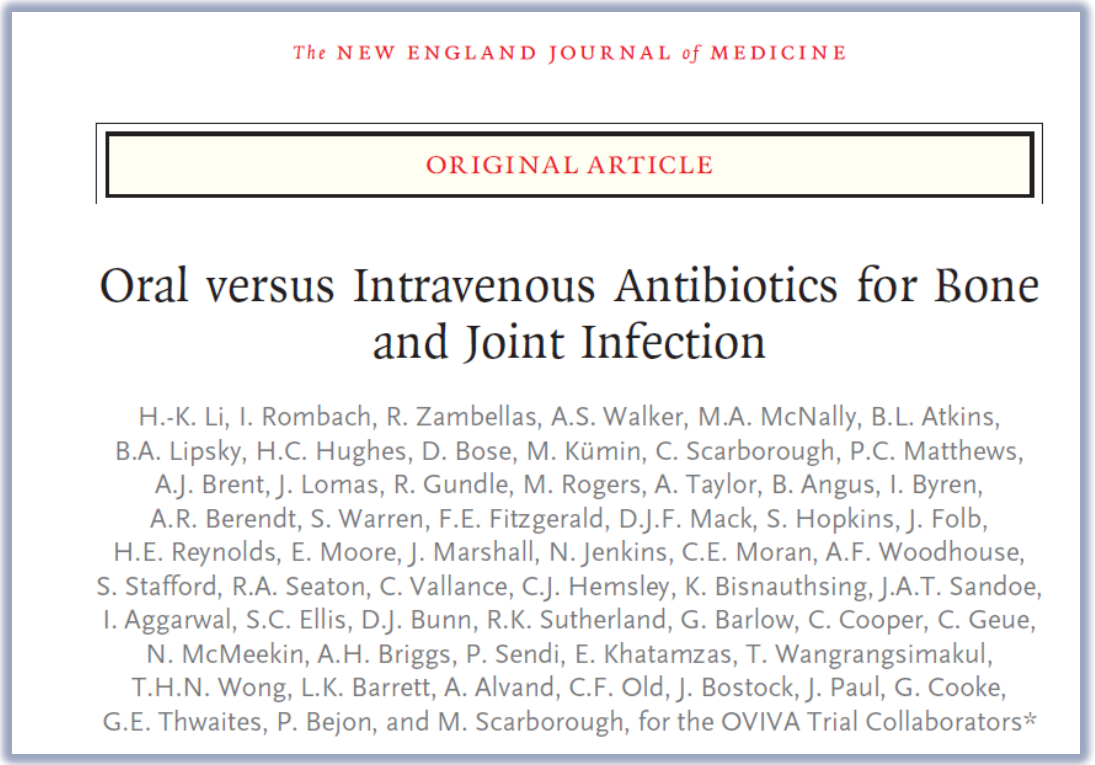
Duration of Treatment?



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

Gariani K et al Diab Obes Metabol 2018;21(2):244-251

Oral vs IV?



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

Li HK et al New Eng J Med 2019;380(5):425-436

Conclusions

- The microbiology of the diabetic foot is an ever changing challenge
- We try and keep up to date – but there is still a lot of work to do
- Think about parenteral antibiotics as a way of avoiding admissions

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

An Update on Antibiotic Management of Infection in the Diabetic Foot

www.norfolkdiabetes.com

ketan.dhatariya@nnuh.nhs.uk

@ketandhatariya