Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

What Should a National Antibiotic Formulary for the Diabetic Foot Look Like?

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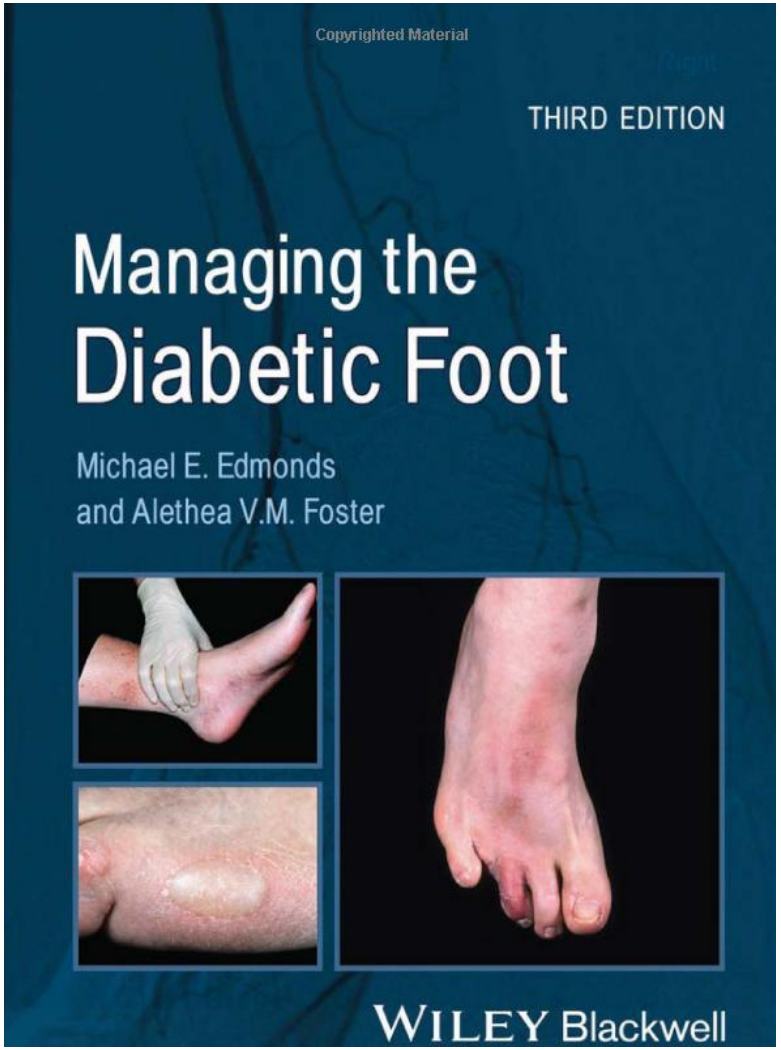
A Quote From Someone We All Know

"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

The Size of the Problem

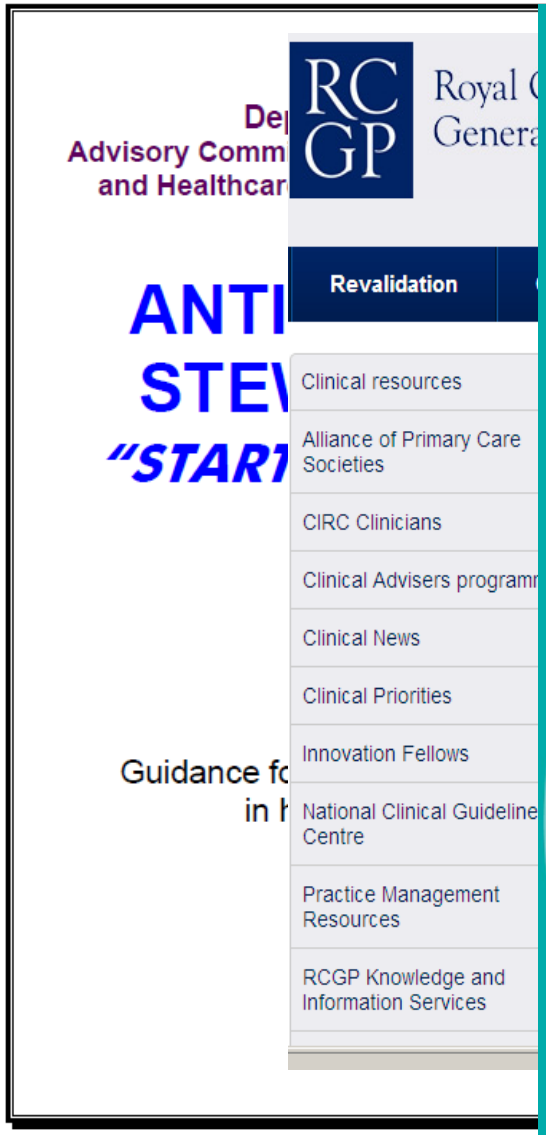
- Diabetes related foot infections are common
  - 58% of newly presenting foot ulcers in the Eurodiale study
- The are the most common reason for a ‘diabetes specific’ acute hospital admission
- They cost a lot of money
  - £1 in every £150 spent in the NHS is spent on the ‘diabetic foot’

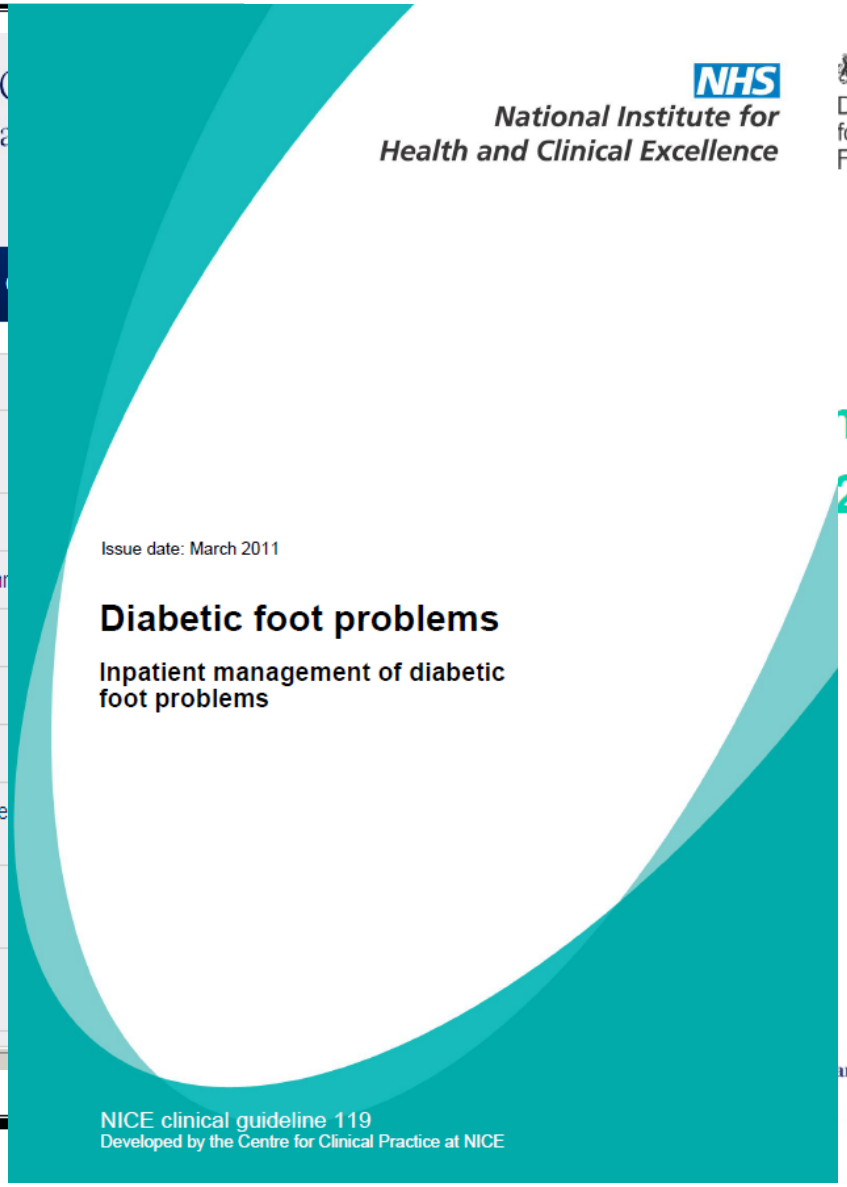
Prompers L et al. Diabetologia 2007;50(1):18-25
Kerr M. NHS Diabetes 2012

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





Year Antimicrobial
nce Strategy
2018

Llywodraeth Cymru
Welsh Government

The Scottish Government
Riaghaltas na h-Alba

What Are the Challenges?

- Does everyone know how to diagnose ‘Mild’, ‘Moderate’, and ‘Severe’ infections?
- As prescribers of the future you’ll need to take that responsibility to get it right first time for the ‘at risk feet’
- Will you have the ability to decide the best form of antibiotic administration?

The Perpetual Challenge of Antimicrobial Resistance

Fauci AS & Marston HD JAMA 2014 DOI 10.1001/jama.2014.2465

What Are the Challenges?

- Locally available administration techniques
  - District or practice nurse availability / knowledge and skills
  - Availability of outpatient parenteral services
  - Difficulties with administration
    - PICC line use associated with
      - VTE
      - Infection
      - Blockage
      - Radiology time
    - IM antibiotic use associated with
      - Discomfort
      - Injection site reactions

Pikwer A et al Anaesthesia 2012;67(1):65-71
Chopra V et al Lancet 2013;382(9889):311-325
Smith RN et al BMJ 2013;347:f6570
Alejandro I et al Poster P18 DFSG Sitges 2013
Bates M et al Poster P321 DUK 2014

What is Available Already?

- IDSA / IWGDF
- Wagner
- University of Texas
- S(AD)/SAD / SINBAD
- Ulcer Severity Index
- Diabetic Ulcer Severity Score
- DEPA

What is Available Already?

- But these are all wound classification / scoring systems and most do not advice on treatment
- The 2012 IDSA guideline suggested using the presence of systemic inflammatory response syndrome (SIRS) to guide moderate from severe infection
- This was recently validated as a way of differentiating moderate from severe – but in patients already hospitalised

Lipsky BA et al Clin Infect Dis 2012;54(12):e132-173
Wukich D et al Diabetes Care 2013;36(11):3706-3711

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 use an agent covering 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

- Don't treat *P. aeruginosa* unless you have proof it is causing infection
- 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

Which Looks Somehow Familiar…..

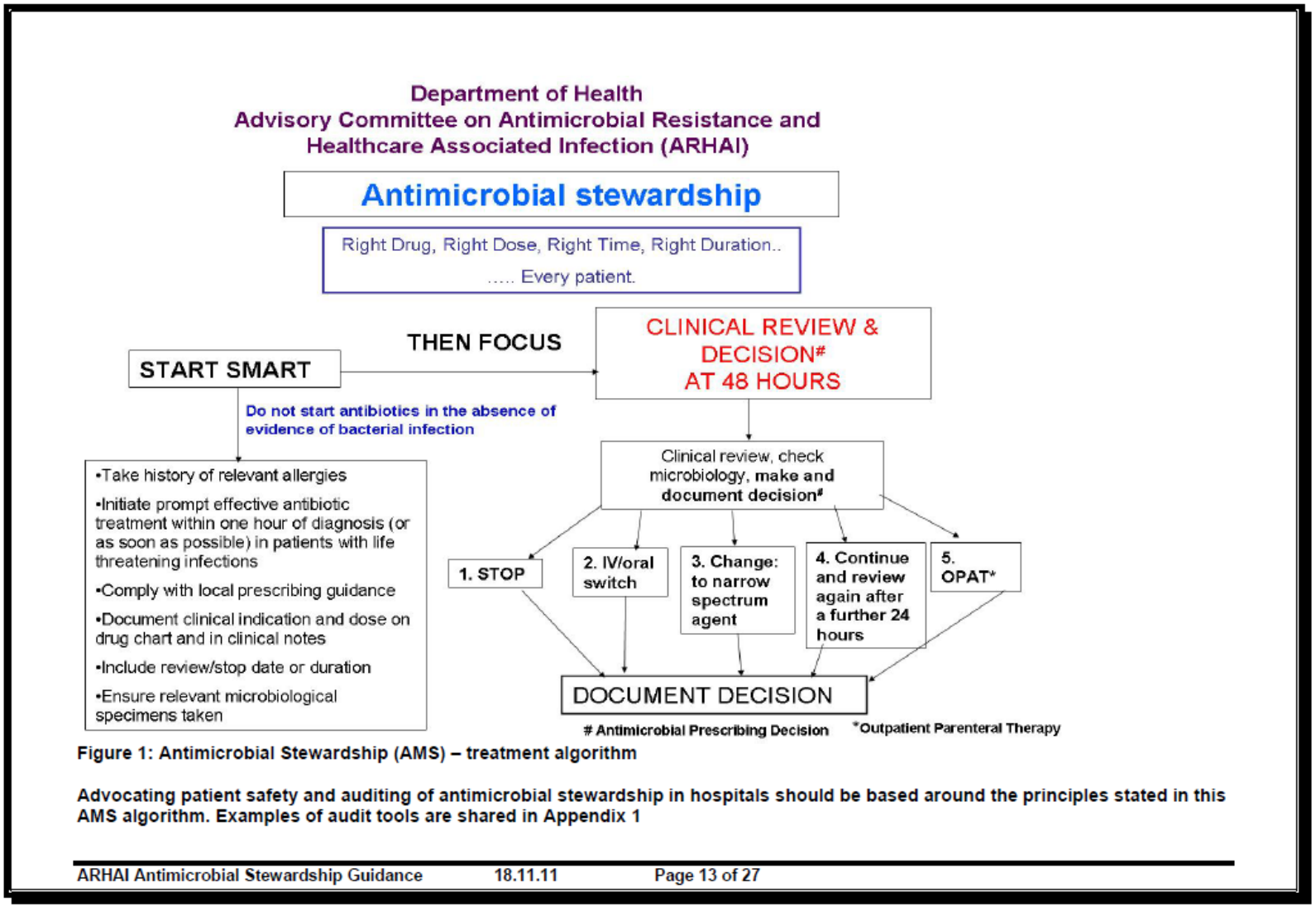


Figure 1: Antimicrobial Stewardship (AMS) – treatment algorithm

Advocating patient safety and auditing of antimicrobial stewardship in hospitals should be based around the principles stated in this AMS algorithm. Examples of audit tools are shared in Appendix 1

www.gov.uk/government/publications/antimicrobial-stewardship-start-smart-then-focus Accessed 1/5/14

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
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	Pseudomonas aeruginosa	***Piperacillin-tazobactam***
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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
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Does NICE Help Us?

- "Due to insufficient evidence, the [Guideline Development Group] felt that it was not possible to make recommendations on individual antibiotics"

- "Although there was insufficient evidence to recommend individual antibiotics, the GDG agreed that antibiotic treatment is crucial to treat diabetic foot infections"

So, no, NICE is not really helpful in this situation

NICE CG 119 http://www.nice.org.uk/nicemedia/live/13416/53556/53556.pdf

Lets Talk About Cost – 1 Month Supply

- Clindamycin - £60.80
- Cephalexin - £6.42
- Levofloxacin - £126.30
- Co-amoxiclav - £12.00
- Doxycycline - £4.48
- Ceftriaxone* - £287.40
- Moxifloxacin - £74.58
- Ertapenem* - £949.50
- Tigecycline* - £1938.60
- Ciprofloxacin - £6.54
- Imipenem/cilastin*- £1080
- Linezolid - £2670
- Daptomycin* - £1860
- Vancomycin* - £389.70
- Tazocin* - £1365.30
- Ceftazidime* - £805.50
- Aztreonam* - £846

Standard doses, generic costs using unbroken pack sizes where applicable - BNF March 2014
* Given IV (nursing and other costs not included)
Assumptions made – 80Kg, normal renal function, antibiotic needed for the whole month

Where Does that Fit In?

Infection Severity	Probable Pathogen(s)	Antibiotic Agent
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Cheaper Treatment Options

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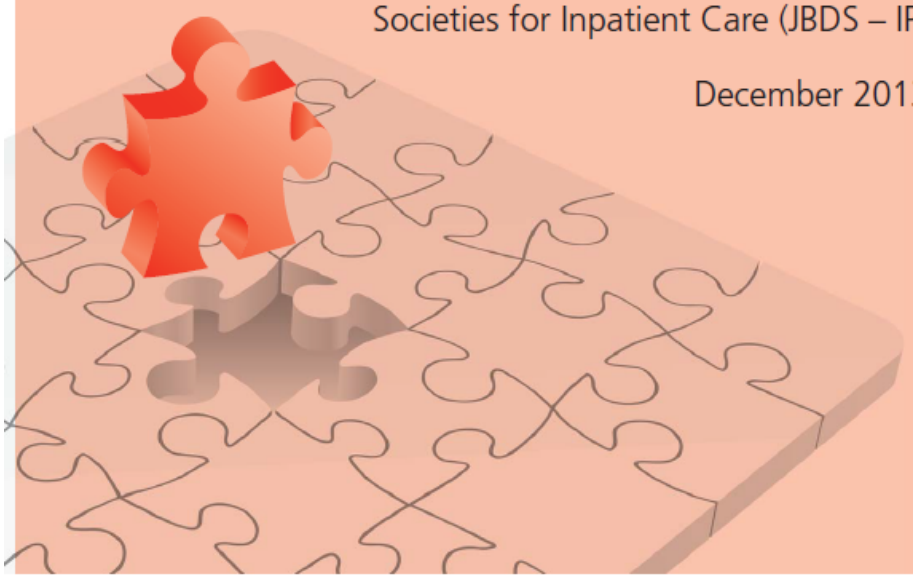
Are There any Limitations to the Available Guidelines?

- 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

Admissions avoidance and diabetes: guidance for clinical commissioning groups and clinical teams

Produced by the Joint British Diabetes Societies for Inpatient Care (JBDS – IP)

December 2013



DIABETES UK CARE. CONNECT. CAMPAIGN.

ABCD

DISN UK GROUP

PCDS Primary Care Diabetes Society

WEDS

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

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

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

What About Osteomyelitis?

- NICE says – 1.2.24 “Do not delay starting antibiotic therapy for suspected osteomyelitis pending the results of the MRI scan”
- However, in the absence of soft tissue infection, osteomyelitis is often chronic and rarely an urgent problem
- You’ll need to follow local protocols to diagnose osteomyelitis – bone biopsy / clinical

NICE CG116 2011 http://www.nice.org.uk/nicemedia/live/13416/53556/53556.pdf Accessed 1/5/14

	FIRST CHOICE		PENICILLIN ALLERGY		DURATION
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Conclusions

- It's not easy
- "You can please some of the people all of the time, you can please all of the people some of the time, but you can't please all of the people all of the time". [?Abraham Lincoln]

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