

Choosing the Right Antibiotic: *The science > art*

LIMB SALVAGE AND COMPLEX WOUND MANAGEMENT

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Primer Case

- 50 yo F hx Mixed Connective Tissue Disease (MCTD), DM1 s/p pancreas/kidney transplant on IS (steroids, tacrolimus, MMF, hydroxychloroquine), with vascular complications resulting in toe ulcerations and acroosteolysis (vs osteomyelitis)
- Comes to ID clinic with c/o
 - Fevers
 - Night Sweats
 - Red toes
 - Drainage from wound on/off x 12-14 months
 - Pain?



Antibiotic Options

1. Conservative vs surgical?

2. Treatment duration?

- a) 0 weeks
- b) 1 weeks
- c) 2 weeks
- d) 4 weeks
- e) 6 weeks

3. What empiric antibiotic regimen

- a) Keflex + Bactrim
- b) Augmentin + doxycycline
- c) Augmentin + doxycycline +
Levofloxacin + Metronidazole
- d) Vancomycin
- e) Vancomycin + Ertapenem
- f) Vancomycin + Zosyn
- g) Linezolid + levofloxacin

Outline

- Primer Case
- Utility of cultures
 - Types of culture
- Empiric Antibiotic Selection
- Therapy Duration

Disclosure: No known conflicts of interest

Treatment Strategy

- 0) Make clinical => laboratory diagnosis
 - > maximal outcome, minimal therapy
- 1) Obtain appropriate specimen for culture
 - ? Surgical intervention
- 2) Empiric antibiotics
 - Antibiotics treat infection, NOT wounds (or providers)
 - Delay in identification of causative organism
 - Risk of treatment failure and side effects
- 3) Determine duration of therapy
- 3) Determine narrowed antibiotic choice

Infection Management Concepts



IWGDF / IDSA Classification

■ Signs symptoms of tissue infection

- Local swelling or induration
- Erythema >0.5 cm around the wound
- Local tenderness or pain
- Local increased warmth
- Purulent discharge

■ Localized vs Systemic

– Fevers, chills, VS alterations, sepsis

SIRS

- T >38 °C or <36 °C
- HR >90 beats/min
- RR >20 breaths/min
 - or PaCO₂ <4.3 kPa (32 mmHg)
- WBC >12 000/mm³
 - or <4000/mm³
 - >10% immature (band) forms

SEPSIS

- = SIRS + ?infection
 - Not just shock
- Mortality 10-50%
- Delay abx >1hr => death

IDSA Guidelines Diabetic Foot Infections, CID 2012
IWGDF Guidance 2019

IWGDF / IDSA Classification

- Mild (2) – No systemic manifestations
 - only the skin or subcutaneous tissue (not deeper tissues) and
 - erythema not >2cm around wound
- Moderate (3) – No systemic manifestations
 - erythema extending ≥ 2 cm from the wound margin
 - involving structures deeper than skin and subcutaneous tissues (e.g. bone, joint, tendon or muscle)
- Severe (4) – any infection with systemic symptoms
 - $T > 38^\circ\text{C}$ or $< 36^\circ\text{C}$, $\text{HR} > 90$ beats/min, $\text{RR} > 20$ breaths/min, $\text{WBC} > 12\,000/\text{mm}^3$ or $< 4000/\text{mm}^3$ or $> 10\%$ bands

IDSA Guidelines Diabetic Foot Infections, CID 2012
IWGDF Guidance, Diabetes Met Res Rev 2017

Consider Treatment Based on Severity

■ Mild: Localized care +/- Oral antibiotics

■ Moderate

- +/- Surgical intervention
- Obtain culture
- Oral vs PO

■ Severe

- Hospitalize, treat for sepsis
- Obtain cultures
- IV fluids, IV antibiotics
- +/- Surgical intervention

Osteomyelitis

- Separate from the IDSA/IWGDF classification
- Clinical diagnosis
- Inflammatory Markers
 - ESR, CRP, +/- procalcitonin
- Imaging
 - Xray
 - MRI, FDG-PET-CT, Tagged WBC)

IDSA Guidelines Diabetic Foot Infections, CID 2012
IWGDF Guidance, Diabetes Met Res Rev 2017

Three major types of pathogens

- Bacterial

- Gram stain negative or positive
- Most bacteria and some fungi will grow
- Polymicrobial

- Fungal

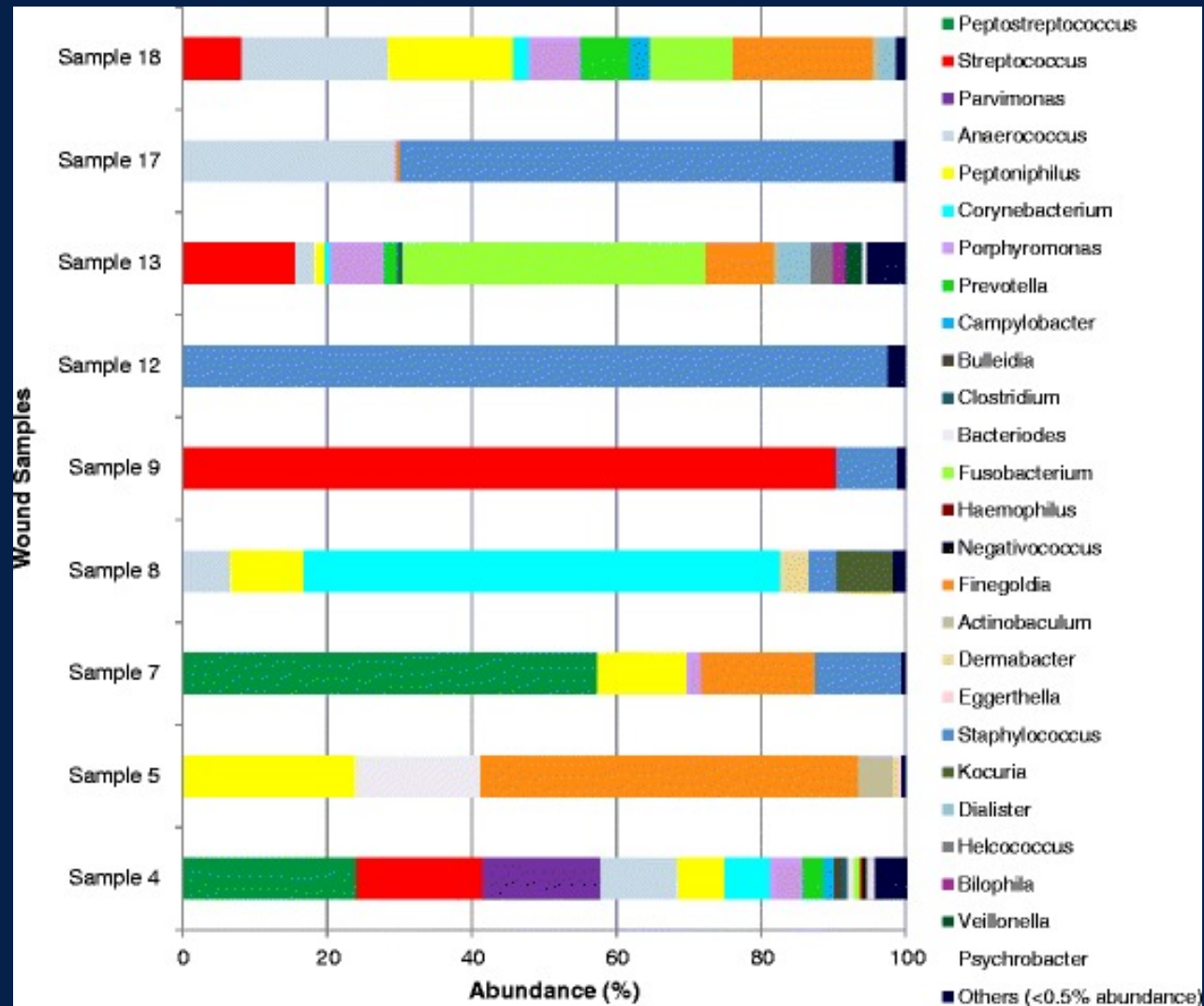
- Mycobacterial

- Chronic non healing wounds
- exposures
- traumatic inoculation

Ulcer Microbiome

- Majority (>67%) of types of bacteria
 - Do not routinely grow in culture
 - Likely not very significant
- Smith et al BMC Microbiol 2016: Diabetic foot ulcers
 - Molecular identification to determine microbiome
 - **Staphylococcus or streptococcus in most ulcers**
- Johani et al Clinical Micro and Infection 2018: Diabetic foot osteo
 - 95% of osteomyelitis associated with an ulcer (and biofilms)
 - 6/20 (30%) only 1 or 2 pathogens, 14/20 (70%) **polymicrobial**

Ulcer Microbiome



Smith et al BMC Microbiol 2016

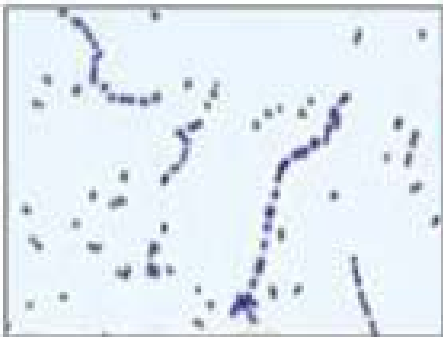
Ulcer Microbiome

- IWGDF 2019 Infection Guidelines
- PICO 5: In a person with diabetes and a foot infection, do the results of molecular (genotypic) microbiological tests better distinguish likely clinically relevant pathogens requiring antibiotic therapy than standard (phenotypic) cultures?
- Recommendation 9: **Do not** use molecular microbiology techniques (instead of conventional culture) for the first-line identification of pathogens from samples in a patient with a diabetic foot infection.
 - (Strong; Low)

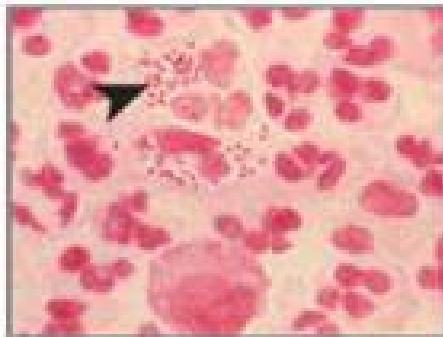
Utility of Gram Stain

- Organisms seen on gram stain
 - Must be in large burden in the sampled site
 - Likely predominant organism
- WBCs on gram stain indicate true infection
- Available in minutes to help guide empiric therapy

Gram-positive cocci



Gram-negative cocci



Gram-positive bacilli



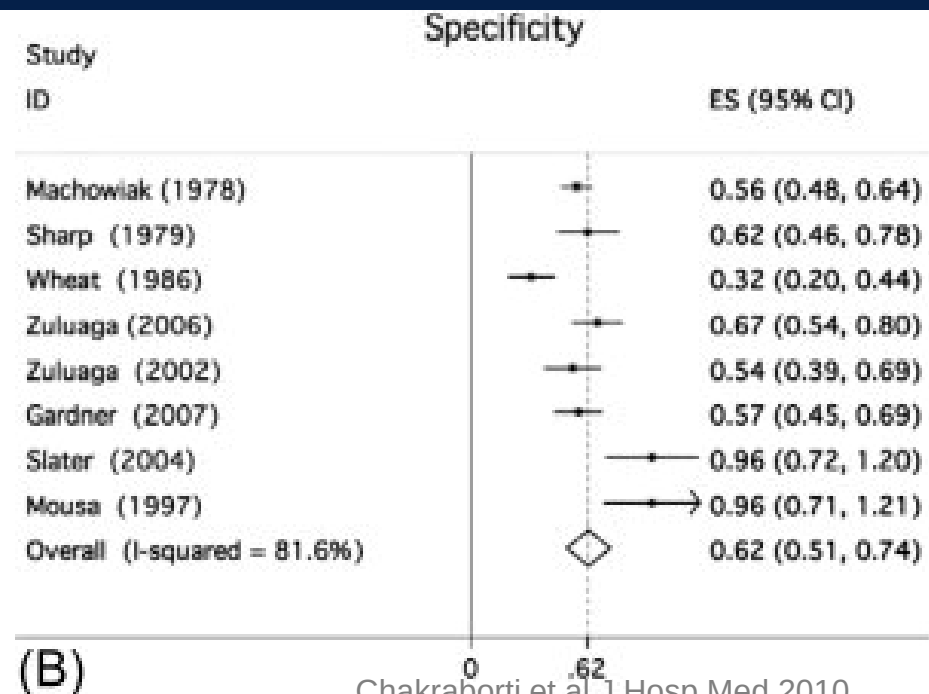
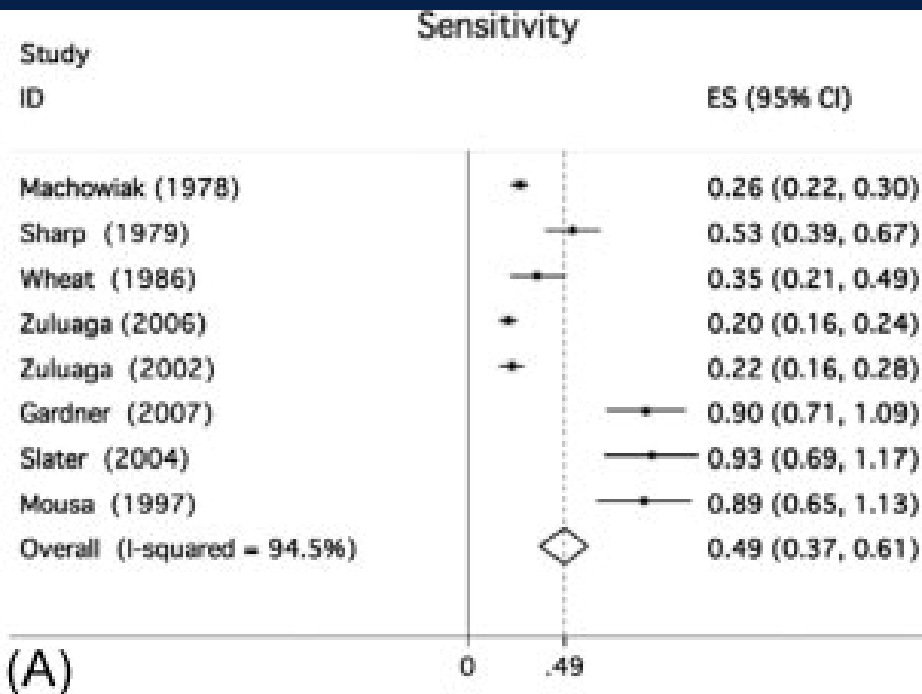
Gram-negative bacilli



IDSA Guidelines Diabetic Foot Infections, CID 2012

Superficial Wound Swabs

- Should not be used to guide management
 - Only have to treat 2 patients to be wrong once!
- Chakraborti et al J Hosp Med 2010



Chakraborti et al J Hosp Med 2010

Wound Swab vs Tissue Sample

- CODIFI (Concordance in Diabetic Foot Ulcer Infection): a cross-sectional study of wound swab versus tissue sampling in infected diabetic foot ulcers in England. Nelson et al, BMJ Open 2018
- Compared wound swab vs tissue swab in the same ulcer
- GPCs ~70%: 44% Staph aureus, 17% Strep spp
 - Pathogen(s) found on:
 - 70% of wound swabs
 - 86% of tissue samples
 - Differed between methods in 58% of patients
 - Overall, tissue sample better than wound swabs in direct comparison but leaves some room for both

Utility of Deep (Tissue/bone) Culture

- Wounds should be debrided and cleansed prior to culturing
- Even very low microbial burden will eventually grow
- Cultures cooking while on empiric antibiotics
 - 2-4 day turnaround
- Determine definitive therapy
 - Dominant bacterial identification
 - Determine if true pathogen (eg MRSA, pseudomonas)
 - Modify empiric antibiotics (eg enterococcus, GAS)

IDSA Guidelines Diabetic Foot Infections, CID 2012
IWGDF Guidance, Diabetes Met Res Rev 2017

Utility of Deep (Tissue/bone) Culture

- Richard et al Diabetes Metab 2011
- French OPIDIA study
 - 291 patients admitted with diabetic foot infections
 - 100% patients received empiric antibiotics
 - 86% had cultures taken
- 56% of patients had antibiotics changed based upon culture results
 - Mismatched antibiotics to susceptibilities
 - Narrowing of empiric therapy

Richard et al Diabetes Metab 2011

When to Perform Deep Cultures

- Any clinically infected wound
 - Sinus tract
 - Abscess
 - Deep soft tissue infection
 - Osteomyelitis suspected
- *May* be ok without cultures
 - Mild wound infection
 - No prior antibiotics
 - No hx MRSA, Pseudomonas, ESBL

IDSA Guidelines Diabetic Foot Infections, CID 2012
IWGDF Guidance, Diabetes Met Res Rev 2017

When to Perform Deep Cultures

- Bone infection / concern for osteomyelitis
 - Soft tissue or sinus tract culture vs bone biopsy
 - 26-49% concordance
 - False negative 52%, False positive 36%
 - Senneville et al, retrospective bone vs wound swab
 - Remission rate 82% vs 50% ($p=0.02$)
 - Bone biopsy culture preferred
 - Get both!
 - Histopathology helpful for duration

Lindbloom et al Foot and Ankle Clinics 2014
Elamurugan et al Int J Surgery 2011
Senneville et al CID 2006
Senneville et al Diabetes Care 2008
Ertugrul J Am Podiatry Med Assoc 2008

Empiric Antibiotics

■ Mild:

- Maybe.... no antibiotics!
- Have to cover Streptococcus species, Staph aureus
 - Keflex, Augmentin, cefpodoxime, TMP/SMX, clindamycin
 - MRSA: TMP/SMX, doxycycline, Clindamycin, Linezolid

■ Mod/Severe:

- PO: Same as above plus add GNR coverage
- IV (severe): vancomycin + GNR coverage
 - Ertapenem, Zosyn, Unasyn, fluoroquinolone

IDSA Guidelines Diabetic Foot Infections, CID 2012
Peters et al Diabetes/Metab Res Rev 2016

Empiric Antibiotics

■ MRSA

- Prior antibiotic exposure, local prevalence (~40% in SF)
 - Vancomycin, tedi/linezolid, daptomycin, clinda, TMP/SMX
 - Dalbavancin, Oritavancin, Televancin (newer, less data)
 - Rifampicin never to be used alone

■ Pseudomonas

- Prior antibiotic exposure, local prevalence (12-25% Cipro R)
- Chronic ulcer (diabetes, vascular, etc), water exposure, climate
 - Zosyn, cefepime, aztreonam, ceftazidime, meropenem, imipenem, fluoriquinolones

IDSA Guidelines Diabetic Foot Infections, CID 2012
Peters et al Diabetes/Metab Res Rev 2016

Ertapenem vs Zosyn

- SIDESTEP trial
 - Prospective RCT of Ertapenem vs Zosyn
 - +/- vancomycin as clinicians choice
 - 576 patients with diabetic foot infections
 - Excluded patients previously known to have resistant organisms
- Favorable clinical response 94% vs 92%
 - No difference in adverse events

Lipsky et al Lancet 2005

Ertapenem vs Zosyn

	Ertapenem (n=173)*	Piperacillin/tazobactam (n=151)*	Observed differences (95% CI)
Gram-positive aerobic cocci	149/176 (84.7%)	132/166 (79.5%)	5.1 (-3.1 to 13.6)
Enterococcus†	19/22 (86.4%)	8/9 (88.9%)	-2.5
<i>Enterococcus faecalis</i>	13/15 (86.7%)	12/16 (75.0%)	11.7 (-19.2 to 41.1)
<i>Staphylococcus aureus</i>	75/90 (83.3%)‡	62/79 (78.5%)	4.9 (-7.6 to 17.2)
Meticillin resistant	14/18 (77.8%)	10/15 (66.7%)	11.1 (-19.8 to 42.7)
Meticillin susceptible	60/71 (84.5%)	52/64 (81.3%)	3.3 (-9.9 to 17.1)
<i>Streptococcus agalactiae</i>	15/21 (71.4%)	22/26 (84.6%)	-13.2 (-38.3 to 10.9)
Gram-negative aerobic bacilli	64/73 (87.7%)	43/56 (76.8%)	10.9 (-2.3 to 25.2)
Enterobacteriaceae§	36/42 (85.7%)	26/33 (78.8%)	6.9 (-11.1 to 25.9)
<i>Pseudomonas aeruginosa</i>	15/18 (83.3%)	7/10 (70.0%)	13.3 (-18.2 to 48.7)
Gram-positive anaerobic cocci	66/74 (89.2%)	48/62 (77.4%)	11.8 (-0.8 to 25.2)
<i>Peptostreptococcus magnus</i>	34/38 (89.5%)	24/27 (88.9%)	0.6 (-15.4 to 20.6)
<i>Peptostreptococcus asaccharolyticus</i>	10/11 (90.9%)	7/11 (63.6%)	27.3 (-10.9 to 58.6)
Gram-positive anaerobic bacilli¶	23/26 (88.5%)	12/17 (70.6%)	17.9 (-6.9 to 45.1)
Gram-negative anaerobic bacilli	33/40 (82.5%)	28/40 (70.0%)	12.5 (-7.2 to 31.3)
Gram-negative anaerobic coccobacilli**	21/25 (84.0%)	11/16 (68.8%)	15.3 (-10.8 to 43.3)

Data are number of pathogens with associated favourable assessment/number of pathogens assessed (observed response) unless otherwise indicated. *Number observed calculated by pooling across baseline severity. †No species identified. ‡Oxacillin susceptibility not provided for one isolate. §Includes *Enterobacter* spp, *Escherichia* spp, *Klebsiella* spp, *Morganella* spp, *Proteus* spp, *Providencia* spp, and *Serratia* spp. ¶Includes *Clostridium* spp, *Eubacterium* spp, and *Propionibacterium* spp. ||Includes *Porphyromonas* spp and *Prevotella* spp. **Includes *Bacteroides* spp.

Table 5: Favourable clinical response rates, for species with at least 20 isolates at FUA, by baseline pathogen

- No difference even with *Pseudomonas* or *Enterococcus* infection

Lipsky et al Lancet 2005

Antibiotic Duration

- SSTI present
 - Tissue or fluid culture to direct antibiotics
 - Anticipate at 1-2 weeks of antibiotic therapy (10-14d)
 - IDSA recommends 2-4 weeks for severe
 - 3-4 weeks for bad peripheral arterial disease
- Penicillins and cephalosporins achieve good soft tissue penetration
 - Do not need to add therapy for GNR unless cultured
 - Consider Bactrim for GNRs if susceptible
 - Preferred over fluoroquinolones due to side effect risks

IDSA Guidelines Diabetic Foot Infections, CID 2012
IWGDF Guidance, Diabetes Met Res Rev 2017

Antibiotic Duration

- Residual bone infection present
 - No way to see margins without a microscope
 - Very wide resection margin 2-5d abx (?no abx)
 - 6 weeks antibiotic therapy
 - 12 weeks no benefit
- No surgery or residual dead bone
 - IDSA recommends 3+ months
- IV then PO when improving
 - 6+ weeks of empiric antibiotics raises risks

IDSA Guidelines Diabetic Foot Infections, CID 2012
Spellberg et al CID 2012

Antibiotic Side Effects

- Renal failure, Liver failure
- Diarrhea, Cdiff
- Rashes
 - Benign to life threatening
 - DRESS
 - Stevens Johnson Syndrome (SJS)
 - Toxic epidermal necrolysis (TEN)
- Development of resistance
- Expensive, delay discharge, Need ID approval



Stevens Johnson Syndrome Clinical Presentation. Medscape.com

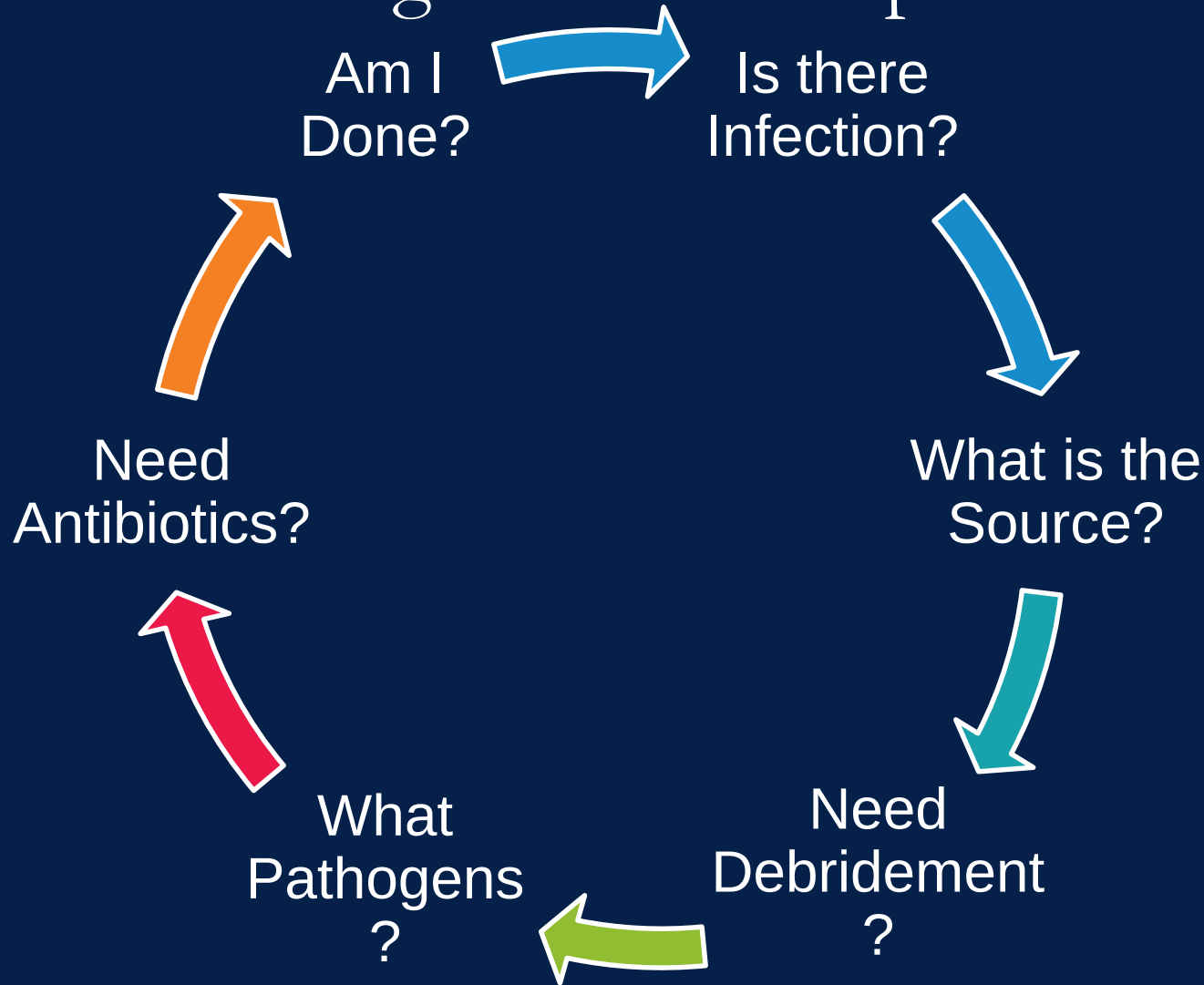
Antibiotic Side Effects

- July 2016 new FDA black box warning on fluoroquinolones
 - Ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin
 - Delafloxacin (Baxdela) new 2017, treats MRSA + PsA
- Issued regarding use in simple UTI, sinusitis, chronic bronchitis
- “These medicines are associated with disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient. As a result, we revised the *Boxed Warning*, FDA’s strongest warning, to address these serious safety issues. We also added a new warning and updated other parts of the drug label, including the patient Medication Guide.”

Primer Case

- 50 yo F hx Mixed Connective Tissue Disease (**MCTD**), DM1, s/p pancreas/kidney transplant on IS (**steroids, tacrolimus, MMF, hydroxychloroquine**), with **vascular complications** resulting in toe ulcerations and acroosteolysis vs osteomyelitis
- Comes to ID clinic with c/o **Fevers**
 - On/off drainage x 12-14 months
 - Asked for deep tissue cultures, but patient hesitant
- Podiatrist unroofs dead skin, finds purulence and sinus track into very soft bone
 - Debrides, resects to proximal hard healthy bone
 - Starts Augmentin + Doxycycline

Infection Management Concepts



Antibiotic Options

1. Conservative vs surgical?

2. Treatment duration?

- a) 0 weeks
- b) 1 weeks
- c) 2 weeks
- d) 4 weeks
- e) 6 weeks

3. What empiric antibiotic regimen

- a) Keflex + Bactrim
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- c) Augmentin + doxycycline +
Levofloxacin + Metronidazole
- d) Vancomycin
- e) Vancomycin + Ertapenem
- f) Vancomycin + Zosyn
- g) Linezolid + levofloxacin

Primer Case

- 50 yo F hx Mixed Connective Tissue Disease (**MCTD**) and s/p pancreas/kidney transplant on IS (**steroids, tacrolimus, MMF, hydroxychloroquine**), with **vascular complications** resulting in toe ulcerations and acroosteolysis vs osteomyelitis
- New draining sinus tract to soft bone, s/p resection, started on Augmentin/Doxycycline
- No gram stain available (lab was closed over the weekend)
- Fevers improving, redness improving
- Cultures grow:
 - *Pseudomonas aeruginosa*

Antibiotic Options

1. Conservative vs surgical? – clean margins
2. Treatment duration?
 - a) 0 weeks
 - b) 1 weeks
 - c) 2 weeks
 - d) 4 weeks
 - e) 6 weeks
3. What empiric antibiotic regimen
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 - d) Vancomycin
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Key Concepts

- Recognize severity of infection
- Wound swabs are bad
 - Bone > tissue >>> swab
- Treatment options hinge on culture data
 - Good cultures lead to better antibiotic regimens
 - Target therapy, don't get it wrong
 - Least antibiotic exposure
 - Side effects of antibiotics can be bad
- Cure is possible
 - Combination of appropriate surgical + antibiotic Tx



University of California
San Francisco

Primer Case

- 71 yo M DM2, PVD, right BKA, recurrent ulcers
 - p/w diabetic ketoacidosis
 - noted to have left foot/toe gangrene and purulent drainage
 - Hx penicillin allergy (hives)
- L foot deep tissue I+D necrotic tissue debrided
 - Wound swab gram stain GPCs
- L foot TMA wide margins
 - No bone cultures taken
 - Pathology with osteomyelitis at margins

Antibiotic Options

1. Treatment duration?

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Primer Case

- 71 yo M DM2, PVD, right BKA, recurrent ulcers
 - p/w **diabetic** ketoacidosis
 - noted to have left foot/toe **gangrene** and **purulent** drainage
 - Hx **penicillin allergy** (hives)
- L foot deep tissue I+D necrotic tissue debrided
 - Wound swab gram positive cocci (**GPCs**) on stain
- L foot TMA wide margins
 - **No bone cultures** taken
 - Pathology with **osteomyelitis at margins**

Antibiotic Options

1. Treatment duration?

- a) 0 weeks
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- f) Vancomycin + Zosyn
- g) Linezolid + Meropenem

Primer Case

- 71 yo M DM2, PVD, right BKA, recurrent ulcers, DKA, L foot infection s/p I+D, angioplasty, TMA with positive margins no cultures

1. Treatment duration?

- a) 0 weeks
- b) 1 weeks
- c) 2 weeks
- d) 4 weeks
- e) 6 weeks

2. What antibiotic regimen

- a) Keflex + Bactrim
- b) Augmentin + doxycycline
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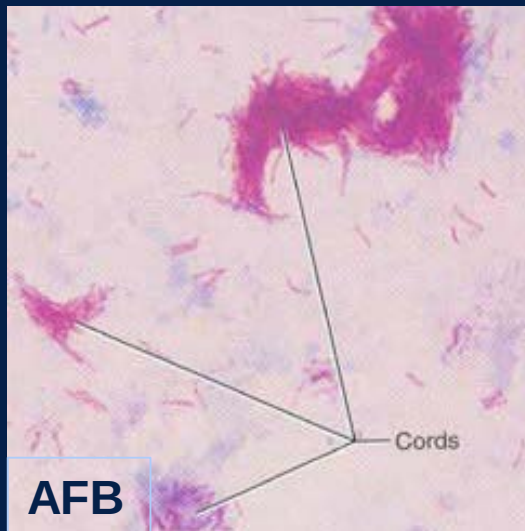
Tigecycline vs Ertapenem+Vancomycin

- Phase 3 randomized double blind trial, multisite international
- Diabetic foot infections +/- osteomyelitis
 - Acute infection or failing prior antibiotics
- Cure rate worse with Tigecycline
 - Tigecycline 77.5% vs Vanc/Erta 82.5%
 - $P = 0.05$
 - 36% vs 64% if osteomyelitis
- More adverse events with tigecycline
- Black box warning: increased risk of death

Lauf et al Diagn Microbiol Inf Dis 2014

Wound Swabs

- Bacterial only
 - Gram stain & bacterial culture
 - Interferes with fungal and AFB cultures
- Need tissue or fluid for fungal and AFB cultures



Ponka. Can Fam Physician 2014.
<http://faculty.mc3.edu/jearl/ML/ml-6.htm>

When NOT to Perform Deep Cultures

- Gardner et al Diabetes Care 2014
 - 77 subjects with diabetic foot ulcers at the Iowa City VA
 - Excluded vascular ulcer, osteomyelitis, those on abx in past 2 weeks, systemic infection
 - Routine debridement, offloading, wound care, etc
- NO antibiotics given
 - 65 (84%) ulcers healed over 26 weeks f/u
 - 5 (6.5%) had infection-related complication (?underpowered)
 - No correlation between culture data and outcome

Gardner et al Diabetes Care 2014

Utility of Cultures

- Mild infections
 - I+D with wound care +/- abx for simple cellulitis
 - No cultures
 - No swabs
- Moderate to severe infections
 - Treating with antibiotics
 - Deep tissue biopsy
- Osteomyelitis
 - Bone biopsy for pathology and culture

Antibiograms

- Infectious Disease Management Program
- idmp.ucsf.edu

Organism	Total Isolates	PCN	NAF	ERY	CLIN	CIP	DOX	T/S	VANC
<i>Staphylococcus aureus</i>	352	0	61	46	66	59	94	96	100
MRSA	136	N/A	N/A	10	44	19	90	95	100
MSSA	216	0	100	69	80	85	97	97	100

Wound Swabs

- Copeland-Halperin J Wound Care 2016
 - Meta-analysis of any wound culture
 - Wound swabs frequently performed
 - unable to determine colonization vs infection
 - Punch biopsy of deep tissue
 - ~100% sensitive, 90% specific
 - More sensitive for antibiotic-resistant wounds