The Asymptomatic Wound with Positive Cultures: To Treat or Not to Treat?

J. Alex Viehman, MD
Clinical Assistant Professor of Medicine, Division of Infectious Diseases
University of Pittsburgh Medical Center

Disclosures

- I have no financial disclosures
- I will not discuss/recommend any non-FDA approved medications or off-label use

Overview/Learning Objectives

- Discuss the pathophysiology of chronic wounds (will not discuss acute wounds)
- Evaluate the utility of systemic antibiotics for treatment of chronic wound settings
- Review important factors in deciding if/when to treat chronic wound with systemic antibiotics

Case

- A 55-year-old male has Type II Diabetes complicated by peripheral neuropathy
- He developed a callous on the plantar surface of the Right First MTP joint
- He underwent bedside debridement of nonviable tissue and was given offloading shoe, wound at that time was ~1.5 cm in diameter
- 3 months later he has a 2 cm diameter wound with 0.5 cm depth, and comes for follow-up

Physical exam

- T 37, P 85, BP 133/72
- Right foot with well circumscribed ulcer 2 x 0.5 cm, with <0.5 cm erythema surrounding
- Granulation tissue noted in wound, with thick clear fluid on gauze, no foul odor
- No warmth or tenderness at site, sensation decreased below ankle
- Pulses 1+ PT/DP
- Labs: WBC 9.3 ESR 35 Hgb A1c 8.9
- Wound culture has Streptococcus intermedius

Questions

1. What would be the aim of treatment with antibiotics in this patient?
2. Should a culture have been obtained in this patient?
3. Is this patient truly asymptomatic ?
4. Should systemic antibiotics be given?

What would be the aim of treatment with antibiotics in this patient?

- Treatment of possible acute infection? (>2cm size, persistence x3 months, non-purulent drainage)
- Prevention of severe infection/sepsis?
- Promotion of wound healing/prevention of amputation?

Wound epidemiology

- The rate of diabetic foot ulceration is 6-13% in diabetic patients
- The rate of acute infection is up to 7% per year for patients with and ulcer or following with a diabetic foot center
- However, there is no convincing evidence that treatment with systemic antibiotics for uninfected ulcers prevents infection
- IDSA guidelines suggest only treating with antibiotics if there is purulence or two or more classic symptoms: erythema, warmth, tenderness, pain, or induration

Sorber and Abularrage, Seminars in Vascular Surgery, 2021 34 (1): 47-53
Joesph et al, Journal of Vascular Surgery 2010 Sep;52(3 Suppl):67S-71S
Lipsky et al Clinical Infectious Diseases2012 June 54(12): e132-73

Infection prognosis

University of Texas

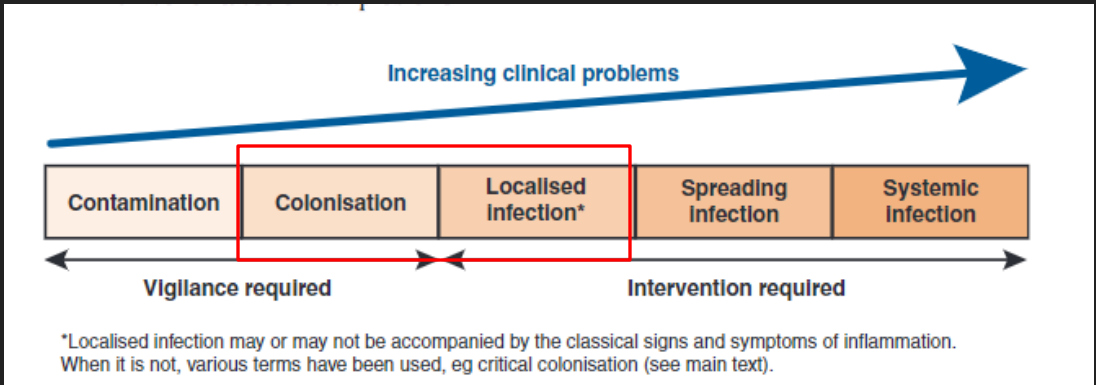
	GRADE			
STAGE	0	1	2	3
A	Pre-ulcerative lesions No skin break	Superficial wound No penetration	Wound penetrating tendon or capsule	Wound penetrating bone or joint
B	With infection	With infection	With infection	With infection
C	With ischemia	With ischemia	With ischemia	With ischemia
D	With infection and ischemia	With infection and ischemia	With infection ad ischemia	With infection and ischemia

- Infection is associated with worse limb outcomes
- Presence of infection associated with significant increase in amputations
- However, this does **not** imply antibiotics improve outcome if no acute infection

Table II: Association of WIFi, University of Texas, and Wagner classifications with Outcomes

Classification system		Medical or minor surgical n=46 (%)	Major amputation n=17 (%)	p value
WIFi stratification	Very Low	7 (15.22)	0	0.000
	Low	10 (21.74)	0	
	Moderate	23 (50.00)	2 (11.76)	
	High	6 (13.04)	15 (88.24)	
University of Texas by stage	A	0	0	0.070
	B	33 (71.74)	7 (41.18)	
	C	1 (2.17)	1 (5.88)	
	D	12 (26.09)	9 (52.94)	
University of Texas by grade	0	0	0	0.001
	1	13 (28.26)	0 (17.65)	
	2	19 (41.30)	3 (82.35)	
	3	14 (30.43)	14 (82.35)	
Wagner grade	0	0	0	0.000
	1	6 (13.04	0	
	2	18 (39.13)	1 (5.88)	
	3	11 (23.91)	3 (17.65)	
	4	9 (19.57)	4 (23.53)	
	5	2 (4.32)	9 (52.94	

Boulton et al. The Diabetic Foot. In: Feingold KR, South Dartmouth (MA): 2000-. Figure 2
Vera Cruz et al. Malaysian Orthopaedic Journal 2020 Nov;14(3):114-123



CHRONIC WOUNDS

e.g. diabetic foot ulcers, venous leg ulcers, arterial leg/foot ulcers or pressure ulcers

Localized infection	Spreading infection
■ New, increased or altered pain* ■ Delayed (or stalled) healing* (Box 5, see page 10) ■ Periwound oedema ■ Bleeding or friable (easily damaged) granulation tissue ■ Distinctive malodour or change in odour ■ Wound bed discoloration ■ Increased or altered/purulent exudate ■ Induration (Box 5, see page 10) ■ Pocketing (Figure 2) ■ Bridging (Figure 3)	As for localised infection PLUS: ■ Wound breakdown* ■ Erythema extending from wound edge ■ Crepitus, warmth, induration or discoloration spreading into periwound area ■ Lymphangitis (Box 5, see page 10) ■ Malaise or other non-specific deterioration in patient's general condition

Notes

- In patients who are immunocompromised and/or who have motor or sensory neuropathies, symptoms may be modified and less obvious. For example, in a diabetic patient with an infected foot ulcer and peripheral neuropathy, pain may not be a prominent feature[4]
- Arterial ulcers – previously dry ulcers may become wet when infected
- Clinicians should also be aware that in the diabetic foot, inflammation is not necessarily indicative of infection. For example, inflammation may be associated with Charcot's arthropathy

*Individually highly indicative of infection. Infection is also highly likely in the presence of two or more of the other signs listed

Infections in Chronic Wounds

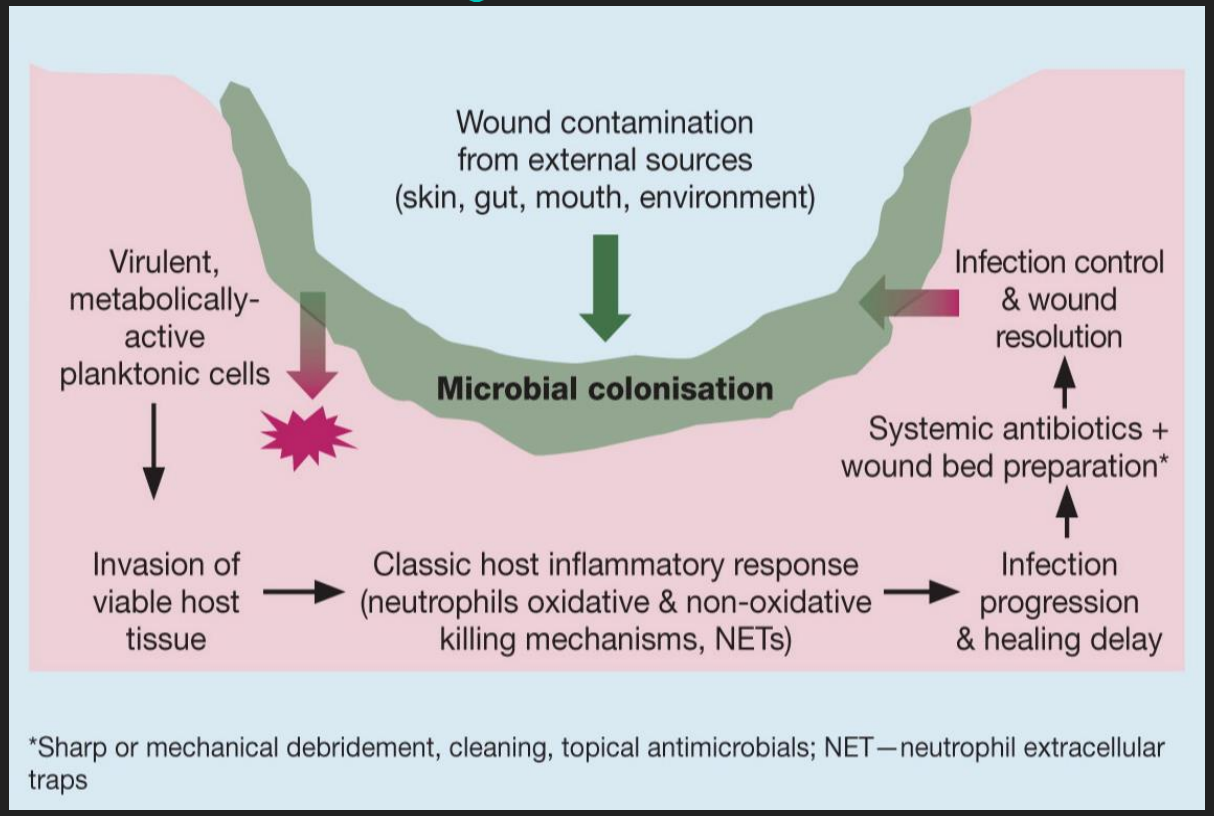
- The World Union of Wound Healing Societies has a developed different approach to infection in chronic wounds
- Classic signs of infection may be less reliable to for chronic wounds and **localized infection/critical colonization** at these sites can be more subtle

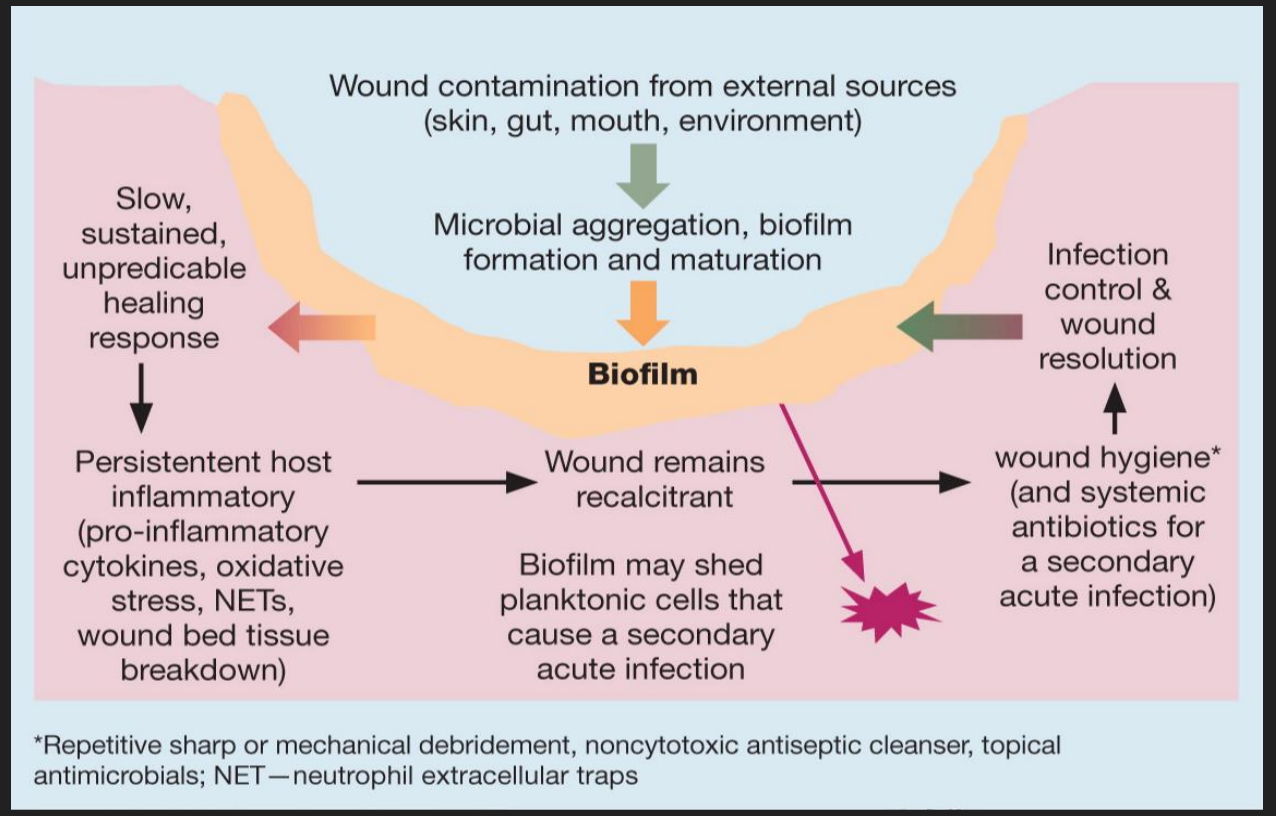
Harding et al. Wound infection in clinical practice. 2008 An international consensus International Wound Journal, 5: iii-11.

Acute vs Chronic Wound Infections

	Acute	Chronic
Symptoms	Overt- purulence, erythema, pain, warmth, swelling, fluctuance	Subtle- pocketing, stalled healing, non-purulent discharge, change in odor/pain, friable tissue
Systemic symptoms	Fever, leukocytosis often present	Rare, unless progressed to acute secondary infection
Invasion of surrounding tissue	Common/early	Rare/later complication
Microbiological etiology	Replicating, metabolically active organisms	Biofilm with mostly dormant/immobile/non-dividing bacteria
Inflammatory etiology	Neutrophils attack pathogens, with intracellular killing, acute oxidative damage	Ineffective neutrophil response to biofilm without killing, chronic oxidative damage, increased IL-18/TNF-alpha

Acute vs Chronic Wound Infections



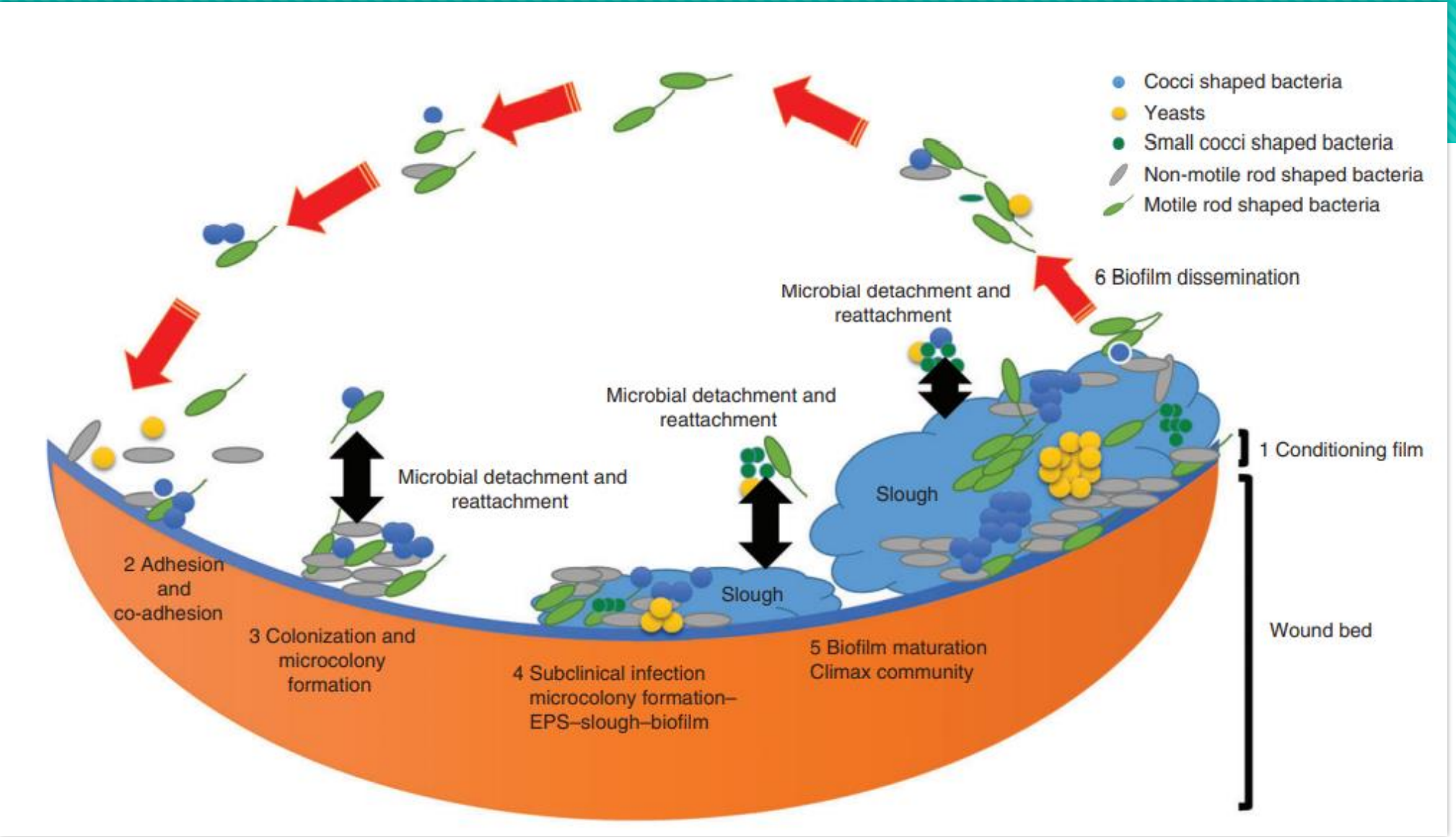


Hurlow and Bowler Journal of Wound Care 2020 May 2, ; 31(5) 436-445

Key Components of Biofilm

- Extracellular polymeric substance:
  - Polysaccharides
  - Glycolipids, proteins
  - Extracellular enzymes
  - Other debris (DNA, blood products etc.)
- Mono- or poly- microbial colonies of organisms
- Surface attachment
  - Abnormal surfaces:
    - Central venous catheters, prosthetic joints
    - Bronchiectatic airways (cystic fibrosis)
    - Dental surfaces
    - Wounds (lack of skin epithelial protection)

Biofilm



Percival. British Journal of Surgery 2018 Jan 104(2) e85-94

Antibiotics- Mechanisms of Action

- **Cell division**
  - Inhibit cell wall formation, arresting cell division
    - Beta-lactams (Penicillins, Cephalosporins, Carbapenems)
    - Glycopeptides (Vancomycin, Daptomycin)
  - Inhibit DNA replication, arresting cell division
    - Fluoroquinolones (Ciprofloxacin, Levofloxacin, Moxifloxacin)
  - Inhibit folate synthesis, arresting DNA replication
  - Sulfonamides (TMP/SMX)
- **Protein synthesis**
  - Inhibit 30S ribosomal subunit
    - Aminoglycosides (Gentamicin, Tobramycin)
    - Tetracyclines (Doxycyline, Tigecycline)
  - Inhibit 50S ribosomal subunit
    - Clindamycin
    - Oxsazlidinones (Linezolid, Tedizolid)
    - Macrolides (Azithromycin)

Biofilm- A Problem for Antibiotics

- Bacteria in biofilm avoid antibiotic killing by:
  - **Avoiding penetration** of agents due to extracellular matrix
    - Biofilm in wounds not amenable to vascular delivery of antibiotics
  - **Not replicating**, avoiding division acting agents
  - Being relatively **metabolically inert**, not relying on much protein synthesis
  - Relying on **extracellular enzymes** to scavenge nutrients

Treatment for Biofilm

1. Assumption of presence (estimated 60-90% of all chronic wounds)
2. Debridement- Surgical, enzymatic, mechanical etc.
3. Antisepsis and antibiofilm agents ->

Table 1. *Summary of antibiofilm agents—mechanisms and levels of evidence*

Product	*Mechanism of Antibiofilm Action*	*Antibiofilm Evidence (Method, Model)*	*Healing Outcomes Evidence (Outcome Measure, Wound Type)*
Polyhexanide (polyhexamethylene biguanide or PHMB)	Disruption and increased permeability of bacterial cell membranes	Level VI[21] (PRB, porcine *in vivo*)	Level IV[22] (% size reduction, varied)
Poloxamer-based surfactants (PluroGel®, Medline Industries, Inc., Northfield, IL)	Inhibition of bacterial surface adherence Reduces cohesion of constituent biofilm molecules	Level VI[25] (PRB, Porcine *ex vivo*)	Level IV[26] (complete healing, varied) Level IV[24](complete healing, varied)
AWG (BlastX™, Next Science, St. Paul, MN)	Dissolves the extracellular polysaccharide matrix, exposing encapsulated bacteria for removal Osmotic lysis of cell wall	Level VI[8] (MTP and murine *in vivo*, CLSM)	Level I[28] (50% size reduction at 4 weeks, varied) Level I[27] (% size reduction or complete closure, varied)
Cadexomer Iodine (IODOSORB™; Smith and Nephew, London, United Kingdom)	Directly destroys biofilms Collapses bacterial glycocalyx Traps bacteria within beads.	Level VI[29] (MTP, CLSM) Level VI[30] (porcine *in vivo* and *ex vivo*, HPT) Level IV[31] (clinical DFUs, SEM/FISH)	Level I[32] (Complete healing at 4–12 weeks, VLUs)
Honey	High osmolarity Low pH Peroxide produced by breakdown of glucose	Level VI[35] (MTP, CVS, and CLSM)	Level I[34] (Various, partial thickness burns)
Hypochlorous acid	Chemical inactivation of various cellular processes, including amino acid modification and protein synthesis	Level VI[36] (MTP, PRB, and CVS)	Low-to-strong based on wound type[37] (Expert consensus panel)
Lasers and phototherapy	Induction of oxidative stress Impaired polysaccharide production	Level VI[38] (CLSM, flow chamber) (HPT, murine)	None
Low frequency ultrasound	Microstreaming and cavitational effects	Level VI[41] (CLSM, plated biofilms)	Varies[40]
Electroceuticals	Disruption of electrostatic adhesion forces Superoxide production Bacterial membrane enzyme disruption	Level VI[43] (CVS + HPT, flow chamber) Level VI[42] (SEM, polycarbonate filter) Level VI[46] (SEM, porcine *in vivo*)	Level VI[46] (acute wound closure time, porcine *in vivo*) Level III[45] (time to complete closure and rate of size reduction, varied)

Mechanisms of action and levels of evidence for available antibiofilm agents for wound care.
AWG, antimicrobial wound gel; CLSM, confocal laser scanning microscopy; CVS, crystal violet staining; DFUs, diabetic foot ulcers; FISH, fluorescence *in situ* hybridization; HPT, histopathology; MTP, microtiter plate; PRB, plating of recoverable bacteria; SEM, scanning electron microscopy; VLUs, venous leg ulcers.

Weigelt et al Advances in Wound Care 2021 Jan;10(1):13-23
Evelhoch Surgical Clinics of North America 2020; 100(4): 727-732

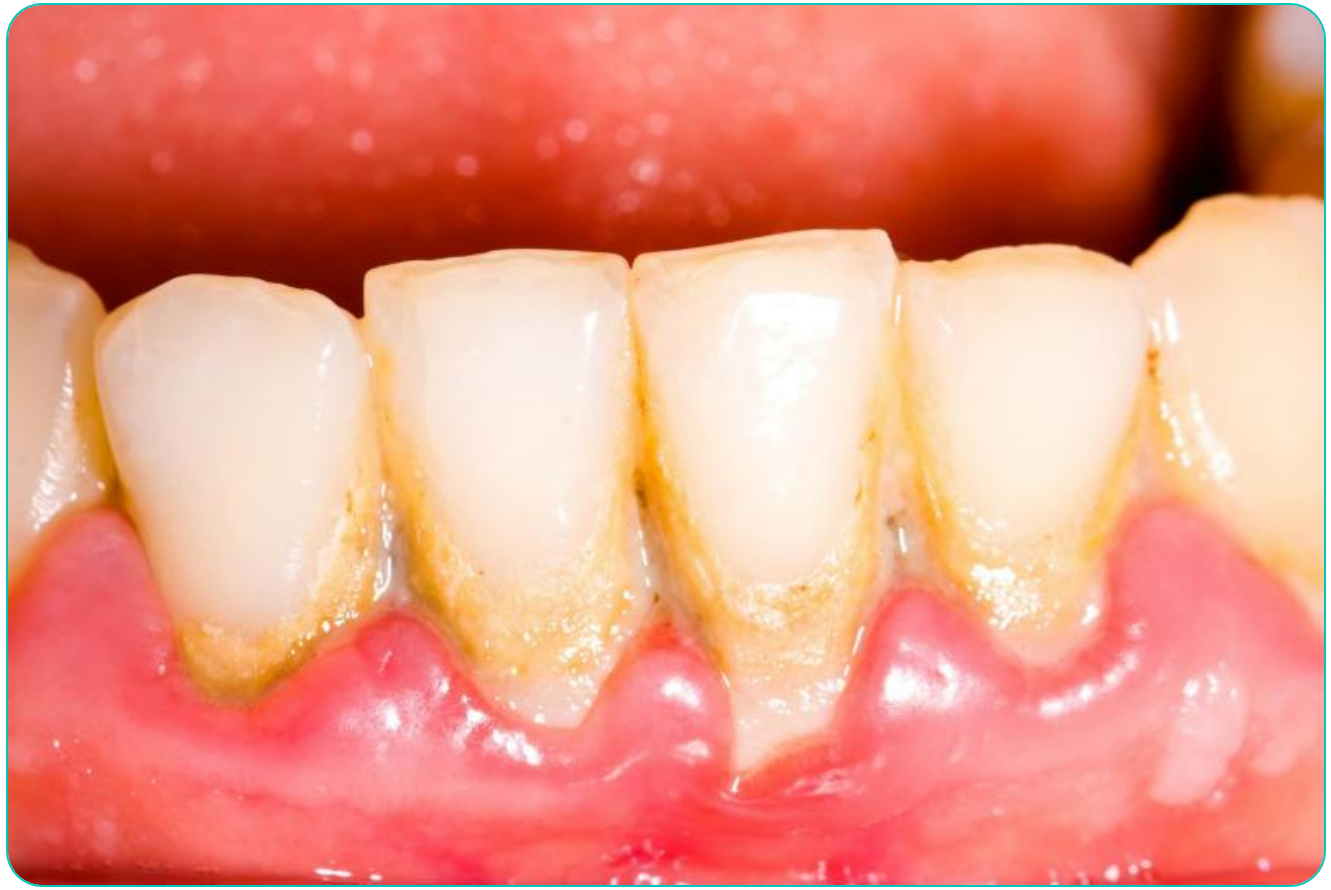
Back to our case

- A 2 cm diabetic foot ulcer with non-purulent drainage and slow healing (3 months)
- Should a culture be taken?
- Should antibiotics be given?

Decision to culture

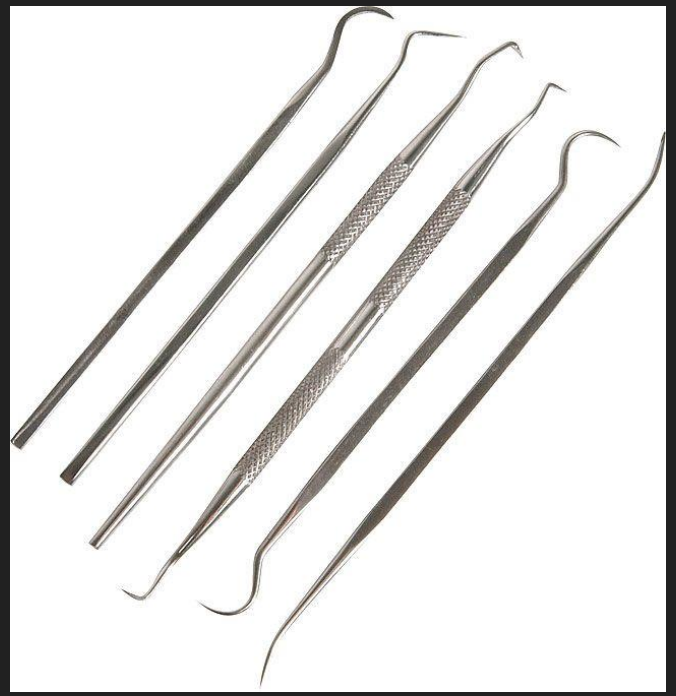
- In a patient without indications for systemic treatment- no wound cultures should be obtained, **and a positive cultures should not change decision to treat**
- In a patient with equivocal indications for systemic treatment, would cultures can help with type of treatment decisions **but should not be the sole factor** in determining ***if*** treatment in indicated

A related question- How would you treat this condition?



Choose Your Fighter?

OR



To Treat or not to Treat?

- In a truly asymptomatic wound:
  - Do not culture unless planning to treat
  - Treat only:
    - If the patient is **unable** to mount a response: e.g. severe neutropenia, profound immunosuppression
    - In the setting of sepsis of **without other** clear etiology

To Treat or not to Treat? (2)

- In a patient with a few signs/symptoms of chronic wound infection/critical colonization (friable tissue, non-purulent discharge, pocketing, stalled healing etc.)
  - In addition to debridement and biofilm management, consider treatment with antibiotics only if:
    - Severe immunocompromise, neutropenia etc.
    - Significant change in pain pattern/severity without other cause
    - Fever, night sweats or other nonspecific symptoms without other cause
    - Increased inflammatory markers without other etiology
    - Suspicion for developing cellulitis undrained abscess

		Jafari (2014) [16]	Al-Shammaree (2017) [17]	Umapathy (2017) [18]- requested	Efat (2018) [19]	Korkmaz (2018) [20]	El-Kafrawy (2019) [21]	Zakariah (2020) [22]	Todorova (2021) [23]
ESR (mm/hr)	Cut-off value	40.5	31.5	42.7*	Not	42	40.5	Not	Not Available
	Sensitivity %	90	100	52.7*	Available	73.68	77	Available	
	Specificity %	94	93	86.2*		84.21	40		
	AUC	0.967	1	0.74		0.962	0.631		
CRP (mg/L)	Cut-off value	71	Not	35*	Not	28	385	319.2	512.4
	Sensitivity %	80	Available	58.9*	Available	100	83	80	80
	Specificity %	74		95.4*		97.37	63	89	79
	AUC	0.871		0.78		0.998	0.827	0.91	0.856

Sharma et al PLOS ONE 2022;17(4): e0267412.

Biomarkers

- Inflammatory markers can be helpful adjunct information, but are nonspecific
- Sedimentation rate can be elevated in chronic wounds without infection
- In patient where there is evidence of chronic infection and possible early acute infection, the CRP may the most helpful biomarker
  - A recent comparison of WBC, ESR, CRP and procalcitonin showed CRP had the best sensitivity, but the cutoff values varied significantly

Empiric Treatment?

1. If decision is made to treat, cultures should be obtained from tissue after debridement
2. Empiric therapy while awaiting cultures can be given, but in most cases prefer waiting for definitive therapy
3. Targets if empiric therapy chosen:
    - Staph aureus (including MRSA if known colonizer or high suspicion)
    - Streptococci
    - E. Coli/Klebsiella can be considered especially is stool contaminated (e.g. sacral ulcers)

Which Pathogens to Target

- Important pathogens that should be targeted if in the wound
  - **Staph aureus (MSSA/MRSA)**
  - **Streptococcus species**
  - **E coli/Klebsiella**
- These bacteria may not always require targeted treatment, especially in polymicrobial cultures
  - **Proteus ("Swarm")**
  - **Pseudomonas, Acinetobacter (often in tap water)**
  - **Strict Anaerobes (depending on debridement quality, oxygen deliver to tissue)**
- These organisms frequently do not require target treatment
  - **Enterococcus (including VRE)**
  - **Candida**
  - **Coagulase-negative Staphylococcus**
  - **Corynebacterium/Bacillus**

Duration of Therapy

1. Systemic antibiotics in a chronic infection (excluding osteomyelitis) are targeted strikes given at times of suspected tissue invasion
2. Improvement should be expected within days
3. Duration should be considered for 5-10 days, not to exceed 2 weeks
4. Frequent courses and longer duration of therapy put the patient at risk for drug resistance in the future

Conclusions

1. Most of the time, cultures from asymptomatic chronic wound should not be treated with systemic antibiotics
2. Symptoms of chronic infection are more subtle than acute infection, and chronic infection may lead to acute secondary infection
3. Debridement is the most effective tool against biofilm, which is the driver of chronic wound infection
4. Systemic antibiotics are unlikely to help a chronic infection unless there is suspected superimposed acute infection
5. In this setting, post debridement cultures may be obtained, and a trial of systemic antibiotics given, with culture-directed therapy for 5-10 days

Questions?

Thank you for the invitation to speak at the 9th Annual Comprehensive Wound Care Symposium!