Use of Chronic Antibiotics:
What does the Evidence Tell Us?

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Disclosures

- None.

Objectives

- To discuss the role of chronic suppressive antibiotics in the setting of chronic prosthetic joint infections and osteomyelitis
- To discuss the utility of using suppressive antibiotics in patients with recurrent cellulitis
- To discuss the use of chronic antibiotics in elderly patients with recurrent urinary tract infections
- To review some implications of chronic antibiotic use including emergence of resistance and side effects
- Take home highlights

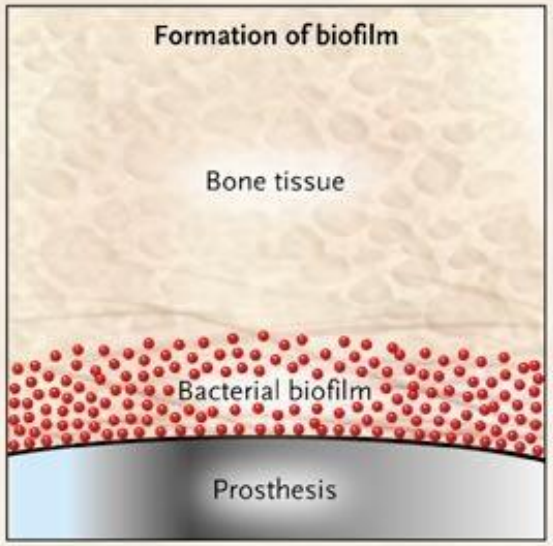
Clinical Scenario

- A 76yo man with a h/o DM, CAD, CVA, COPD, and OA is being seen regarding sepsis. He presented with an infected/ischemic toe wound with purulent drainage and associated cellulitis. 2/2 blood cultures + MSSA. On the 3rd day of his hospital stay he develops worsening pain in his R hip where he had a prosthetic joint placed 4 years prior.
- Joint aspirate reveals 95K WBCs with 90% neutrophils
- Cultures from joint aspirate are positive for MSSA
- What now?

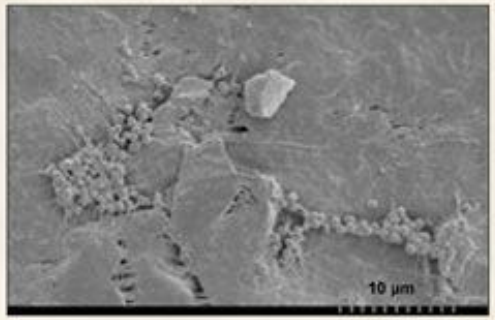
Common causes of prosthetic-knee and prosthetic-hip infection

- Gram-positive cocci (approximately 65%)
  - Coagulase-negative staphylococci
  - *Staphylococcus aureus*
  - Streptococcus species
  - Enterococcus species
- Aerobic gram-negative bacilli (approximately 6%)
  - Enterobacteriaceae
  - *Pseudomonas aeruginosa*
- Anaerobes (approximately 4%)
  - Propionibacterium species
  - Peptostreptococcus species
  - *Finegoldia magna*
- Polymicrobial (approximately 20%)
- Culture-negative (approximately 7%)
- Fungi (approximately 1%)

Formation of biofilm



Electron micrograph of *S. epidermidis* biofilm

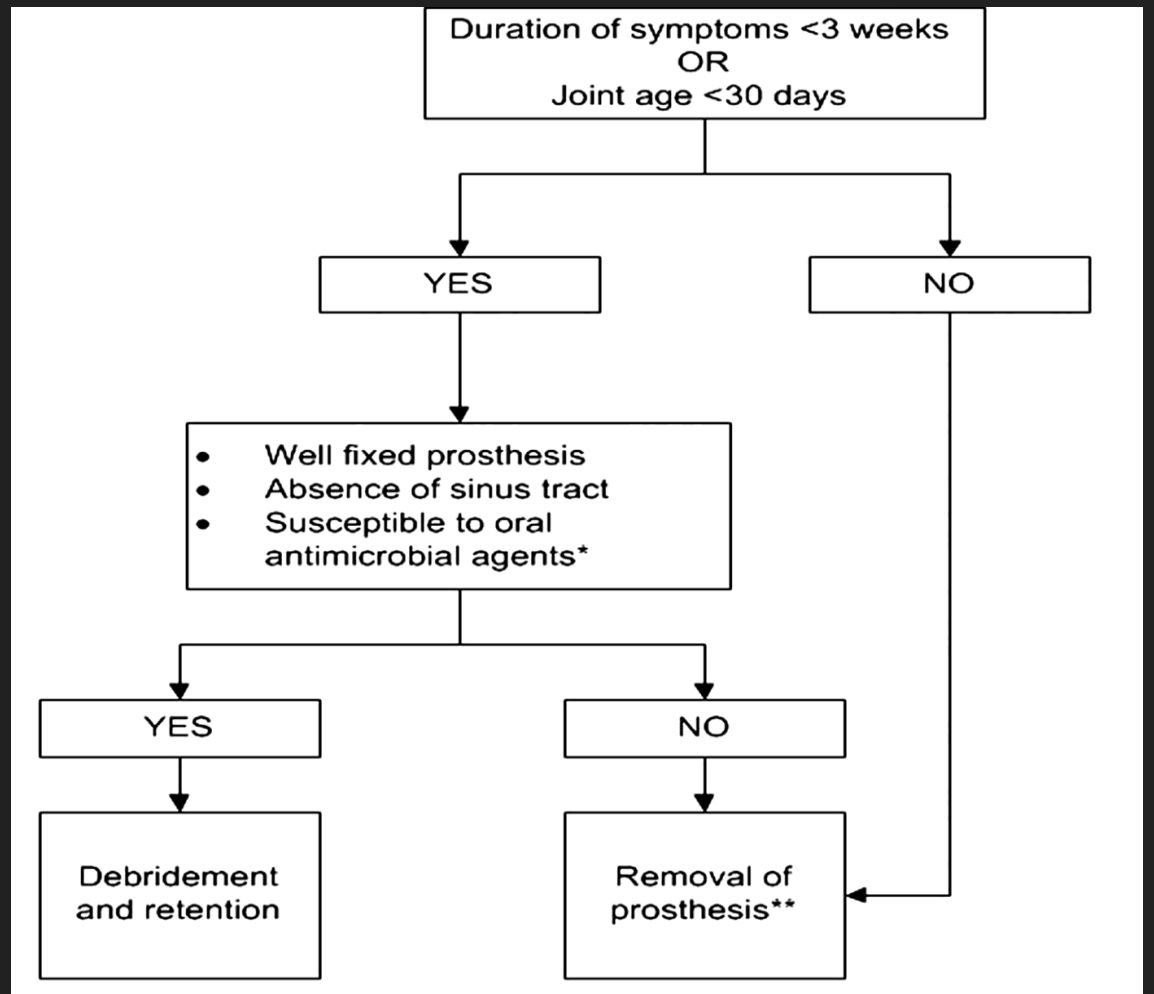


Prosthetic Joint Infections

- IDSA definition – presence of a sinus tract that communicates with the prosthesis, the presence of purulence surrounding the prosthesis without another known etiology, or two or more intraoperative cultures or a combination of pre-operative aspirate and intraoperative cultures that yield the same organism
- Management almost always necessitates the need for removal of the prosthesis and prolonged antibiotics
- A "two stage" procedure is the standard of care in most cases >30 days after implantation of hardware, but what happens when hardware cannot be explanted?

Osmon DR et. al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013;56(1):e1-e25.

IDSA Guidelines for Early Infection



*Antimicrobial agents that are recommended for prolonged use for chronic suppression or treatment of biofilm bacteria (see text for details)
**See Figure 3 and recommendation 18 and accompanying Evidence Summary for possible exceptions

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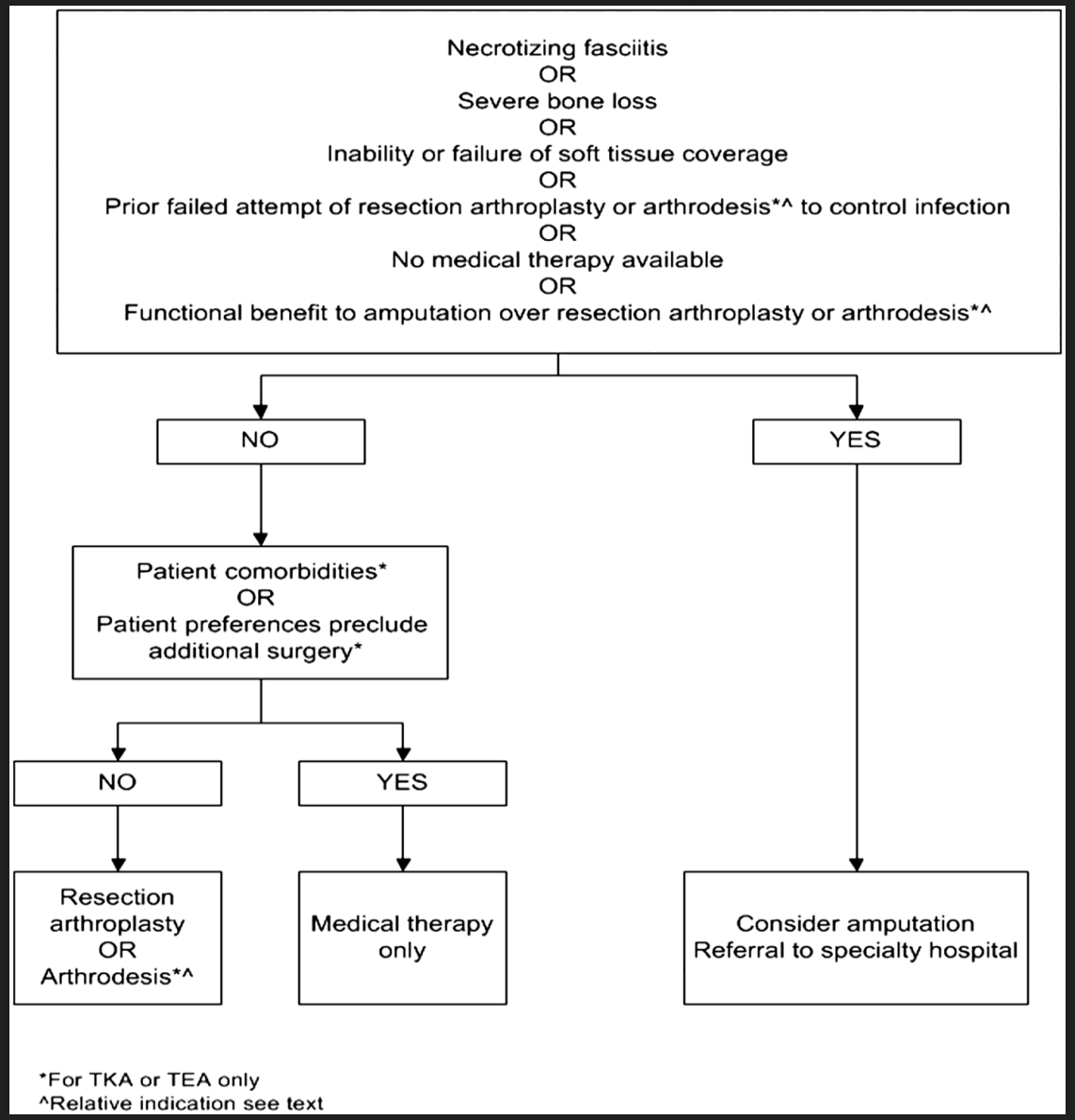
IDSA Guidelines for Complicated Infection



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Typical Course

- If it is decided hardware must be retained, consideration for an orthopedic I&D/washout/poly exchange as able with intraoperative cultures
- Long course ~6+ weeks of targeted IV antibiotics +/- rifampin
- Suggestion for chronic oral suppression thereafter with cephalexin, dicloxacillin, minocycline, doxycycline or targeted in non-staph isolates
- Expected outcome?
  - Around 60% success in patients (no relapse, need for further surgeries, sepsis, amputation)
  - Outcomes worse with immunocompromise, MRSA, and duration of symptoms prior to surgery

Outcome of Prosthetic Joint Infections Treated with Debridement and Retention of Compnents. Marculescu et. al. Clin Infect Dis. February 2006.

Approaches to Antibiotic Suppression

- Targeted oral suppressive antibiotics begin after the standard IV course of treatment
  - Duration of therapy is variable 6 weeks, 3mo, 6mo, 12mo, indefinite – all have been studied
  - Failure includes when pain worsens, further surgical intervention is needed, or death occurs
- Success as high as 90% for a standard prosthesis vs. one needed for oncologic or other complex issues
  - Highest success with CNS and strep species - 67-83%
  - Lowest success with MRSA – 50%

Wouthuyzen-Bakker et.al. J Bone Joint Infect 2017; 2(2): 77-83.

Outpatient Management?

- Patients are generally seen every 2-4 weeks, sooner if needed
- Check CBC, CMP, ESR, CRP
- Discuss pain, functionality of chronically infected joint
- Provide prescription refills – lowest dose, duration?
  - IDSA PJI guidelines state 3-6mo is the standard

Pathogen-driven decision for implant retention in the management of infected total knee prostheses. Zurcher-Pfund et.al. Int Orthop 2013.

Clinical Scenario

- A 53yo man presents to the office in consultation regarding a 5th episode of cellulitis in his LLE in the last 2 years. One of these episodes required hospitalization where he was found to have blood cultures positive for GAS.
- Patient responds briskly to IV and oral antibiotics – but reports he gets very little notice as to when a flare will happen.
- He is at your office today to discuss preventative strategies.

Typical Suggestions

- Attention to edema
  - Varicose veins, chronic stasis/edema
  - Use of graded compression stockings/wraps
  - Elevation as able
- Attention to skin integrity
  - Wound care for any open/chronic wounds
  - Topical emollients
  - Antifungal creams/powders
- Weight loss, diabetic foot and nail care

Antibiotic Prophylaxis?

- A significant portion of those who have an occurrence of cellulitis will develop a recurrence (16-30%)
- Meta-analysis of 1472 articles including patients with at least one relapse and >16yo
  - PATCH studies 2012 (Prophylactic Antibiotics for Treatment of Cellulitis at Home)
    - 535 participants with 260 on antibiotics (PCN) and 275 on placebo/no treatment
    - Duration 6, 12, 18mo
- Antibiotic prophy reduced the risk in patients with a h/o recurrent cellulitis
  - In the instance of 2 or more episodes, the risk reduction was found to be ~50%

Choon et.al. Antibiotic Prophylaxis for preventin recurrent cellulitis: A systematic review and meta-analysis. J Infect (2014), http://dx.doi.org/10/1016/j.jinf.2014.02.011

Outpatient Management?

- Patients seen in follow-up every 3-4mo, sooner if needed
- Preventative measures, compression, elevation, topical therapies encouraged
- Remission periods discussed
- Refills of suppressive medications vs. consideration for discontinuation if extended cellulitis-free periods

Clinical Scenario

- An 82yo woman presents to you with a c/o recurrent UTIs. Symptoms include occasional weakness and concentrated urine. No dysuria or hematuria. No fevers. No flank pain. She always asks for a UA at every visit because she states "sometimes I have a UTI and don't even know it."
- She has had one hospital stay in the past year for sepsis due to e.coli and has been on 5 courses of p.o. antibiotics for e.coli and klebsiella isolates. She is now resistant to ciprofloxacin and nitrofurantoin.
- What now?

Non-antibiotic considerations?

- Continence care
  - Peri-area cleaning, frequent diaper/pad changes
- Cranberry supplementation
  - Contain proanthocyanidins which prevent e.coli bacteria from attaching to the lining of the bladder and urethra
- D-mannose
  - Attaches to e.coli bacteria and causes bacteria to stick to each other instead of bladder and urethral linings
- Estrogen creams
  - Vaginal skin integrity
- Methenamine Hippurate
  - When urine is acidic, methenamine turns into formaldehyde to kill bacteria in the GU tract

Antibiotic Suppression for UTIs

- Long-term low-dose antibiotics have been a suppressive approach for many years
  - Antibiotic resistance has created a scenario where medications don't work as well
  - One study demonstrated after 1mo of TMP/SMX prophylaxis, resistance went from 20-40% to 85-90% among patient with recurrent UTIs due to e.coli
- Optimal duration of therapy is not known – most studies 6-12mo, a few with TMP/SMX use up to 5 years
- Overall reduction in UTIs with pooled data ~24%

Beerepoot MAJ, ter Riet G, Nys S, et al. Lactobacilli vs antibiotics to prevent urinary tract infection: a randomized, double-blind, noninferiority trial in postmenopausal women. Arch Intern Med. 2012;172(9):704-71

Additional Outcomes

- In a double-blinded, placebo controlled study women receiving daily PPX had 1-3 UTIs per year vs. 2-6 UTIs per year with prophylaxis
  - In a total of 404 enrolled patients, 181 on treatment:
  - 22 patients experienced adverse events including rash, GI distress, candida infections
  - Evolution of resistance in isolates was doubled in all groups (nitrofurantoin, trimethoprim, and cotrimoxazole) vs. placebo
- Of note – no large studies on recurrent UTI issues in older men

Fisher et.al. Continuous low-dose antibiotic prophylaxis for adults with repeated urinary tract infections (AnTIC): a randomised, open-label trial. Lancet Infect Dis 2018; 18:957-968

Prevention of Intercourse Related UTIs

- Some studies suggest a single dose of oral antibiotic after intercourse may be of benefit in preventing UTIs
  - Single strength Bactrim within 2 hours
  - Ciprofloxacin 125mg p.o. within 2 hours
- No good evidence to support a benefit of urination pre- and post-coitus
- Favorable evidence in a self-start of antibiotics in patients with UTIs
  - A 3 day course of antibiotics can be on hand for use when symptoms arise, no need to provide a specimen beforehand
  - In patients with "classic" symptoms there is a 92% correlation between symptoms and positive cultures

Dason et.al. Guidelines for the diagnosis and management of recurrent urinary tract infection in women. Can Urol Assoc J. 2011 Oct; 5(5): 316–322.

Emergence of Resistance

- Antibiotics used for UTI suppression have the greatest increase in resistance over time
  - Biggest failures are with TMP/SMX and nitrofurantoin over time due to resistance
- Antibiotics being used for PJI and cellulitis generally are ones with very low MICs and work well over time
  - Evolving infections elsewhere, however, may show resistance
  - Ex: A patient on daily cephalexin for recurrent cellulitis may develop a UTI showing isolated cephalosporin resistance

Side Effects

- In all of the studies reviewed, the following side effects were those most frequently leading to discontinuation of prophylactic antibiotic therapies:
  - Rash
  - GI distress including instances of c.diff but also abdominal pain, N/V/D, appetite suppression
  - Candidal infections including vaginitis and thrush

Take Home Points

- Patients not able to undergo a "two stage" procedure for an infected joint prosthesis should be given 3-6mo of targeted oral antibiotics as a standard after IV antibiotic course is complete
- In patients with >2 episodes of recurrent cellulitis, consideration for suppressive antibiotics may reduce the risk of a subsequent episode by ~1/2
- Long term, low-dose antibiotic suppression is a consideration for older women experiencing recurrent UTIs
  - Emerging resistance is a concern
- Consideration for non-antibiotic suppression strategies – D-mannose, estrogen creams, cranberry supplementation can help decrease the frequency of UTIs