Device Associated Infections

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Objectives:

❖ To understand when an infected device (prosthetic joint or central line) can be retained, and when it must be removed.

❖ To be aware of the optimal type, route, and duration of antimicrobial therapy for various device-associated infections, including local (non-parenteral) therapies.

❖ To outline the differences in management of catheter-related bloodstream infections between short- and long-term central venous catheters, and to discuss the role of antimicrobial lock therapy in the maintenance or salvage of long-term central venous catheters.
| **In the past 2 years I have been an employee of:** | N/A |
| **In the past 2 years I have been a consultant of:** | N/A |
| **In the past 2 years I have held investments in the following pharmaceutical organizations, medical devices companies or communications firms:** | N/A |
| **In the past 2 years I have been a member of the Scientific advisory board of:** | N/A |
| **In the past 2 years I have been a speaker for:** | Pfizer Canada |
| **In the past 2 years I have received research support (grants) from:** | N/A |
| **In the past 2 years I have received honoraria from:** | Pfizer Canada |
| **I agree to disclose approved and non-approved indications for medications in this presentation:** | YES |
| **I agree to use generic names of medications in this presentation:** | YES |
It’s all about that base… [sic]

- … of extracellular polymeric matrix, AKA biofilm
- Biofilm organisms are 10–1,000-fold less susceptible to antimicrobial agents than free growing (planktonic) versions of the same bacteria
- Even non-specific disinfectants do not work as well: 600-fold increase in concentration of hypochlorite need to kill biofilm (vs. planktonic) *Staphylococcus aureus* cells

Resistance in biofilm

PLACEHOLDER - Table 4 - Ramirez et al.
PMID: 8289214

(shows $\text{MBC}_{\text{attached organisms}} / \text{MBC}_{\text{planktonic organisms}}$ for two strains of S. epidermidis, and a variety of antimicrobials)
Strategies to treat:

❖ Remove the device (and the biofilm…)
❖ Easier with short term CVCs and urinary catheters
❖ Not so easy with implanted orthopaedic devices and long-term CVCs
Strategies to treat:

❖ Treat with the device in-situ
❖ Give high concentrations of antimicrobial agents to overcome relative resistance within biofilm
❖ Give longer duration of biofilm-penetrating antimicrobials, to eradicate persisting organisms
Case 1

- 71 year old woman, Hx DM II, HTN, obesity (BMI 33)
- Revision right hip arthroplasty - prolonged procedure (3.5 hours) otherwise uncomplicated.
- At discharge, small area of distal wound separation (1.5 cm diameter), modest drainage, referred to home care

Case 1

- Week 4 post op - wounds healed, but increasing pain
- Seen by her orthopaedic surgeon, bloodwork and joint aspirate done:
  - CRP 16 mg/L, ESR 22 mm/hr
  - Aspirate - 4300 WBC, 83% neutrophils
  - Gram stain - NBS; culture - *S. aureus*, subsequently MSSA, (S) rifampin, doxy, TMP-SMX, levo MIC 0.25
Can her prosthesis be salvaged?
PJI Incidence

- Kurtz et al\(^1\) - Medicare 5% national administrative database:
  - 10 years data, 69,663 elective TKAs, 1400 TKA infections
  - Early-onset (<2 years) vs. late-onset (>2 years)
  - Multivariate analysis re. risk factors
  - Incidence 1.55% 0-2 years; 0.46% 2-10 years (one quarter of all infections)

- Confirmed age, comorbidities, male gender, duration of procedure, socioeconomic status (surrogate) as risk factors

\(^1\)Kurtz SM et al. Clin Orthop Relat Res. 2010 Jan;468(1):52-6
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- 10 years data, 69,663 elective TKAs, 1400 TKA infections
- Early-onset (<2 years) vs. late-onset (>2 years)
- Multivariate analysis re. risk factors

**Hips: incidence 1.63\% 0-2 years; 0.59\% 2-10 years\textsuperscript{2} (one quarter of all infections)**

- Confirmed age, comorbidities, male gender, duration of procedure, socioeconomic status (surrogate) as risk factors

\textsuperscript{1}Kurtz SM et al, Clin Orthop Relat Res. 2010 Jan;468(1):52-6
\textsuperscript{2}Ong K et al. J Arthroplasty 2009;24(S6):105-9
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\[\text{PLACEHOLDER - Figures 1 and 2 - Kurtz et al.} \]

\[\text{PMID: 18534466} \]

(shows # and % infected knee/hip arthroplasties, Nationwide Inpatient Sample database, 1990-2004)
Surgical Options

- Amputation (severe sepsis, multiple prior failed Tx, et al)
- Removal of components without replacement
- Exchange arthroplasty
  - Two stage procedure (best job of removing biofilm)
  - One stage procedure (incomplete biofilm removal)
- Debridement and retention of prosthesis (incomplete removal)
Two stage revision:

- “Gold-standard” - biofilm effectively debulked / debrided
- Antimicrobial impregnated cement spacer used for mechanical and microbiological support
- Four to six weeks directed (parenteral) therapy
  - Consider repeat aspirate >2 weeks off antimicrobials, with repeat debridement / antimicrobials if +
- Post-operative parenteral antimicrobials until cultures negative
Reinfection Rates: Two Stage

PLACEHOLDER - Figure 1 - Kubista et al.
PMID: 21553042
(Shows probability of reinfection over 10 years, time-to-failure curve - just under 90% infection free at 2 years [short-term]

Surgical Options

❖ Single stage revision - see Gehrke T. et al\(^1\)

❖ ADVANTAGES - one operation - cost savings\(^2\), convenience for patient

❖ Requirements:
  ❖ Good condition of bone and soft tissues
  ❖ Microbiology known \textit{preoperatively}
  ❖ Use antimicrobial-impregnated cement (lower [ ], culture-directed)
  ❖ Use longer course of antimicrobial therapy (12 weeks) advocated

Sidebar about cement...

- Several different types of cement - some better suited to the addition of ABs
  - Elute antimicrobials more effectively; clear biofilm more effectively; more stable
- Problem - antimicrobials can compromise integrity of cement
  - Generally: 1g aminoglycoside/2g vancomycin per 40g bag of cement will maximize local tissue concentrations/preserve mechanical characteristics of the cement

Single- vs. Two-stage

- Beswick et al\(^1\) - review of hip revisions for PJI
  - 66 articles: outcomes 1- vs. 2-stage revision
    - Overall: 10.1% (8.2 – 12%) 2-year failure rates
      - Single-stage: 8.6% (4.5 – 13.9%)
      - Two-stage: 10.2% (7.7-12.9%)
  - Knees - multiple studies - 73-98% success rates for single-stage\(^2,3,4,5\)
    - Clinical outcomes no different\(^5\)

DAIR *

Role of Rifampin for Treatment of Orthopedic Implant–Related Staphylococcal Infections
A Randomized Controlled Trial

Werner Zimmerli, MD; Andreas F. Widmer, MD, MSc; Marianne Blatter, MD; R. Frei, MD; Peter E. Ochsner, MD; for the Foreign-Body Infection (FBI) Study Group

*Debridement, antimicrobials, and implant retention

Zimmerli et al. JAMA. 1998;279:1537-1541
Zimmerli, 1998

- Only 33 patients enrolled; only 24 completed follow-up
  - Symptoms <21 days
  - Only stable implants (x-ray, intraoperative)
  - Staphylococcal infections only (known pre-op)
    - All *Staph* were fluoroquinolone/rifampin susceptible

Zimmerli et al, JAMA. 1998;279:1537-1541
Only 33 patients enrolled; only 24 completed follow-up

PLACEHOLDER - Table 1 - Zimmerli (2012).
PMID: 22309166
(shows cure rates, experimental device-associated
*S. aureus* infections, highest with cipro/rif)

All *Staph* were fluoroquinolone/rifampin susceptible

Zimmerli, 1998

- Treatment (after debridement):
  - Two weeks appropriate IV therapy ± rifampin
  - Oral stepdown therapy, with ciprofloxacin ± rifampin
    - 3 months total for hips; 6 months total for knees
  - EMPIRIC - based on perceived differences soft-tissue milieu/mechanical stresses, knees vs. hips
  - All of the cipro / rif patients were “cured”; cipro: 58%

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Zimmerli et al, JAMA. 1998;279:1537-1541
PMID: 9605897
(shows time to failure curve, cipro/rif vs. cipro monotherapy)
Zimmerli, 1998

- Limitations: small numbers/restricted microbial applicability (no MRSA, only 2 MRSE)/empiric determination treatment duration

- Criteria for DAIR *de facto*:
  - Stable implant, < 3 months old
  - Duration of symptoms <3 weeks (whether early, or late onset)
  - Pathogen with susceptibility to antimicrobial agents active against surface adhering organisms
  - No sinus tract or abscess
Symptoms ≤ 3 weeks or <30 days post-op and stable implant and no sinus tract and organism susceptible to oral antimicrobials, active in biofilm

Adequate soft tissues/bone stock; microbiology known

Damaged soft tissues, sinus tract or abscess; immune compromise

Drug resistant, or difficult to treat organism (e.g. rifampin-resistant S. aureus, small colony variant S. aureus, enterococci, fluoroquinolone-resistant GNB, fungi)

Patient is not a candidate for surgery

Functional status unlikely to improve with replacement of prosthesis

YES

DAIR

NO

One-stage revision

Two-stage revision

Long-term suppressive therapy (with or without debridement)

Implant removal without replacement, time-limited antimicrobials

Adherence to algorithm is key...

- Zimmerli et al - adherence to protocol assessed for hip\(^1\) and knee\(^2\) PJI at their institution, WRT:
  - choice of surgical therapy - per algorithm, or *more* invasive, vs. less invasive
  - duration and choice of antimicrobial therapy - adequate if ≥3 months total, and ≥2 weeks IV; partially adequate if 2-3 months total, or <2 weeks IV; inadequate
  - Hips (n=63) - 88% cure if managed according to algorithm\(^1\); knees (n=40) - 89% cure per algorithm

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Adherence to Algorithm

- Betsch et al, 2008
  - 68 PJIs, mostly hips
  - Overall adherence 88%
    - Only 17% for DAIR
  - 24 months: 51.5% infection-free
  - HR failure 2.34 for non-algorithm surgery

PLACEHOLDER - Figure 1
- Betsch et al.
  PMID: 18444859
  (shows time to failure curves, by adequate/partially adequate/inadequate therapy, according to protocol)
Antimicrobials: more is not better….

- Byren et al, 2009
  - 112 PJIs (52 hips, 51 knees, 9 other) - DAIR, not algorithmic (many were elderly, with comorbidities)
  - No constraints on duration of antimicrobial therapy
  - Findings:
    - Failures associated with arthroscopic debridement, *S. aureus* infection, and previous revision surgery
    - Failures also more common in first three months after stopping antimicrobials, regardless of duration of treatment prior to stopping

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**PLACEHOLDER** - Figure 4 - Byren et al.

PMID: 19336454

(shows time to failure curves, for infection relapse, according to duration of therapy prior to stopping)

- Failures also more common in first three months after stopping antimicrobials, regardless of duration of treatment prior to stopping
## Duration of Antimicrobial Tx

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>IV THERAPY</th>
<th>ORAL THERAPY</th>
<th>TOTAL DURATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAIR</td>
<td>2-4 weeks</td>
<td>To complete 3 (hip) or 6 (knee) months</td>
<td>3 (hip) or 6 (knee) months (see later)</td>
</tr>
<tr>
<td>SINGLE-STAGE</td>
<td>2-6 weeks</td>
<td>To complete 3 (hip) or 6 (knee) months</td>
<td>3 (hip) or 6 (knee) months (see later)</td>
</tr>
<tr>
<td></td>
<td>(4-6 if no rifampin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TWO-STAGE</td>
<td>4-6 weeks*</td>
<td>None required</td>
<td>(Consider aspirate &gt;2 weeks off antimicrobials; repeat debridement if +)</td>
</tr>
<tr>
<td>RESECTION</td>
<td>4-6 weeks</td>
<td>None required</td>
<td></td>
</tr>
</tbody>
</table>

*Some would recommend reimplantation after as little as two weeks, assuming no difficult-to-treat organisms.

“Abbreviated” Therapy

❖ Darley et al, UK\(^1\):

❖ 17 two stage THR; 4 single stage THR

❖ Treated with 10-14 days IV therapy, then p.o. for 6-8 weeks (two stage) or 6-12 weeks (single)

❖ No treatment failures

❖ All gram positive, no MRSA, most used rif.

❖ Similar results elsewhere\(^2\) - 2 months for hips, 3 for knees\(^2\), 88% per-protocol success (range of microbiology)

“Abbreviated” Therapy

❖ Hsieh et al:

❖ Consecutive 2-stage hip revisions with antimicrobial impregnated spacers*

❖ First 51 - four weeks IV ± 2 weeks p.o.

❖ Next 56 - 1 week IV only

❖ 91% and 89% cure

Hsieh PH et al. Journal of Antimicrobial Chemotherapy (2009) 64, 392–397 *Vanco/aztreo or vanco/gent
Are systemic antimicrobials necessary?

- 44\textsuperscript{1} and 114\textsuperscript{2} hip PJIs, treated with two-stage revision, and antimicrobial-impregnated spacers (vancomycin/gentamicin) with either 2 weeks vancomycin\textsuperscript{1}, or perioperative prophylaxis only\textsuperscript{2}

- Spacers maintained median 21-24 weeks

- Claimed 92.7\textsuperscript{1} and 87.7\textsuperscript{2} rates of eradication

- Principally low-grade, gram positive pathogens

\textsuperscript{1} Whittaker JP et al, J Bone Joint Surg (Br) 2009;91:B44-51; \textsuperscript{2} Stockley I et al, J Bone Joint Surg (Br) 2008;90:B145-8
PLACEHOLDER - Table 3 -
Zimmerli et al.
PMID: 22309166
(shows choices for IV and oral therapy, by infecting organism)

Antimicrobial selection: will vary depending on microbial isolate
Rifampin for all?

- Used by some for all gram positive infections treated with DAIR

- Evidence: *no role* for rifampin in *Enterococcus* infection (non-additive, possibly antagonistic), *Propionibacterium* (no clinical data), streptococci (no clinical data, highly susceptible to alternate therapies, favourable outcomes without\(^1\)), or GNB (possible exception – with colistin)\(^2\)

- Some continue as combination therapy in chronic suppression - NOT widely endorsed\(^3,4\)

Difficult to Treat?

- MRSA
  - Lora-Tamayo et al, 2014 - S. aureus PJIs treated with DAIR
    - Poor response overall 55%, but no significant difference MRSA vs. MSSA
  - If MRSA is susceptible to rifampin, response rates similar to MSSA can be expected
  - Encouraging data from animal models/patients re. linezolid and daptomycin with DAIR or other revision[^2][^3][^4][^5]

Difficult to Treat?

- **GNB**
  - If meet DAIR criteria, and fluoroquinolone susceptible, 79% success; if FQ resistant, 40%\(^1\)

- **Enterococci**
  - Variable results: DAIR 47-80% success; two-stage 57-94%\(^2,3\)
  - Preferred treatment is two stage revision.

- **Yeast**
  - Two-stage revision recommended\(^4\)

Same, same, but different
Case 2

- 53 y.o. man - 10 years ago, non-alcoholic pancreatitis → mesenteric thrombosis → small bowel ischemia and extensive resection → short gut syndrome, and long-term TPH via right subclavian Broviac
- Unwell 2 days - myalgias, chills, $T_{\text{max}}$ 37.6°C, no other illness
- Line insertion site NAD
- Sent to lab - WBC 12.1/10.0; creatinine normal, blood cultures from line and periphery - positive at 12 and 16 hours respectively for GNB: *K. pneumoniae*, broadly susceptible
- Treatment? Leave line, or remove?
Background

- HPN has been around for over 40 years
- Requires longterm venous access
  - Silicon, tunneled central catheters are preferred (*permanent* access)
  - Implanted ports are occasionally used
  - PICC-lines - short term, not recommended for HPN patients
- Line-associated infections occur at low, but definable rates
- TPN itself is a risk factor for line infection¹

Scope of the problem:

- CLABSI rates:
  - CNISP - adult ICUs - 0.86 per 1000 catheter days\(^1\)
  - Long-term catheters likely range 0.5-3 per 1000 days\(^2,3,4,5\)
  - 20\% of the patients are responsible for 75\% of infections \(\text{(Dibb M et al. Gut 2012;61:A14-5)}\)


\(^5\) Santarpia L et al. JPEN J Parenter Enteral Nutr. 2010;34:254-62
Scope of the problem:

❖ Consequences of CVC-associated infections:
  ❖ Sepsis related morbidity / mortality
  ❖ Loss of line use, if not the line itself

❖ Costs:
  ❖ Central line infections are among the most expensive HAIs - est. USD ~10K - 45K per episode, attributable resource utilization\(^1,2,3\)

Routes of infection

- From the TPN itself
- Bacteremia from a distant site, seeding catheter
- From the skin surface, along the outside of the catheter
- From the hub, on the inner lumen of the catheter
Routes of infection

- From the skin surface, along the outside of the catheter
- From the hub, on the inner lumen of the catheter

- For catheters in place < 10 days, colonization/infection is predominantly extraluminal; for those in place >30 days, predominantly intraluminal

Biofilm in CVCs

- Machado et al\(^1\)- central catheters in place >48 hours already will already have developed biofilms (not necessarily infected)

- Catheters in place <24 hours - “conditioning film” - acute inflammatory response

\(^1\) Machado J et al. JPEN J Parenter Enteral Nutr. 2009;33:397-403
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1 Machado J et al. JPEN J Parenter Enteral Nutr. 2009;33:397-403

PLACEHOLDER - Figure 1e - Machado et al. PMID: 19401480
(electron micrograph of fibrin + acute inflammatory response on catheter that was in situ <48 hours)

1 Machado J et al. JPEN J Parenter Enteral Nutr. 2009;33:397-403
Treatment

❖ Any patient with suspected tunnel/port-pocket infection must have the line removed (A-II); treat with systemic therapy

❖ For uncomplicated exit site infections (no bacteremia, no signs of systemic infection) - culture drainage, treat with topical agent (e.g. mupirocin, fuscidic acid)
  ❖ if not resolving by three days, treat with systemic therapy (tailored)
  ❖ if STILL not resolving, REMOVE (B-III)

Treatment

- For documented CRBSI, catheter must be removed if:
  - severe sepsis/septic shock (without alternate explanation)
  - failure to clear cultures/resolve fever by 72 hours
  - endocarditis, septic thrombophlebitis, abscess, osteomyelitis, et al
  - patient’s condition deteriorates on Tx
  - specific pathogens: *Staphylococcus aureus* (+), MRSA, *Candida sp.*

Catheter Salvage

- Line exchange (= access, or “site” salvage)
- Antimicrobial lock therapy (ALT) - treatment, and secondary prevention
Antimicrobial lock therapies most commonly used:
- Antibiotics, with or without heparin/citrate
- Ethanol (varying concentrations - with or without antibiotics)
- Others - as available, and necessary
Antimicrobial lock solutions

Multiple other lock solutions studied: e.g. amikacin, imipenem, antimicrobials at side but without anticoagulant


→ gentamicin 5.0 mg/ml/heparin 5000 U/ml

PLACEHOLDER - Table 9 - Mermel et al. PMID: 19489710 (shows several options for antimicrobial lock solutions)

Ethanol lock therapy

- Method/principle same as for antibiotic locks
  - Ethanol is a non-specific microbicide - disrupts cell membranes, denatures proteins
  - No concern re. bug/drug matching
  - Some concern re. toxic effects, especially if flushed into patient
  - High concentration EtOH precipitates with heparin - often given alone (no anticoagulant), but stable with EDTA and citrate
  - 70% concentration most commonly used for treatment
Ethanol lock therapy

- Outcome studies for CRBSI heavily weighted toward paediatric/oncology populations, and prophylaxis
- Small numbers, limited data from case series/animal or biofilm models on treatment efficacy
- 2009 - Mermel et al: “At this time, there are insufficient data to recommend an ethanol lock for the treatment of CRBSI”

Since then...

- **Slobbe 2010**, retrospective, adults, n=376, 70%, 15 min., 1º prevention, 0.7 v. 1.19
- **Cober 2011**, retrospective, peds, n=15, 70%, ≥ 2h, 2º, 8.0 → 1.3.
- **Wales 2011**, retrospective, peds, n=10, 70%, ≥ 4h, 2º, 10.2 → 0.9
- **John 2012**, retrospective, adults, n=30, 70%, ~12h, 2º, 3.53 → 1.65
- **Pieroni 2013**, retrospective, peds, n=14, 70%, 2h PER WEEK, secondary, 9.8 → 2.7
- **Cochrane Review 2013** - peds, 1º, 2 RCT, 1 controlled trial, 9 case series - re. first three: no difference ALT plus systemic Tx, vs. systemic alone.
- **Kubiak 2014**, retrospective, adults, 20% TPN, 89% LT catheters, n= 45 (episodes), 70% 4-12h, 5days, 11% persistent or relapsed bacteremia; 62% retained CVC, median 71 days
Ethanol lock therapy

Potential concerns:

- Catheter integrity - especially with long-term, primary or secondary prophylaxis (disputed)\(^1\)
- Possibly, increased rates of catheter thrombosis (case reports - paediatrics)\(^2\)

\(^2\) Wong T et al. JPEN J Parenter Enteral Nutr. 2012 May;36(3):358-60
\(^3\) Laird J et al. J infect 2005;51:338
Lock therapy - taurolididine

- Taurolididine - non-specific antimicrobial; also anti-neoplastic and anti-endotoxemic; studied in variety of infections, including peritonitis

- Interacts with constituents of fungal/bacterial cell wall, affects cell adherence - time and concentration dependent\(^1\)

- *Most* of the CVC data is around primary and secondary prevention\(^2\)

- Commercial formulation (1.35% taurolididine/4% sodium citrate solution) available in Europe, not licensed in Canada

\(^1\)[http://en.wikipedia.org/wiki/Taurolidine]

Ethanol and taurolididine in Canada

- Medical grade ethanol for compounding (lock therapy) has not been available for MANY MONTHS
  - Manufacturer has addressed facility issues - back on market end of this month?
- Taurolididine - imported from Switzerland, Health Canada Special Access Program
  - Logistical challenges (250 ml vials - short shelf life after opened)
ALT outcomes:

- Two clinical trials: antibiotic lock/systemic therapy - 92 patients, **cure in 75%** of ALT group, 58% of the control subjects (Rijnders 2005; Fortun 2006).

- 21 “open” trials of ALT for long-term catheters, with or without concomitant parenteral therapy, **cure in 77%**.

- Larger case series: 115 CRB in 98 patients - overall success **78%** GPC; **92%** GNB; **88%** polymicrobial.

References:

ALT outcomes:

- Am. J. Nephrol. 2011 O’Horo - systematic review and meta-analysis of 8 studies using ALT + systemic therapy, 1988-2010 - mix of dialysis > adult/peds oncology > TPN catheters, only half were prospective
- 20% of ALT group relapsed (vs. 30%, NS)
- 10% of ALT required catheter replacement (vs. 33%)
- Emphasizes the lack of controlled data, relatively small numbers of S. aureus and yeast CLABSIs
ALT outcomes:

- In aggregate: **mean success rates around 67%**\(^1\)
- Contemporary recommendations **continue** to support 10-14 days (B-II) with appropriate systemic therapy\(^2\)
- Dwell times of 24 hours recommended, but shorter dwell times have reasonable success rates (depending on the regimen)

Summary:

- Success or failure of a specific intervention for PJI depends heavily on the appropriate choice of intervention, based on established criteria.
- There is enough uncertainty around the optimal components/dwell time/duration of ALT that every case should be entered in a registry.
- Institutions that use ALT should create formal policy documents (HPN/Nephrology/Critical Care, in consultation with ID and pharmacy);
- Performance measures should be adopted/developed for both PJI and long-term CVC management.