AMMI 2015 - Charlottetown

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.

CONFLICT OF INTEREST DISCLOSURE SLIDE

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**
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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[1]
- 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[2]

[1] Davies D. Nat Rev Drug Discov. 2003 Feb;2(2):114-22. [2] Luppens SB et al. Appl. Environ. Microbiol 2002;68:4194–200

Resistance in biofilm

PLACEHOLDER - Table 4 - Ramirez et al.
PMID: 8289214
(shows $MBC_{(attached\ organisms)}/MBC_{(planktonic\ organisms)}$ for two strains of S. epidermidis, and a variety of antimicrobials)

Ramirez de Arellano E. et a. J Med Microbiol. 1994 Jan;40(1):43-7

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

Zimmerli W., Best Pract Res Clin Rheumatol 2006;20:1045-63; Berbari E. et al, Clin Infect Dis 1998;27:1247-54
Bozic KJ et al. J Bone Joint Surg Am. 2012;94:794-800

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

Case 1

- 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

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
- Hips: incidence 1.63% 0-2 years; 0.59% 2-10 years[2] r of all infections)
- Confirmed age, comorbidities, male gender, duration of procedure, socioeconomic status (surrogate) as risk factors

[1] Ku [2] Ong K et al. J Arthroplasty 2009;24(S6):105-9 52-6

PJI Incidence

- Kurtz et al[1] - Medicare 5% national administrative database:

PLACEHOLDER - Figures 1 and 2 - Kurtz et al.
PMID: 18534466
(shows # and % infected knee/hip arthroplasties, Nationwide Inpatient Sample database, 1990-2004)

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

[1]Kurtz et al, J Arthroplasty 2008;23:984-91 52-6

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)

Surgical Options

- 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)

Kubista B et al.International Orthopaedics (SICOT) (2012) 36:65–71

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 *preoperatively*
  - Use antimicrobial-impregnated cement (lower [ ], culture-directed)
  - Use longer course of antimicrobial therapy (12 weeks) advocated

[1] Gehrke T. et al. Bone Joint J 2013;95-B, Supple A:77–83 [2] Klouche S et al. Orthop Traumatol Surg Res 2010, 96:124-132

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

Fink B. et al.Clin Orthop Relat Res (2011) *469*:3141–3147

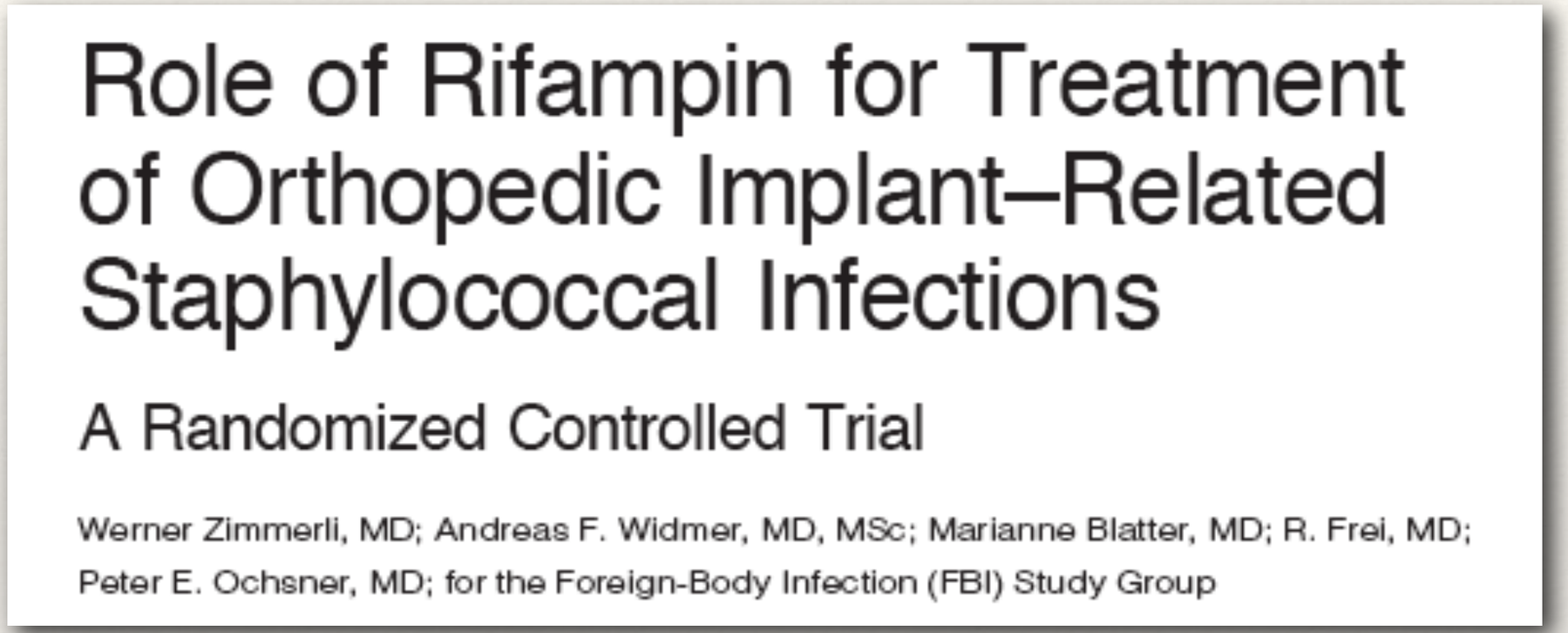
Cui Q et al. J Bone Joint Surg Am. 2007;89:871-82

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]

[2] Haddad FS et al. Clin Orthop Relat Res (2015) 473:8–14; [3] Masters JPM et al BMC Musculoskelet Disord. 2013;14:222; [4] Tibrewal S. et al. Bone Joint J 2014;96-B:759–64 [5] Jämsen E. et al Acta Orthop 2009, 80:67-77

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

Zimmerli, 1998

- 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 et al. FEMS Immunol Med Microbiol 65 (2012) 158–168

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%

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

Zimmerli, 1998

- Treatment (after debridement):
  - Two weeks appropriate IV therapy ± rifampin
  - [redacted]
  - milieu/mechanical stresses, knees vs. hips
  - All of the cipro/rif patients were "cured"; cipro: 58%

PLACEHOLDER - Table 1 - Zimmerli (1998). PMID: 9605897
(shows time to failure curve, cipro/rif vs. cipro monotherapy)

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

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 agains 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

YES → **DAIR**

NO

Adequate soft tissues/bone stock; microbiology known → **One-stage revision**

Damaged soft tissues, sinus tract or abscess; immune compromise → **Two-stage revision**

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

Patient is not a candidate for surgery → **Long-term suppressive therapy (with or without debridement)**

Functional status unlikely to improve with replacement of prosthesis → **Implant removal without replacement, time-limited antimicrobials**

Adapted from Zimmerli et al. FEMS Immunol Med Microbiol 65 (2012) 158–168 *and* Del Pozo et al, N Engl J Med 2009;361:787-94

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

[1] Giulieri SG et al. Infection 2004;32:222-8; [2] Laffer RR et al. Clin Microbiol Infect 2006;12:433-9

Adherence to algorithm is key…

- Zimmerli et al - adherence to protocol assessed for hip[1] and knee[2] PJI at their institution. WRT:
  - According to protocol, or *more* invasive
  - **PLACEHOLDER** - Figure 1 - Giulieri et al. PMID: 15293078 (shows time to failure curve, cases managed *more* aggressively than protocol mandated, vs patients managed *less* aggressively)
  - ≥ 3
  - *Less* invasive that protocol mandate
- Hips (n=63) - 88% cure if mana algorithm[1]; knees (n=40) - 89% cure per algorithm

[1] Giulieri SG et al. Infection 2004;32:222-8; [2] Laffer RR et al. Clin Microbiol Infect 2006;12:433-9

Adherence to Algorithm

- Betsch et al, 2008[1]
- 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)

Betsch BY et al. Clin Infect Dis 2008;46:1221-6

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

Byren I. et al, J Antimicrob Chemother (2009) 63, 1264–1271

Antimicrobials: more is not better….

- Byren et al, 2009
  - 112 PJIs (52 hips, 51 knees, 9 other) - DAIR, not algorithmic
  - (shows time to failure curves, for infection relapse, according to duration of therapy prior *aureus* to stopping)
    - Failures also more common in **first three months after stopping** antimicrobials, *regardless* of duration of treatment prior to stopping

PLACEHOLDER - Figure 4 - Byren et al. PMID: 19336454

Byren I. et al, J Antimicrob Chemother (2009) 63, 1264–1271

Duration of Antimicrobial Tx

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

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

[1] Zimmerli et al. N Engl J Med 2004;351:1645-54

"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)

[2] Puhto AP et al. Clin Microbiol Infect. 2012 Nov;18(11):1143-8 – 86

"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[1] and 114[2] hip PJIs, treated with two-stage revision, and antimicrobial-impregnated spacers (vancomycin/gentamicin) with either 2 weeks vancomycin[1], or perioperative prophylaxis only[2]
- Spacers maintained median 21-24 weeks
- Claimed 92.7%[1] and 87.7%[2] rates of eradication
- Principally low-grade, gram positive pathogens

[1] Whittaker JP et al, J Bone Joint Surg (Br) 2009;91:B44-51; [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

Zimmerli et al. FEMS Immunol Med Microbiol 65 (2012) 158–168

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]

[3] Osmon DR et al. Clin Infect Dis. 2013 Jan;56(1):e1-e25; [4] Osmon DR et al. Clin Infect Dis. 2013 Jul;57(1):162-4

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]

[2] Rao N et al.Diagn Microbiol Infect Dis. 2007 Oct;59(2):173-9; [3] Morata L et al. Infect Dis Ther (2014) 3:235–243;
[4] Niska JA. Antimicrob Agents Chemother 2013;57(10):5080-6; [5] John AK et al. Antimicrob Agents Chemother 2009;53(7):2719-24

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]

[4] Kuiper JWP et al. Acta Orthopaedica 2013; 84 (6): 517–523

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_{max} 37.6ºC, 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 infection[1]

[1] Beghetto MG et al. JPEN J Parenter Enteral Nutr. 2005 Sep-Oct;29(5):367-73

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 *(Dibb M et al. Gut 2012;61:A14-5)*

[1] http://publications.gc.ca/collections/collection_2014/aspc-phac/HP40-90-2013-eng.pdf - accessed 2014-05-27

[2] Elfassy et al. JPEN J Parenter Enteral Nutr. 2015 Feb;39(2):147-53 [3] Reimund JM et al. Clin Nutr 2002;21:33-8.; [4] Gillanders L et al. Clin Nutr. 2012;31:30-4; [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]

[1] Halton K et al. Emerg Infect Dis 2007;13:815-23; [2] Zimlichman E et al. JAMA Intern Med. 2013 Dec 9-23;173(22):2039-46
[3] Gillanders L et al. Clin Nutr. 2012 Feb;31(1):30-4

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*[1]

[1] Raad I et al. J Infect Dis. 1993 Aug;168(2):400-7.

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

Biofilm in CVCs

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- ❖

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)

Mermel et al. IDSA Guidelines for Intravascular Catheter-Related Infection: Clin Infect Dis 2009; 49:1-45

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.*

Mermel et al. IDSA Guidelines for Intravascular Catheter-Related Infection: Clin Infect Dis 2009; 49:1-45

Catheter Salvage

- Line exchange (= access, or “site” salvage)
- Antimicrobial lock therapy (ALT) - treatment, and secondary prevention

ALT

- 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

1

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

Multiple other lock solutions studied: e.g. amikacin, imipenem, antimicrobials at side but *without anticoagulant*[3]

REVIEW: Bookstaver et al. Am J Health Syst Pharm. 2013 Dec 15;70(24):2185-98

→ gentamicin 5.0 mg/ml/heparin 5000 U/ml[2]

[1] Mermel LA et al. Clin Infect Dis. 2009 Jul 1;49(1):1-45 [2] Chow KM et al. Hong Kong Med J 2010;16:269-74 [3] O'Horo JC et al. Am J Nephrol 2011;34:415-22

Ethanol lock therapy

- Method/principle same as for antibiotic locks
  - Ethanol is an 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"[1]

Mermel et al. IDSA Guidelines for Intravascular Catheter-Related Infection: Clin Infect Dis 2009; 49:1-45

Since then…

- Slobbe 2010, retrospective, adults, n=376, 70%, 15 min., 1° prevention, 0.7 v. 1.19
- Cober 2011, retrospective, peds, n=15, 70%, ≥ 2h, 2°, 8.0 → 1.3.
- Wales 2011, retrospective, peds, n=10, 70%, ≥ 4h, 2°, 10.2 → 0.9
- John 2012, retrospective, adults, n=30, 70%, ~12h, 2°, 3.53 → 1.65
- Pieroni 2013, retrospective, peds, n=14, 70%, 2h *PER WEEK*, secondary, 9.8 → 2.7
- Cochrane Review 2013 - peds, 1°, 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]

[1] Crnich C et al. Infect Control Hosp Epidemiol. 2005 Aug;26(8):708-14

[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 - taurolidine

- Taurolidine - 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% taurolidine/4% sodium citrate solution) available in Europe, not licensed in Canada

[1] http://en.wikipedia.org/wiki/Taurolidine

[2] Bisseling et al. Clin Nutr. 2010 Aug;29(4):464-8; A. Touré et al. Clin Nutr 31 (2012) 567e570

Ethanol and taurolidine 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?
- Taurolidine - 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%**[1]
- Larger case series:115 CRB in 98 patients - overall **success 78%** GPC; **92%** GNB; **88%** polymicrobial[2]

[1] Mermel LA et al. Clin Infect Dis. 2009 Jul 1;49(1):1-45

[2] Fernandez-Hidalgo et al. J Antimicrob Chemother 2006;57:1172-80

ALT outcomes:

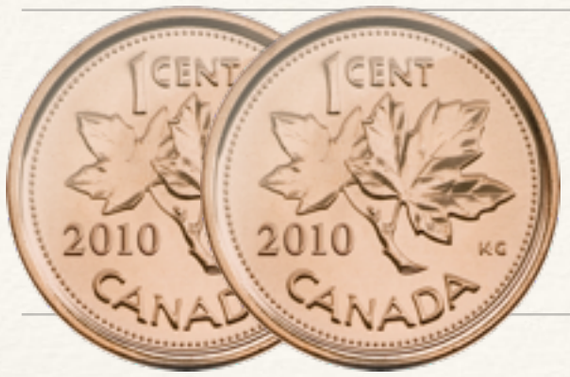
- Am. J. Nephrol. 2011 O'Horo - systematic review and meta-analyisis of 8 studies using ALT + systemic therapy, 1988-2010 - mix of dialysis > adult/peds oncology > TPN catheters, only half were prospective
  - 20% of ALT group relapsed (vs. 30%, NS)
  - 10% of ALT required catheter replacement (vs. 33%)
  - 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)

Mermel et al. IDSA Guidelines for Intravascular Catheter-Related Infection: Clin Infect Dis 2009; 49:1-45

[2] Hentrich M et al. Ann Oncol. 2014 May;25(5):936-47



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