Hemodialysis catheter-related infections

Renal Pharmacists Network Education Day
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Conflicts of interest

I have no conflicts of interest to declare

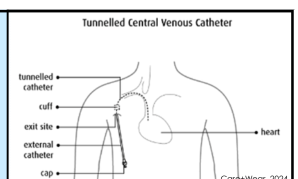
Learning objectives

1) Review the prevalence of catheter-related blood stream infections
2) Compare and contrast identification and management of exit site vs. tunnel vs. catheter-related bloodstream infections (CRBSI)
3) Highlight causative organisms and treatment principles
4) Discuss management of CRBSIs at St. Michael's Hospital
5) Evaluate new evidence for antibiotic treatment duration for select organisms

Introduction

- Infection is the leading cause of hospital admission and 2nd most common cause of death in dialysis patients
- Associated with high cost burden
- Dialysis confers a 100- to 300-fold higher mortality from sepsis than the general population
- Compared to AV fistulas, tunneled CVCs are associated with a 15-fold greater risk of bacteremia
- In a 2013 study, Canada had the highest use of catheters (45%) and the lowest use of arteriovenous fistula (49%) among 14 countries.

Definitions



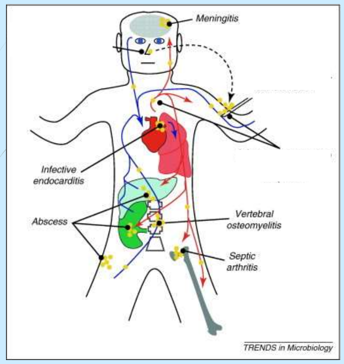
Exit site infection	Tunnel infection	Catheter-related blood stream infection (CRBSI)
• Signs of inflammation <2 cm surrounding the catheter exit site <u>and</u> • Presence of exudate that is culture-positive	• Inflammation extends beyond 2 cm from exit site **<u>&</u>** track towards the vein entry site • Associated with pain and tenderness along subcutaneous track <u>and</u> • Culture-positive exudate at exit site that may not be seen unless expressed by palpation	• Isolation of the same pathogen from blood culture drawn through central line and peripheral vein

Symptoms

- Pain, swelling, discharge from exit site
- Redness, tenderness surrounding or along subcutaneous track
- Fever (>38°C), chills
- Sepsis- altered mental status, hypotension, elevated WBC count, lethargy, fatigue

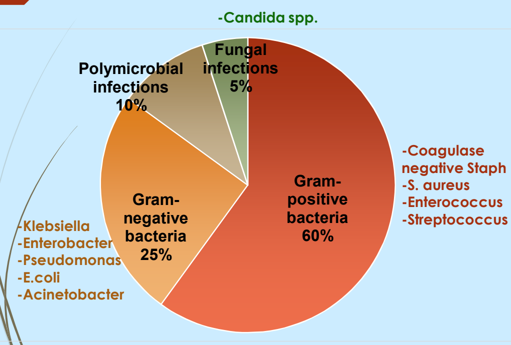
Kidney International 2011; 79; 587-98

Complications



Trends in Microbiology 2011; 19(4): 184-190

Causative organisms



Management options (summary)

- Antimicrobial therapy
- Line removal
- Antimicrobial lock therapy

IDSA 2009

Pathogen	Preferred antimicrobial agent	Example, dosage[a]	Alternative antimicrobial agent
Gram-positive cocci			
Staphylococcus aureus			
Meth susceptible	Penicillinase-resistant Pen[b]	Naf or Oxa, 2 g q4h	Cfaz, 2 g q8h; or Vm, 15 mg/kg q12h
Meth resistant[e]	Vm	Vm, 15 mg/kg q12h	Dapto, 6–8 mg/kg per day, or linezolid; or Vm plus (Rif or Gm); or TMP-SMZ alone (if susceptible)
Coagulase-negative staphylococci			
Meth susceptible	Penicillinase-resistant Pen	Naf or Oxa, 2 g q4h	First-generation Csp or Vm or TMP-SMZ (if susceptible)
Meth resistant	Vm	Vm, 15 mg/kg iv q12h	Dapto 6 mg/kg per day, linezolid, or Quin/Dalf
Enterococcus faecalis/Enterococcus faecium			
Amp susceptible	Amp or (Amp or Pen) ± aminoglycoside	Amp, 2 g q4h or q6h; or Amp ± Gm, 1 mg/kg q8h	Vm
Amp resistant, Vm susceptible	Vm ± aminoglycoside	Vm, 15 mg/kg iv q12h ± Gm, 1 mg/kg q8h	Linezolid or Dapto 6 mg/kg per day
Amp resistant, Vm resistant	Linezolid or Dapto	Linezolid, 600 mg q12h; or Dapto 6 mg/kg per day	Quin/Dalf 7.5 mg/kg q8h
Gram-negative bacilli[d]			
Escherichia coli and *Klebsiella* species			
ESBL negative	Third-generation Csp	Ctri, 1–2 g per day	Cipro or Atm
ESBL positive	Carbapenem **	Erta, 1 g per day; Imi, 500 mg q6h; Mero, 1 g q8h; or doripenem, 500 mg q8h	Cipro or Atm -Tobra, gent
Enterobacter species and *Serratia marcescens*	Carbapenem	Erta, 1 g per day; Imi, 500 mg q6h; Mero, 1 g q8h	Cefepime or Cipro
Acinetobacter species	Amp/Sulb or carbapenem	Amp/Sulb, 3 g q6h; or Imi, 500 mg q6h; Mero, 1 g q8h	-Tobra, gent

-Vanco 15-20 mg/kg IV x 1 load, then 10-12 mg/kg IV post-IHD maintenance

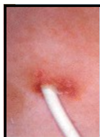
IDSA 2009

Stenotrophomonas maltophilia	TMP-SMZ	TMP-SMZ, 3–5 mg/kg q8h	Tic and Clv
Pseudomonas aeruginosa	Fourth-generation Csp or carbapenem or Pip and Tazo with or without aminoglycoside	Cefepime, 2 g q8h; or Imi, 500 mg q6h; or Mero, 1 g q8h; or Pip and Tazo, 4.5 g q6h, Amik, 15 mg/kg q24h or Tobra 5–7 mg/kg q24h	... -Ceftaz 2g post IHD -Tobra
Burkholderia cepacia	TMP-SMZ or carbapenem	TMP-SMZ, 3–5 mg/kg q8h; or Imi, 500 mg q6h; or Mero, 1 g q8h	...
Fungi			
Candida albicans or other *Candida* species	Echinocandin or fluconazole (if organism is susceptible) -Fluconazole	Caspo, 70-mg loading dose, then 50 mg per day; micafungin, 100 mg per day; anidulafungin, 200 mg loading dose followed by 100 mg per day; or fluconazole, 400–600 mg per day	Lipid AmB preparations

-Tobra 2 mg/kg x 1 load, then 1 mg/kg IV post-IHD maintenance

Thrice weekly dosing strategy with ertapenem

Geerlings CJ, et al. (2013) ***Ertapenem 1g 3x/week***	• Total 10 infected patients on IHD • Received ertapenem 1g IV post-IHD (following 4 hour high flux session) • Ertapenem levels were maintained above the determined MICs between dialysis sessions • 80% clinical success rate • No severe adverse events
Ueng YF, et al (2019) ***Ertapenem 500 mg 3x/week***	• **P:** Total 22 patients, on IHD, Taiwanese • **I:** 500 mg IV 3x/week post-IHD (11 pts) • **C:** 500 mg IV daily (11 pts) • **O:** Drug concentrations in intervention group remained above MIC of 2. Control group exceeded MIC of 2.



Management of exit site infection (no bacteremia)

- Line removal not necessary
- Topical +/- systemic antibiotics (mainly gram-positive)
- Typical duration 7-14 days depending on organism

Prevention strategies:

- 2% chlorhexidine wash for daily skin cleansing
- Povidone iodine antiseptic ointment or bacitracin/gramicidin/polymyxin B ointment at the dialysis catheter exit site at the end of each dialysis session

(BC Renal, 2021)

Management of tunnel infection (no bacteremia)

- Always require catheter removal
  - Without catheter exchange over a guidewire
- When blood cultures negative, insertion of new catheter at another site
- Systemic antibiotics- empiric gram-positive & gram-negative coverage
- Typical duration 7-14 days depending on organism

(BC Renal, 2021)

Management of catheter-related bloodstream infection (positive blood culture)

- If suspected (fever > 38°C, chills, hypotension, elevated WBC count, no apparent source other than catheter)
  - Blood cultures
  - Culture from most purulent aspect of exit site
  - Start empiric antibiotics (gram-positive + gram-negative)
    - Cefazolin, vancomycin, ceftazidime, aminoglycoside

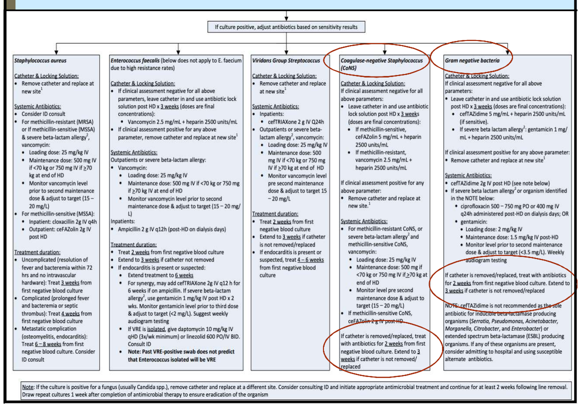
(BC Renal, 2021)

Management of catheter-related bloodstream infection (positive blood culture)

- Line removal?
  - Clinical signs & symptoms of sepsis, hemodynamic instability
  - Temperature > > 38°C for over 48 hours
  - Recent catheter-related infection
  - Exit site or tunnel infection noted
  - Uncuffed catheter
  - On immunosuppressants
  - Prosthetic heart valve
- If clinically stable, consider giving antibiotics, leaving catheter in situ and locking with antibiotic solution (depending on culture)

(BC Renal, 2021)

Treatment of CRBSI (BC Renal, 2021)



If culture positive, adjust antibiotics based on sensitivity results

Staphylococcus aureus

Catheter & Locking Solution:
- Remove catheter and replace at new site[1]

Systemic Antibiotics:
- Consider ID consult
- For methicillin-resistant (MRSA) or If methicillin-sensitive (MSSA) & severe beta-lactam allergy[2], vancomycin:
  - Loading dose: 25 mg/kg IV
  - Maintenance dose: 500 mg IV if <70 kg or 750 mg IV if ≥70 kg at end of HD
  - Monitor vancomycin level prior to second maintenance dose & adjust to target (15 – 20 mg/L)
- For methicillin-sensitive (MSSA):
  - Inpatient: cloxacillin 2g IV q4h
  - Outpatient: ceFAZolin 2g IV post HD

Treatment duration:
- Uncomplicated (resolution of fever and bacteremia within 72 hrs and no intravascular hardware): Treat 3 weeks from first negative blood culture
- Complicated (prolonged fever and bacteremia or septic thrombus): Treat 4 weeks from first negative blood culture
- Metastatic complication (osteomyelitis, endocarditis): Treat 6 – 8 weeks from first negative blood culture. Consider ID consult

Enterococcus faecalis (below does not apply to E. faecium due to high resistance rates)

Catheter & Locking Solution:
- If clinical assessment negative for all above parameters, leave catheter in and use antibiotic lock solution post HD x 3 weeks (doses are final concentrations):
  - Vancomycin 2.5 mg/mL + heparin 2500 units/mL
- If clinical assessment positive for any above parameter, remove catheter and replace at new site[1]

Systemic Antibiotics:
Outpatients or severe beta-lactam allergy:
- Vancomycin:
  - Loading dose: 25 mg/kg IV
  - Maintenance dose: 500 mg IV if <70 kg or 750 mg if ≥70 kg IV at end of HD
  - Monitor vancomycin level prior to second maintenance dose & adjust to target (15 – 20 mg/L)

Inpatients:
- Ampicillin 2 g IV q12h (post-HD on dialysis days)

Treatment duration:
- Treat 2 weeks from first negative blood culture
- Extend to 3 weeks if catheter not removed
- If endocarditis is present or suspected:
  - Extend treatment to 6 weeks
  - For synergy, may add cefTRIAXone 2g IV q12 h for 6 weeks if on ampicillin. If severe beta-lactam allergy[2], use gentamicin 1 mg/kg IV post HD x 2 wks. Monitor gentamicin level prior to third dose & adjust to target (<2 mg/L). Suggest weekly audiogram testing
  - If VRE is isolated, give daptomycin 10 mg/kg IV qHD (3x/wk minimum) or linezolid 600 PO/IV BID. Consult ID
  - **Note: Past VRE-positive swab does not predict that Enterococcus isolated will be VRE**

Viridans Group Streptococcus

Catheter & Locking Solution:
- Remove catheter and replace at new site[1]

Systemic Antibiotics:
- Inpatients:
  - cefTRIAXone 2 g IV Q24h
- Outpatients or severe beta-lactam allergy[2], vancomycin:
  - Loading dose: 25 mg/kg IV
  - Maintenance dose: 500 mg IV if <70 kg or 750 mg IV if ≥70 kg at end of HD
  - Monitor vancomycin level pre second maintenance dose & adjust to target 15 – 20 mg/L

Treatment duration:
- Treat 2 weeks from first negative blood culture
- Extend to 3 weeks if catheter is not removed/replaced
- If endocarditis is present or suspected, treat 4 – 6 weeks from first negative blood culture

Coagulase-negative Staphylococcus (CoNS)

Catheter & Locking Solution:
If clinical assessment negative for all above parameters:
- Leave catheter in and use antibiotic lock solution post HD x 3 weeks (doses are final concentrations):
  - If methicillin-sensitive, ceFAZolin 5 mg/mL + heparin 2500 units/mL
  - If methicillin-resistant, vancomycin 2.5 mg/mL + heparin 2500 units/mL

If clinical assessment positive for any above parameter:
- Remove catheter and replace at new site.[1]

Systemic Antibiotics:
- For methicillin-resistant CoNS, or severe beta-lactam allergy[2] and methicillin-sensitive CoNS, vancomycin:
  - Loading dose: 25 mg/kg IV
  - Maintenance dose: 500 mg if <70 kg or 750 mg IV if ≥70 kg at end of HD
  - Monitor level pre second maintenance dose & adjust to target (15 – 20 mg/L)
- If methicillin-sensitive CoNS, ceFAZolin 2 g IV post HD

If catheter is removed/replaced, treat with antibiotics for 2 weeks from first negative blood culture. Extend to 3 weeks if catheter is not removed/replaced

Gram negative bacteria

Catheter & Locking Solution:
If clinical assessment negative for all above parameters:
- Leave catheter in and use antibiotic lock solution post HD x 3 weeks (doses are final concentrations):
  - cefTAZidime 5 mg/mL + heparin 2500 units/mL (if sensitive).
  - If severe beta lactam allergy[2]: gentamicin 1 mg/mL + heparin 2500 units/mL

If clinical assessment positive for any above parameter:
- Remove catheter and replace at new site[1]

Systemic Antibiotics:
- cefTAZidime 2g IV post HD (see note below)
- If severe beta lactam allergy[2] or organism identified in the NOTE below:
  - ciprofloxacin 500 – 750 mg PO or 400 mg IV q24h administered post-HD on dialysis days; OR
  - gentamicin:
    - Loading dose: 2 mg/kg IV
    - Maintenance dose: 1.5 mg/kg IV post-HD
    - Monitor level prior to second maintenance dose & adjust to target (<3.5 mg/L). Weekly audiogram testing

If catheter is removed/replaced, treat with antibiotics for 2 weeks from first negative blood culture. Extend to 3 weeks if catheter is not removed/replaced

NOTE: cefTAZidime is not recommended as the sole antibiotic for inducible beta-lactamase producing organisms (*Serratia, Pseudomonas, Acinetobacter, Morganella, Citrobacter*, and *Enterobacter*) or extended spectrum beta-lactamase (ESBL) producing organisms. If any of these organisms are present, consider admitting to hospital and using susceptible alternate antibiotics.

Note: If the culture is positive for a fungus (usually Candida spp.), remove catheter and replace at a different site. Consider consulting ID and initiate appropriate antimicrobial treatment and continue for at least 2 weeks following line removal. Draw repeat cultures 1 week after completion of antimicrobial therapy to ensure eradication of the organism

Treatment duration (organism specific)

- **From first negative blood culture, if line removed:**
  - **S. aureus → 14 days (if no endocarditis, metastatic infection)**
  - **Coagulase-negative staphylococci → 7 days or less?**
  - **Enterococci → 14 days**
  - **Gram negative bacilli → 7 days**
  - **Candida → 14 days (if no retinitis)**

Research | Open access | Published: 29 January 2019

Catheter-related bloodstream infections with coagulase-negative staphylococci: are antibiotics necessary if the catheter is removed?

Ursula Patricia Hebeisen, Andrew Atkinson, Jonas Marschall & Niccolò Buetti

Treatment duration (organism specific)

- From first negative blood culture, if line removed:
  - S. aureus → 14 days (if no endocarditis, metastatic infection)
  - Coagulase-negative staphylococci → 7 days or less?
  - Enterococci → 14 days
  - Gram negative bacilli → 7 days
  - Candida → 14 days (if no retinitis)

Duration of antibiotic treatment for Gram-negative bacteremia – Systematic review and individual participant data (IPD) meta-analysis

Adi Turjeman,[a,b,*] Elodie von Dach,[c,d] José Molina,[e,f,g] Erica Franceschini,[h] Fidi Koppel,[i] Dana Yelin,[j] Yael Dishon-Benattar,[i,k] Cristina Mussini,[h] Jesús Rodríguez-Baño,[g,l] José Miguel Cisneros,[e,f,g] Angela Huttner,[c] Mical Paul,[i,k] Leonard Leibovici,[a,b] and Dafna Yahav[b,j]

Antimicrobial locks

- Premise: Biofilm coating inner surface of CVC is the major source of CRBSI
- Antibiotic lock (+ anticoagulant) instillation into lumen may reduce CRBSI by sterilizing biofilm
- Consensus: Routine prophylactic antimicrobial locks not recommended across the board for preventing CRBSIs
- KDOQI 2020 suggests **selective use** of specific prophylactic antibiotic locks considered in patients in need of long-term CVC who are at risk of CRBSI

KDOQI 2020

Antimicrobial locks

Table 24.1. Intraluminal Strategies: Effect of Antibiotic and Antimicrobial Catheter Lock Solutions on CRBSI: Summary of Randomized Clinical Trials

Agents Studied	Patients, n	Relative Risk (95% CI)	Anticipated Incidence of CRBSI (95% CI)		Quality of Evidence
Locking Solutions That Can Be Used Selectively for CRBSI Prophylaxis					
Cefotaxime[593-595] (3 RCTs)	227	0.42 (0.25-0.72)	Without antibiotic: 67.5%	With cefotaxime: 23.6%	Moderate
Gentamicin[583-585,596] (4 RCTs)	555	0.18 (0.07-0.46)	Without antibiotic: 22.1%	With gentamicin: 4.0% (1.5-10.2)	Moderate
Weekly TPA[506] (1 RCT)	225	0.30 0.11-0.85)	Heparin: 13%	Weekly TPA: 5%	Moderate
Cotrimoxazole[597] (1 RCT)	87	0.16 (0.04-0.69	Without antibiotic: 4.4 per 1,000 days	With antibiotic: 0.58 per 1,000 days	Low
Methylene blue[598] (1 RCT)	407	0.29 (0.12-0.70)	Heparin: 0.82 per 1,000 days	Methylene blue% 0.24 per 1,000 days	Low
No Significant Effect or Very Low Evidence, Cannot Be Recommended (below)					
Taurolidine/citrate[533,599]	183	0.49 (0.20-1.24)	Heparin: 21.5%	Taurolidine/citrate: 10.5% (4.3%-26.7%)	Low
Vancomycin or linezolid[600] (1 RCT)	152		Without antibiotic: 6.7 per 1,000 days	With vancomycin: 1.2 per 1,000 days With linezolid: 0 per 1,000 days	Very low
Vancomycin + gentamicin[601] (1 RCT)	86	0.18	Without antibiotic: 4.0 per 1,000 days	With antibiotic: 0.7 per 1,000 days	Very low
Cefazolin[602,603] (2 RCTs)	159	0.58 (0.32-1.04)	Without antibiotic: 29.3%	With cefazolin: 17.0% (9.4%-30.5%)	Very low
Cefazolin + gentamicin[604] (1 RCT)	120	0.14	Without antibiotic: 3.12 per 1,000 days	With antibiotic: 0.44 per 1,000 days	Very low
Minocycline[605] (1 RCT)	204	0.32 (0.14-0.71)	Without antibiotic: 4.3 per 1,000 days	With antibiotic: 1.1 per 1,000 days	Not reviewed by ERT
Antimicrobial solutions					
EDTA[606] (1 RCT)	117	0.34 (0.04-3.24)	Heparin: 1.08 per 1,000 days	EDTA: 0.14 per 1,000 days	Very low
Ethanol/heparin[607] (1 RCT)	49	0.17 (0.02-0.63)	Heparin: 13%	Ethanol/heparin: 4%	Very low
Ethanol/citrate[608] (1 RCT)	40		Heparin: 5%	Ethanol/citrate: 0%	Very low
Hypertonic saline[544] (1 RCT)	59	—	Heparin: 10%	Hypertonic saline: 15%	Very low
30% citrate[528] (1 RCT)	291	(0.13-0.36)	Heparin: 4.1 per 1,000 days	30% citrate: 1.1 per 1,000 days	Not reviewed by ERT
46.7% citrate[526] (1 RCT)	232	—	46.7% citrate: 0.7 per 1,000 days	Heparin: 0.7 per 1,000 days	Not reviewed by ERT

KDOQI 2020

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