Antibiotic Lock Therapy

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Presentation Overview

- Overview of catheter-related bloodstream infections
- Highlight IDSA guidelines on prevention and management of catheter-related bloodstream infections
- Describe concept of using antibiotic lock therapy
- Review literature and patient case on use of antibiotic lock therapy

Catheter-Related Bloodstream Infections (CRBSI)

- In the US, >150 million intravascular devices are purchased yearly
  - > 5 million catheters inserted per year
  - Administration of IV fluids, medications, parenteral nutrition, hemodialysis
- Estimated 250,000 cases of central line related bloodstream infections occur in US hospitals annually
  - 80,000 CRBSIs in ICUs
- Central (vs. peripheral) venous catheters cause serious infections and complications
  - Excess hospital length of stay - 9 to 12 days \(^1,2\)
  - Excess medical cost - $296 million to $2.3 billion \(^3\)
  - High mortality rates - 2,400 – 20,000 deaths per year \(^3\)

**Most Common Organisms Isolated from Bloodstream Infections**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Gram-negative rods</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>


**Catheters and Biofilm**

- CRBSI arise from bacterial biofilm
- Host proteins coat interior and exterior surface of catheter → bind bacteria → form biofilm
- CoNS: fibronectin and polymer surfaces
- S. aureus: fibrinogen and fibronogen
- Candida albicans: fibrin
- Microorganisms on biofilm not affected by phagocytes or antibodies produced by host
- Biofilm highly resistant to antibiotics
- Decreased penetration of antibiotics

Aslam S. *Assoc Prof Inf Cont Epid*. 2008;36:S175e9-11
### Risk Factors for Catheter-Related Bloodstream Infections

- Emergent catheter insertion
- Frequency of catheter manipulation
  - Fluids/drugs administration
- Site of catheter insertion
  - CVC insertion preferred in subclavian vs. femoral or jugular vein
- Duration catheter in place
- Catheter used for parenteral nutrition

CVC = Central venous catheter; PVC = Polyvinyl chloride

### IDSA Guidelines (2009)

Management for Catheter-related infections

- Empirically initiate systemic antimicrobial therapy upon suspicion or diagnosis
- Antimicrobial choice will depend on
  - Disease severity
  - Most likely organism(s)
  - Local antimicrobial susceptibility data
  - Risk factors for multidrug resistant pathogens
- De-escalation upon culture results
- Removal of source of infection (catheter)
  - Tunnel or pocket infection, implanted port pocket infection, complicated infections
- Consider retaining precious catheters (long-term catheters)


### Catheter Retained: IV Antibiotics as Monotherapy

- Mean success rate of treating CRBSI with parenteral therapy alone is 67%
  - In 14 open trials, success was seen in 342/514 episodes
- Success varies based on site of infection and organism
  - Tunnel or pocket infections are unresponsive to salvage
  - CoNS responds better than S. aureus or P. aeruginosa infection
  - Recurrent bacteremia more likely after completion of IV antimicrobials if catheter retained
  - Inability of most antimicrobials to kill organisms in biofilm
  - IDSA endorses use of antibiotic lock therapy to increase treatment success rate in adjunct to IV antibiotics

CoNS = Coagulase-negative staphylococci

Antibiotic Lock Therapy (ALT)

- Highly concentrated antibiotic solution instilled in catheter lumen
  - Antibiotics choice based on culture and sensitivities
  - Concentration must be 100 – 1,000x greater to kill bacteria in biofilm
- Goal of ALT
  - Kill organisms embedded in biofilm in colonized catheter lumen
  - Not effective for CRBSI from extra-luminal colonization (in place <2 wks)

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Antibiotic Lock Therapy (ALT) cont’d

- Solution usually contains heparin to maintain patency of catheter
- Lock solutions consists of about 2 – 5 mL to fill catheter lumen
  - If multiple lumens will have multiple locks
- Prolonged indwelling time within catheter
  - High concentrated maintained for extended amount of time to maximize bactericidal activity and biofilm penetration

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Antibiotic Lock Antimicrobial Selection

- Pathogen and antimicrobial susceptibilities
- Organism characteristics
  - Adherence to host proteins
  - Biofilm production
- Pharmacodynamic properties of antimicrobial
  - Concentration dependant killers (i.e. Aminoglycosides, FQ)
  - Time dependant killers (i.e. B-Lactams)

FQ = Fluoroquinolones
Depends on stability of combined solutions
- Usually 8 to 12 hours per day
- i.e., Vancomycin, cefazolin, ceftazidime remains stable in heparin solution at 25°C-37°C for several days
- Antimicrobial must be compatible with catheter
- Antibiotic lock should be used during off hours
- Should generally not exceed 48 hours before reinstallation
- In patients undergoing hemodialysis, lock solution can be instilled after each hemodialysis session

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In patients undergoing hemodialysis, lock solution can be instilled after each hemodialysis session

Management of Catheter-Related Infection: Role of Antibiotic Lock Therapy (ALT)

"Antibiotic lock therapy is indicated for CRBSI involving long-term catheters when catheter salvage is the goal" [B-II]
- Patients with no evidence of exit site or tunnel infection
- "ALT should be used in adjunct to systemic antibiotics" [B-II]
  - ALT alone if multiple positive catheter-drawn blood cultures (+) CoNS or GNB and concurrent (-) peripheral blood cultures
  - "Catheter removal recommended for CRBSI due to S. aureus and Candida spp." [A-II]
    - Unless extenuating circumstances

In 21 open trials, long-term catheter salvage with ALT + IV antibiotics occurred in 77% of episodes

CoNS and GNB had best success rates with ALT

S. aureus and Candida CRBSI are more difficult to treat with ALT

S. aureus bacteremia may cause cardiac or musculoskeletal complications

Candida CRBSIs hard to eradicate with ALT

Catheter removal should be treatment of choice

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CONS = Coagulase-negative staphylococci; GNB = Gram-negative bacteria
**Outcome Studies for Antibiotic Lock Treatment (ALT)**

<table>
<thead>
<tr>
<th>Treatment of long-term intravascular catheter-related bacteremia with antibiotic lock: randomized, placebo-controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objectives</strong></td>
</tr>
<tr>
<td>• Identify failure to cure with antibiotic lock for treatment of CRBSI</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
</tr>
<tr>
<td>• Randomized, blinded, multicenter trial comparing ALT containing vancomycin-heparin for GPB or ceftazidime-heparin for GNB with placebo (heparin alone), in addition to IV antibiotics</td>
</tr>
<tr>
<td><strong>Results</strong></td>
</tr>
<tr>
<td>• 46 patients were included in analysis during 30 month study</td>
</tr>
<tr>
<td>• Majority of organisms were CoNS and E. coli or Klebsiella species</td>
</tr>
<tr>
<td>• On study day 100 by Kaplan-Meier analysis, 33% (7/21) in ALT arm and 57% (13/23) met primary endpoint (hazard ratio 0.55, p = 0.1)</td>
</tr>
<tr>
<td>• Relapse with same strain occurred in 923 with placebo and 3/21 with ALT arm (p = 0.06)</td>
</tr>
</tbody>
</table>

**CRBSI = Catheter-related bloodstream infection; GPB = Gram-positive bacteria; GNB = Gram-negative bacteria; CoNS = Coagulase-negative staphylococci**


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**Outcome Studies for Antibiotic Lock Treatment (ALT)**

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<tr>
<th>Treatment of long-term intravascular catheter-related bacteremia with antibiotic-lock therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objectives</strong></td>
</tr>
<tr>
<td>• Primary endpoint: failure to cure episode of CRBSI</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
</tr>
<tr>
<td>• Compared ALT consisted with vancomycin/H (for GPB) or ciprofloxacin or gentamicin/H (for GNB) in adjunct to IV antibiotics vs. control (IV antibiotics only)</td>
</tr>
<tr>
<td><strong>Results</strong></td>
</tr>
<tr>
<td>• 48/92 CRBSI were included in analysis over 44 month study period</td>
</tr>
<tr>
<td>• Majority of organisms were CoNS and P. aeruginosa</td>
</tr>
<tr>
<td>• Catheter removal occurred in 1/19 episode from ALT arm vs. 7/29 in control arm</td>
</tr>
<tr>
<td>• Relapse of bacteremia after treatment occurred in 2 patients from ALT vs. 3 patients from control arm</td>
</tr>
<tr>
<td>• Successful treatment was achieved in 84% of ALT and 65% of the episodes in control group (p=0.27)</td>
</tr>
</tbody>
</table>

**CRBSI = Catheter-related bloodstream infection; GPB = Gram-positive bacteria; GNB = Gram-negative bacteria; H = heparin; CoNS = Coagulase-negative staphylococci**


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**IDSA Management for Catheter-Related Bloodstream Infection (CRBSI)**

- **Treatment of Choice:** Catheter removal + antibiotics
  - *S. aureus*, *P. aeruginosa*, *Mycobacterium* - and *Candida* species-infected catheter
  - Complicated CRBSI with suppurative thrombophlebitis, severe sepsis, endocarditis, and osteomyelitis
  - Persistent bacteremia >72h despite treatment
  - Treat with ALT + antibiotics

**ALT = Antibiotic Lock Therapy**

**Patient Case**

- **HPI:** 46 y/o AAF from group home was sent by dialysis unit for fever and lethargy. Patient had multiple admissions in months prior for catheter-related bacteremia.
  - VS: BP 111/65 mmHg; P 100 bpm; R 20; Temp 100.2 F
- **Allergies:** Penicillin
- **PMH:** HTN, ESRD with femoral CVC, schizophrenia
  - Patient is known to pull out all her central/peripheral lines
  - She has poor hygiene
- **Previous blood cultures**
  - 06/09: *Enterobacter cloacae*
  - 07/09: *Proteus mirabilis* and *Pseudomonas aeruginosa*

**Patient case cont'd...**

- **ID was consulted and empirically started antibiotics**
  - Vancomycin 1.5 g post HD
  - Gentamicin 100 mg post HD
  - Aztreonam 1g Q12H
- **Patient was found to be non-compliant with non-HD IV antibiotics and Aztreonam was changed to Ciprofloxacin PO**
Cultures:
- 11/20 BC (+) Enterobacter cloaceae (R to only Unasyn)
- 11/25 & 11/27 BC (+) Staphylococcus simulans (R) Oxacillin
- 11/27 BC (+) Coagulase-negative Staphylococcus

Catheter was not able to be removed due to patient’s non-cooperation
Decided to start ALT (genta+vanco+heparin) + IV abx
- After completion of therapy, IV antibiotics were stopped but ALT was continued for prevention of CRBSIs

Antibiotic Lock Therapy (ALT) for Prevention of Catheter-Related Infections

Randomized, Double-Blind Trial of an Antibiotic-Lock Technique for Prevention of Gram-Positive Central Venous Catheter-Related Infection in Neutropenic Patients with Cancer

Objectives
- Primary: Significant colonization of the catheter hub
- Secondary: Presence of catheter-related bacteremia

- N = 117 neutropenic patients with nontunneled, multilumen CVC
  - Heparin 10 units/mL (n = 57) vs. Heparin 10 units/mL + Vancomycin 25 mcg/mL (n = 60)
- Solution instilled in catheter lumen and allowed to dwell for 1 h every 2 days
- Insertion-site and hub swabs taken twice daily

Results
- Significant colonization of hub in heparin (15.8%) vs. ALT (0%) group [p = 0.001]
- No catheter-related bacteremia in ALT group vs. 7% in heparin group [p<0.05]

CVC = Central venous catheters

Strategies for Prevention of Catheter-Related Infections
- Hand hygiene and aseptic technique
- Skin antiseptics (e.g., chlorhexidine gluconate)
- Catheter site dressing regimens
- Catheter securement devices
- In-line filters
- Antimicrobial/antiseptic impregnated catheter/cuffs
- Topical/systemic antibiotic prophylaxis
- Antibiotic lock therapy
Examples of Desired Antibiotic Lock Solution (IDSA)

<table>
<thead>
<tr>
<th>Antibiotic and dosage</th>
<th>Heparin or saline, u/mL</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin, 2.5 mg/mL</td>
<td>100</td>
<td>(252, 258)</td>
</tr>
<tr>
<td>Vancomycin, 2.5 mg/mL</td>
<td>10</td>
<td>(278)</td>
</tr>
<tr>
<td>Cefazolin, 0.8 mg/mL</td>
<td>0 or 500</td>
<td>(278, 279)</td>
</tr>
<tr>
<td>Ceftazolin, 0.8 mg/mL</td>
<td>185</td>
<td>(129)</td>
</tr>
<tr>
<td>Gentamicin, 0.5 mg/mL</td>
<td>5000</td>
<td>(190)</td>
</tr>
<tr>
<td>Gentamicin, 1 mg/mL</td>
<td>5000</td>
<td>(190)</td>
</tr>
<tr>
<td>Ampicillin, 10 mg/mL</td>
<td>10 or 1000</td>
<td>(278)</td>
</tr>
<tr>
<td>Ertapenem, 75%</td>
<td>0</td>
<td>(129)</td>
</tr>
</tbody>
</table>

Note: These antibiotic lock solutions are not prescribed at the given concentrations. Cefazolin is the preferred agent for treatment of meticillin-resistant Staphylococcus and vancomycin is the preferred agent for treatment of methicillin-sensitive Staphylococcus. Gentamicin may be used for treatment of Staphylococcus aureus endocarditis, in the absence of other antibiotics, as well as for treatment of pseudomonas aeruginosa. Ertapenem may be used for treatment of pseudomonas aeruginosa. Amikacin is the preferred agent for treatment of pseudomonas aeruginosa and gentamicin is the second choice. If gentamicin is used, use the same aminoglycoside concentration for all non-hemodialysis catheters.

### Examples of Desired Antibiotic Lock Solution

#### For non-hemodialysis catheters

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Concentration (mg/mL)</th>
<th>Heparin Concentration (u/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>2.5</td>
<td>100</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1</td>
<td>100</td>
</tr>
</tbody>
</table>

#### For hemodialysis catheters

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Concentration (mg/mL)</th>
<th>Heparin Concentration (u/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>2.5</td>
<td>2,500</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1</td>
<td>2,500</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>10</td>
<td>5,000</td>
</tr>
<tr>
<td>Gentamicin + vancomycin</td>
<td>2 + 2.5</td>
<td>2,500</td>
</tr>
</tbody>
</table>

### Disadvantages with Antibiotic Lock Therapy

- Optimal concentration and dwell times undetermined
- No consensus on standard formulations
- Limited stability data for certain antimicrobials at body temp
- Resistance developed by microorganisms
- Efficacy may diminish over time due to decreased concentrations in lumen
- Must maintain certain concentration above MIC during entire interval
- Heparin in combination with antimicrobials in ALT solution is controversial
- Alternatives: normal saline or sodium citrate
- Heparin may increase efficacy of antibiotics used in ALT

Ethanol Lock Therapy

- Ethanol – an antiseptic that demonstrates bactericidal and fungicidal activity
  - Broad range of Gram+ and Gram- pathogens
  - Install ethanol containing solution into catheter lumen
  - Mechanism: non-specific protein denaturation
  - Concentration dependent activity
    - >40% ethanol – inhibits bacterial growth in biofilm
    - In artificial material (in-vitro) - 70% ethanol kills
      - Bacteria ≥ 2 hrs dwell time
      - Fungi ≥ 4 hrs dwell time

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Ethanol Lock Therapy

- Advantages
  - Eradicates bacterial colonization irrespective of organism sensitivity
  - Can use against polymicrobial CRBSI
  - Prevention of antimicrobial resistance
  - Readily accessible and inexpensive

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Ethanol Lock Therapy (ELT) for Treatment of Catheter-Related Infections

| CVC • catheter related infection; WBC • white blood cells |

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Ethanol Lock Therapy (ELT) for Prevention of Catheter-Related Infections

| Objectives | • Evaluate use of ELT for the prevention of CRBSI in immunosuppressed hematology patients  
• Primary endpoint – episode of CRBSI |
| Methods | • Randomized, double blind trial comparing ELT (70% ethanol/water) with placebo (heparinized saline lock)  
• Solution instilled in catheter lumen and allowed to dwell for 2 h daily  
• Dual lumen Hickman CVC (tunneled cuffed) |
| Results | • N = 60 immunosuppressed hematology patients (mean: 52.4 yrs) over 64 treatment periods  
• 34 & 30 prophylactic treatment periods in ethanol & control groups respectively  
• CRBSI occurred in 3 (9%, 0.6/100 catheter days) prophylactic treatment periods in ELT group vs. 11 (37%, 3.11/100 catheter days) prophylactic treatment periods in control group [P=0.008]  
• Catheters survived longer without CRBSI in the ethanol group [P=0.003] |

Sanders J et al. JAC 2008;62:809-815

Ethanol Lock Therapy Safety Concerns

• Systemic ethanol absorption (lock withdrawal)  
  • AE: lightheadedness, flushing, nausea, “taste of alcohol”  
  • Not a perfect lock; contents may leak with lock withdrawal  
• Mechanical and structural integrity of catheter with ethanol  
  • Safe to use ELT with select polyetherurethane and silicone catheters  
  • Potential release of plastic components after ethanol lock  
• Patency of catheter  
  • Ethanol is incompatible with heparin however possesses intrinsic anticoagulant activity  
  • 3 cases of catheter occlusion with 100% ethanol lock (precipitate) |


Maximum Theoretical Absorption

• 70% ethanol  
  70 g/100 mL x 0.8 (SG)= 0.56 g/mL  
• 1 ethanol lock  
  5 mL of 70% EtOH = 2.8 g = 2800 mg per lock  
• Volume of distribution of ethanol  
  Vd = 0.53 L/kg  
  Vd/70 kg patient = 37.1 L = 371 dL  
• Blood alcohol conc. if EtOH lock is 100% absorbed  
  2800 mg EtOH / 371 dL = 7.5 mg/dL |

T. Doan
Ethanol intoxication

<table>
<thead>
<tr>
<th>State</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclinical</td>
<td>10-40 mg/dL</td>
</tr>
<tr>
<td>Intoxication</td>
<td>90-250 mg/dL</td>
</tr>
<tr>
<td>Confusion</td>
<td>150-300 mg/dL</td>
</tr>
<tr>
<td>Slurred</td>
<td>250-400 mg/dL</td>
</tr>
<tr>
<td>Coma</td>
<td>350-600 mg/dL</td>
</tr>
<tr>
<td>Death</td>
<td>&gt;450 mg/dL</td>
</tr>
</tbody>
</table>

1 ethanol lock in body = 7.5 mg/dL

Clinical Relevance

Nursing Administration of Antibiotic Lock Solution

- DO NOT INJECT or INFUSE ALT solution
- DO NOT USE if any precipitate is seen
- Pharmacy will dispense ALT solution in plastic syringes and exact volume to be instilled in catheter/port will be determined by types of catheter
- Prior to instillation of ALT solution into catheter lumen, flush with 5 ml of normal saline
  - Clamp catheter or secure caps of the catheter hubs to “lock” solution after instillation of ALT solution
- Prior to infusion of any other IV medication via same catheter, withdraw and discard antibiotic/heparin lock solution
  - Flush catheter with 5 ml of normal saline
- Lock solution should be instilled on off hours when catheter is not in use
- Blood samples should be obtained peripherally or via a lumen without ALT solution when checking vancomycin/aminoglycoside serum levels or PT/INR
  - Smallest amount of lock solution will give misleading results

Nursing Administration of Antibiotic Lock Solution cont’d...
ALT is highly concentrated antimicrobial instilled into the catheter lumen (given in conjunction with systemic antibiotics)

- Used to treat CRBSI while sparing precious catheters
- Consider use in uncomplicated CRBSI with CoNS or GNB
- Catheters > 2 weeks old
- Several studies have shown that ALT can increase catheter retention rates, reduce relapse rates, and increase success of treating CRBSI
- Optimal frequency of antibiotic locks and dwell times are not well established and must be individualized (culture results and stability)
- Use of ELT may be considered if ALT is not feasible
  - Use against polymicrobial CRBSIs
  - Multidrug resistant organisms are embedded in biofilm

**In Summary...**

**Which is False regarding Antibiotic Lock Therapy (ALT)**

A. ALT is a highly concentrated antibiotic solution placed in the catheter lumen
B. ALT concentration is 100-1000x higher in order to kill bacteria in biofilm
C. Antibiotic lock solutions are approximately 2 – 5 mL and should completely fill the catheter lumen
D. ALT has greatest success when used to treat CoNS and *Staphylococcus aureus*

**It is recommended to use ALT in combination with IV antibiotics...**

A. To treat patients with persistent bacteremia
B. To treat tunnel infections
C. To treat a patient with CRBSI and endocarditis
D. To treat CRBSI caused by a catheter that was placed 5 days ago
E. None of the above
When preparing an ALT it is important to..

A. Check the compatibility of all components of the lock solution at specific concentrations (i.e. heparin + antibiotic)
B. Ensure the solution will be compatible at room temperature for the amount of time lock is going to dwell in the lumen
C. Prepare one lock solution per each catheter lumen
D. All of the above

Benefits of ALT Include

A. Non-invasive method to treat CRBSI (with IV antibiotics) when need to salvage precious catheters
B. When used for prophylaxis, can decrease intraluminal colonization and decrease catheter retention time
C. Can reduce relapse rates vs. IV antibiotics alone
D. A & C
E. All of the above

All of the following are FALSE about Ethanol Lock EXCEPT

A. ELT should contain 70% ethanol + heparin in order to prevent catheter occlusion
B. ELT with 70% ethanol should have a dwell time of ≥2 hrs in order to kill bacteria in catheter lumen
C. It is common for persons on ELT to become intoxicated due to the lock
D. When it is time to remove ELT, the nurse should inject the solution into the patient’s bloodstream