Empiric Antibiotics:
- Cefepime PLUS
- Vancomycin AND
gentamicin if severely ill; OR vancomycin if line site infection suspected
- AND antifungal if severely ill and with risk factors for fungal disease

Obtain cultures:
- Initial fever: blood cultures peripherally and from all catheter lumens
- Ongoing fever: cultures may not be necessary in all circumstance
- Catheter site cultures if indicated
- Review clinical status

Exclusion Criteria
- Amb. Clinic patients
- Heme/Onc except Sickle Cell, BMT patients and those on ECMO

Inclusion Criteria
- Inpatients and ED patients with suspected CLI
- Includes PICCs, Broviacs, hemodialysis lines, etc.

Do NOT perform blood cultures if CLI not suspected

Immunocompetent Patient
- High suspicion of CLI, hemodynamically unstable, toxic, or at risk for complications

Empiric Antibiotics:
- Gentamicin if severely ill;
- Vancomycin PLUS Cefepime
- Meropenem PLUS Antifungal if risk factors for fungal disease

Immunocompromised Patient
- Low suspicion of CLI, hemodynamically stable, non-toxic, and low risk for complications (minority of patients)

Empiric Antibiotics:
- Cefepime PLUS Antifungal if risk factors for fungal disease

Defer antibiotics

Allergies? Call ID!

Discontinue Antibiotics

Negative cultures at 48 hours and asymptomatic

Re-evaluate clinical status:
- After first antibiotic doses and fluid resuscitation
- Daily
- Follow culture results

Definition for non-tunneled or tunneled CLs

To Preliminary Cultures: Non-Tunneled CVCs

Positive Cultures

To Preliminary Cultures: Tunneled CVCs
Preliminary Culture PHASE, Non-Tunneled CVCs

Inclusion Criteria
- Inpatients and ED patients with suspected CLI
- Includes PICCs, Broviacs, hemodialysis lines, etc.

Exclusion Criteria
- Amb. Clinic patients
- Heme/Onc except Sickle Cell, BMT patients and those on ECMO
- Remove/exchange non-tunneled catheters promptly in unstable patients; remove all catheters if tunnel infection suspected

Do NOT perform blood cultures if CLI not suspected

Preliminary culture results

Gram-positive organisms
- Consider removing/exchanging the catheter and culturing the catheter tip
- Evaluate for other sources of infection
- Repeat blood cultures (from CL only is acceptable)
- Then add vancomycin if not currently on
- Add vancomycin lock therapy if not removing/exchanging immediately

Yeast
- Remove/exchange the catheter and culture the catheter tip
- Evaluate for other sources of infection
- Repeat blood cultures (from CL only is acceptable)
- Then begin antifungal

Gram-negative organisms
- If CLI, remove/exchange the catheter and culture the catheter tip
- If not a documented CLI, evaluate for other sources of infection and consider remove/exchange of catheter
- Repeat blood cultures (from CL only is acceptable)
- Ensure appropriate gram-negative coverage (e.g., cefepime)
- Add second gram-negative agent if patient unstable

Polymicrobial infections
- CLIs can involve more than one organism
- Do not narrow antimicrobials until all organisms are identified and their susceptibilities known.
- Call ID with questions.

Documenting clearance of CLI
- Repeat blood cultures daily:
  - From CL if retained / possible, otherwise peripherally / arterially
  - Until cultures remain negative for at least 48 hours
- Assure clearance of infection prior to replacing the catheter, if needed

To Definitive Treatment: Non-Tunneled CVCs

Final culture results available

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**Preliminary Culture PHASE, Tunneled CVCs**

**Inclusion Criteria**
- Inpatients and ED patients with suspected CLI
- Includes PICCs, Broviacs, hemodialysis lines, etc.

**Exclusion Criteria**
- Amb. Clinic patients
- Heme/Onc except Sickle Cell, BMT patients and those on ECMO

**Do NOT**
- perform blood cultures if CLI not suspected

**Gram-positive organisms**
- If CLI, consider catheter salvage if patient stable
- If CLI, remove/exchange the catheter if patient unstable
- If not a documented CLI, evaluate for other sources of infection and consider remove/exchange of catheter
- Repeat blood cultures (from CL only is acceptable)
  - Then add vancomycin if not currently on
  - Add vancomycin lock therapy if catheter retained

**Gram-negative organisms**
- Remove/exchange non-tunneled catheters promptly in unstable patients; remove all catheters if tunnel infection suspected

**Yeast**
- Remove/exchange the catheter
- Repeat blood cultures (from CL only is acceptable)
- Then begin antifungal

**Polymicrobial infections**
- CLIs can involve more than one organism
- Do not narrow antimicrobials until all organisms are identified and their susceptibilities known.
- Call ID with questions.

**Documenting clearance of CLI**
- Repeat blood cultures daily:
  - From CL if retained / possible, otherwise peripherally / arterially
  - Until cultures remain negative for at least 48 hours
  - Assure clearance of infection prior to replacing the catheter, if needed

**Final culture results available**
- To Definitive Treatment: Tunneled CVCs
Coagulase-negative Staphylococcus (other than S. lugdunensis)

- If CLI, can consider catheter salvage if patient stable
- Add vancomycin lock therapy if not currently on
- Treat for 10-14 days if CL salvaged, or 5-7 days if removed
- Manage CLI due to S. lugdunensis similarly to recommendations for S. aureus CLI

Definitive culture results (identification and susceptibilities of all organisms finalized)

For questions concerning this pathway, contact: CLI_Pathways@seattlechildrens.org

Definitive Results PHASE, Non-Tunneled CVCs

Inclusion Criteria
- Inpatients and ED patients with suspected CLI
- Includes PICCs, Broviacs, hemodialysis lines, etc.

Exclusion Criteria
- Amb. Clinic patients
- Heme/Onc except Sickle Cell, BMT patients and those on ECMO
- From CL if retained / possible, otherwise peripherally / arterially
- Until cultures remain negative for at least 48 hours
- Assure clearance of infection prior to replacing the catheter, if needed

Day 1 of treatment is the first day of negative cultures without subsequent positives

All Other Organisms

1. Remove/exchange the catheter
2. Staphylococcus aureus:
   - S. aureus antibiotic selection
   - Treat uncomplicated CLI for 14 days.
   - Treat complicated CLI for 4-6 weeks.
   - Perform echocardiography if >1 positive culture
   - Consult Infectious Diseases for all patients with high illness severity or multiple comorbidities.

3. Enterococci:
   - Use vancomycin lock therapy in addition to systemic therapy if the catheter is retained.
   - Enterococcal antibiotic selection
   - Treat for 7-14 days.

4. Gram-negative bacilli:
   - Gram-negative antibiotic selection
   - Treat for 7-14 days for uncomplicated CLI, or ≥4-6 weeks for complicated infections.

5. Candida species:
   - Candida antifungal selection
   - Treat for 14 days for uncomplicated CLI, or ≥4-6 weeks for complicated infections.
**Definitive Results PHASE, Tunneled CVCs**

**Inclusion Criteria**
- Inpatients and ED patients with suspected CLI
- Includes PICCs, Broviacs, hemodialysis lines, etc.

**Exclusion Criteria**
- Amb. Clinic patients
- Heme/Onc except Sickle Cell, BMT patients and those on ECMO

- **If >3 days of positive cultures on appropriate antibiotics, remove/exchange catheter and evaluate for metastatic infection**

**Coagulase-Negative Staphylococcus (other than S. lugdunensis)**
- If CLI, consider catheter salvage if patient stable
- Add vancomycin lock therapy if not currently on
- Treat for 10-14 days if CL salvaged, or 5-7 days if removed
- Manage CLI due to S. lugdunensis similarly to recommendations for S. aureus CLI

**S. aureus, P. aeruginosa, Yeast, AFB, other difficult to eradicate pathogens**
- **Remove / exchange the catheter**
- Employ the narrowest possible antibiotic therapy
- **Staphylococcus aureus recommendations**
- **Pseudomonas aeruginosa recommendations**
- **Candida recommendations**
- **AFB recommendations**
- For other scenarios or if unable to discontinue CL, consult Infectious Diseases

**All Other Organisms**
- **Attempt catheter salvage in stable patients**
- Employ the narrowest possible antibiotic therapy
- **Employ lock therapy**
- **Enterococcus**
- **Gram Negative Bacilli**
- For other scenarios, consult Infectious Diseases

**How to define treatment duration**

**Explanation of Evidence Ratings**

**Citation & Approval**

**Summary of Version Changes**

**Tunneled CVCs**

**Diagnosis and Management of Central Line Associated Bloodstream Infections (CLI) v7.0**

For questions concerning this pathway, contact: CLI_Pathways@seattlechildrens.org

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Last Updated: August 2021

Next Expected Review: June 2018
Background

Millions of indwelling vascular devices are placed annually for administering medications, fluids, and nutrition. These catheters can become infected, which can cause significant morbidity and mortality. Furthermore, the variety both of vascular devices available and organisms that can cause catheter-related infections makes providing simple and easy-to-follow recommendations for the management of such infections difficult.

This pathway’s intent is to standardize – to the extent possible – the diagnosis and management of such central venous catheter infections at Seattle Children’s.
Introduction – Central Line Infections

This clinical standard work pathway is meant to entail the diagnosis and management of patients with Central Line Infections (CLI). The inclusion and exclusion criteria as are follows:

• Inclusion criteria:
  o Presence of a central venous catheter
    ▪ This includes PICC lines, Broviacs, Hickmans, hemodialysis lines, etc.
  o Suspected CLI among inpatients and Emergency Department patients

• Exclusion criteria:
  o Patients without central venous catheters
  o Ambulatory clinic patients
  o Patients on ECMO
  o Hematology / Oncology patients
Definition: Suspected CLI

CLI should be suspected in those with a central catheter in place for >24 hours and a new-onset fever or other systemic or local signs of infection such as hypotension or redness, tenderness, or discharge from their central catheter site.

In NICU patients, consider using this pathway for those >7 days of post-natal age and who have central catheters in place for >24 hours.

To Initial Culture Phase

To Preliminary cultures,
non-tunneled CVC

To Preliminary cultures,
tunneled CVC

To Definitive treatment,
non-tunneled CVC

To Definitive treatment,
tunneled CVC
Definition: Non-Tunneled and Tunneled Catheters

- **Non-tunneled catheters** include peripherally inserted central catheters (PICCs), femoral lines, IJ lines, and other central lines not tunneled under the skin.
- **Tunneled catheters** include those tunneled under the skin and placed surgically, such as Hickman catheters, Broviacs, and ports.
Definition: Risk of Complications

- Low risk:
  - Patients who are immunocompetent, with a single fever or sustained low-grade fever, and without hemodynamic instability, toxic appearance, mental status changes, or indwelling hardware other than their central line (e.g., prosthetic heart valves).

- Higher risk:
  - Patients who are immunocompromised* (receiving immunosuppressive medications, transplant recipients, primary immunodeficiency, HIV), with indwelling hardware other than the central line (e.g., prosthetic heart valves), a right-to-left cardiac shunt of any kind, or otherwise of tenuous clinical status / critically ill.

* If in doubt, assume a patient to be immunocompromised and / or call Infectious Diseases.
Definition: Risk Factors for Fungal Disease

- No clear guidelines for when to begin empiric antifungal therapy exist, but typically empiric antifungal therapy should be begun only in the presence of known risk factors.
- Known risk factors for fungemia include extreme prematurity, prolonged broad-spectrum antibiotics, bone marrow or solid organ transplantation or other abdominal surgery entering a viscus, central venous catheter, corticosteroids, dialysis, necrotizing pancreatitis or ongoing use of parenteral nutrition (Mermel, 2003).
Blood Culture Recommendations: Initial Fever

- Do NOT routinely obtain catheter cultures in the absence of suspected CLI. (Mermel, ✖✖✖✖)
- Obtain blood cultures prior to initiation of antibiotic therapy. (Mermel, ✖✖✖✖)
- Prepare skin and the catheter hub for peripheral culture using either alcohol or tincture of iodine or alcoholic chlorhexidine (10.5%), rather than povidone-iodine, and allow adequate skin contact and drying time. (Mermel, ✖✖✖✖)

Blood Culture Recommendations: Ongoing Fever

- Do NOT obtain further blood cultures for patients who are not immunocompromised, do not show signs of sepsis, and are not changing their antibiotic therapy, if initial cultures remain negative thus far. (Bright Star Collaborative)
- If obtaining further blood cultures, only culture one peripheral site (preferred option) or one single lumen of the central line. (Bright Star Collaborative)

Culture All Lumens and Peripherally

- Catheter-drawn cultures alone are significantly less specific than when peripheral cultures are also performed (Falagas, ✖✖✖O) and result in higher rates of false-positive CLI diagnoses.
- Similarly, culturing all lumens and obtaining peripheral cultures add sensitivity to making the diagnosis of CLI. Studies estimate that between 15.8% and 37.3% of all CLI would be missed if not all lumens are sampled (Guembe, ✖✖O) and that 12.3% of CLI would be missed had peripheral cultures not been drawn (Scheinemann et al., ✖O.DO).
- Arterial samples are an acceptable alternative to peripheral samples. Some central catheters (e.g., in neonates) cannot be sampled directly.
- Culture the catheter skin exit site if signs of local infection (i.e., redness) and discharge are present.
Diagnosis of CLI

Definitive diagnosis of CLI includes any of the following:

- The same organism growing peripherally and from the catheter tip. (Mermel, ≤≥≥≤)
- Growth of microbes from blood drawn through a catheter hub at least 2 hours before microbial growth is detected in blood samples obtained peripherally, with the same volume of blood obtained in each bottle. (Mermel, ≤≥≥≤)
- A quantitative blood culture obtained through the catheter with a colony count of microbes at least 3-fold greater than that from peripheral culture. However, SCH does not currently employ the quantitative blood culture technique.

Diagnosis of CLI (cont’d)

Diagnosis of possible CLI includes the following:

- 2 quantitative blood cultures obtained through 2 catheter lumens in which the colony count for the sample drawn through one lumen is at least 3-fold greater than that from the second lumen. Again, SCH does not currently employ the quantitative blood culture technique. The SCH laboratory does report time to positivity for blood cultures. (Mermel, ≤≥≥≥O)
Empiric Therapy for CLI

Use the first day on which negative blood culture results are obtained as day 1 of therapy. *(Mermel, OOOO)*

Use empirical antibiotics as follows:

- Instill antibiotics through the infected catheter when possible.
- Use *cefepime* for empirical CLI therapy in stable immunocompetent and immunocompromised hosts *(Mermel, OOOO)*.
- Alternatively, for selected immunocompetent patients who are stable and at low risk for complications, antibiotics may be withheld pending culture results *(Local consensus, OOOO)*.
- Use *cefepime* and vancomycin with or without gentamicin for empirical CLI therapy in unstable immunocompetent and immunocompromised hosts *(Mermel, OOOO)*.
- For empirical CLI therapy in patients with hemodialysis catheters, use vancomycin and gentamicin *(Mermel, OOOO)*.

Empiric Therapy for CLI (Cont’d)

- Use *fluconazole* in addition to antibiotics above for patients with any fungal infection risk factors *(see risk factors definition slide; Mermel, OOOO)*. Likewise use fluconazole if initial culture results suggest candidal infection (e.g., yeast identified on culture). Use micafungin instead for empiric treatment of patients who were on prior or ongoing fluconazole prophylaxis at the time of developing their invasive fungal infection or are critically ill. Amphotericin B rather than fluconazole is typically used for empiric antifungal treatment of neonates.
- *Linezolid* should not typically be used for empirical therapy *(i.e., in patients suspected but not proven to have CRBSI; Mermel, OOOO)*.
- Some services (e.g., SCCA, ICU) have specific protocols for empiric antimicrobial therapy that may supersede these recommendations.
- Administer antibiotics through the colonized catheter *(Mermel, OOOO)*.
- Do NOT routinely use urokinase and other thrombolytic agents as adjunctive therapy for patients with CLI *(Mermel, OOOO)*.

When an organism has been identified and susceptibilities are available, tailor the antibiotics to the narrowest effective agent *(see subsequent slides)*.
<table>
<thead>
<tr>
<th>Immunocompetent patients</th>
<th>Antibiotic selection</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable, non-toxic, low risk for complications, ongoing monitoring assured</td>
<td>Can defer antibiotics</td>
<td></td>
</tr>
<tr>
<td>Stable, non-toxic, low risk for complications (most patients)</td>
<td>Cefepime</td>
<td>Use meropenem if documented IgE-mediated allergy to cefepime; discuss Infectious Diseases</td>
</tr>
<tr>
<td>Unstable, toxic, severely ill</td>
<td>Cefepime AND vancomycin AND gentamicin AND micafungin</td>
<td>Use meropenem if documented IgE-mediated allergy to cefepime; discuss Infectious Diseases</td>
</tr>
<tr>
<td>Concern for fungal infection**</td>
<td>Yes Fluconazole</td>
<td>In patients with ongoing therapy or prophylaxis with fluconazole and/or blood culture for yeast; consider micafungin; consult Infectious Diseases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunocompromised* patients</th>
<th>Antibiotic selection</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable, non-toxic, low risk for complications</td>
<td>Cefepime [AND micafungin if risks for fungal disease]</td>
<td>Use meropenem if documented IgE-mediated allergy to cefepime; discuss Infectious Diseases</td>
</tr>
<tr>
<td>Unstable, toxic, severely ill</td>
<td>Meropenem AND vancomycin AND gentamicin AND micafungin</td>
<td>Discuss with Infectious Diseases</td>
</tr>
<tr>
<td>Concern for fungal infection**</td>
<td>Yes Fluconazole or discuss with Infection Diseases</td>
<td>In patients with ongoing therapy or prior prophylaxis with fluconazole and/or blood culture for yeast; consider micafungin; consult Infectious Diseases</td>
</tr>
</tbody>
</table>

*See HemOnc suspected infection pathway for management of these patients

**Known risk factors for fungemia include extreme prematurity, prolonged broad-spectrum antibiotics, bone marrow or solid organ transplantation or other abdominal surgery entering a viscus, central venous catheter, corticosteroids, necrotizing pancreatitis, dialysis or ongoing use of parenteral nutrition (Mermel, 2016)
Lock Therapy with Catheter Salvage

- Use lock therapy for all patients with CLI of a long-term catheter without signs of exit site or tunnel infection and for whom catheter salvage is the goal (Mermel, ⚫⚫⚫⚫).
- Do NOT routinely use antibiotic lock therapy ALONE for CLI; use antibiotic lock therapy in conjunction with systemic antimicrobial therapy, with both regimens administered for 7-14 days (Mermel, ⚫⚫⚫⚫).
- Dwell times for antibiotic locks should be 8-12 hours per day or >2 hours per day for ethanol locks, and the lock solution should be administered 1-2 times daily to each lumen (Local consensus, ⚫⚫⚫⚫). Do NOT routinely allow antibiotic lock solution dwell times to exceed 48 hours before re-instillation of lock solution. Re-instill lock solution every 24 hours for ambulatory patients with femoral catheters (Mermel, ⚫⚫⚫⚫). Re-instill lock solution with each dialysis session for patients undergoing hemodialysis (Mermel, ⚫⚫⚫⚫).

Lock Therapy for CLI Treatment with Catheter Salvage (cont’d)

- Do NOT routinely use antibiotic lock therapy for CLI due to S. aureus or Candida species and instead remove the catheter, unless there are significant extenuating circumstances (Mermel, ⚫⚫⚫⚫).
- When vancomycin lock therapy is used, the vancomycin concentration should be at least 1000 times higher than the minimum inhibitory concentration of the microorganism involved (Mermel, ⚫⚫⚫⚫).
- Do NOT routinely use ethanol lock therapy (Mermel, ⚫⚫⚫⚫); ethanol lock therapy is limited to use in patients with CLI meeting criteria specified in the SCH ethanol lock policy (Local consensus, ⚫⚫⚫⚫).
**Additional Gram-Negative Agent Selection**

*Patients who are critically ill with suspected CLI and who have recent colonization or infection with a multi-drug resistant (MDR) gram-negative pathogen should receive gentamicin (or another agent with broad gram-negative activity from an antimicrobial class different than that of the primary antibiotic, such as ciprofloxacin) in addition to piperacillin/tazobactam and vancomycin as initial therapy; de-escalation of the initial regimen to a single appropriate antibiotic is recommended once culture and susceptibility results are available (Mermel, ). Questions regarding risk or management of possible MDR infection should be directed to Infectious Diseases.*
Other Evaluation After Fungemia Identified

Additional evaluation for patients with fungemia should include an ophthalmologic exam within the first week of therapy, and if persistent/prolonged fungemia should also include abdominal ultrasound or CT scan of liver, kidneys, and spleen, and echocardiogram, to rule out other disseminated sites of infection (Mermel, 2001; Pappas, 2007).

Based on IDSA guidelines for management of Candidiasis, Pappas et al. 2015
Catheter Removal

- Add empiric vancomycin if a line site infection is suspected (e.g., red streaking or purulence at line site)
- Remove and culture non-tunneled catheters if the patient is hemodynamically unstable or has erythema overlying the catheter insertion site or purulence at the catheter insertion site (Mermel, 2000).
- Remove non-tunneled catheters from patients with CLI due to any pathogens other than coagulase-negative staphylococci (e.g., gram-negative bacilli, S. aureus, enterococci, fungi, and mycobacteria (Mermel, 2000)).
- Remove tunneled catheters from patients with CLI associated with any one of the following complications (Mermel, 2000; Freifeld, 2000): severe sepsis; suppurative thrombophlebitis; endocarditis; tunnel infection; port abscess; exit site infections that are severe or fail to resolve with antibiotic therapy; CLI due to S. aureus, P. aeruginosa, fungi, or mycobacteria; or any bloodstream infection that continues despite 72 h of antimicrobial therapy to which the infecting microbes are susceptible.

Catheter Removal (Cont'd)

- Remove catheters after blood culture contamination is ruled out on the basis of multiple positive culture results, with at least 1 blood culture sample drawn from a peripheral vein, for non-tunneled and tunneled CLI due to less virulent microbes that are difficult to eradicate (e.g., Bacillus species, Micrococcus species, or Propionibacteria), (Mermel, 2000).
- In any situation when salvage of the catheter is attempted, remove the catheter if blood cultures obtained 72 hours after the initiation of appropriate therapy remain positive (Mermel, 2000; Freifeld, 2000).
Recommendations for Persistently Positive Cultures

- Once bacteremia or fungemia has been identified, obtain blood cultures daily until cultures remain negative for at least 48 hours to document sterilization (Local consensus, Shah).

- Whenever salvage of the catheter is attempted in a patient with CLI due to any pathogen, remove the catheter if blood cultures obtained 72 hours after the initiation of appropriate therapy remain positive (Mermel).

- Evaluate patients with persistently positive blood cultures (bacterial or fungal) and/or ongoing fevers for >72 hours after line removal aggressively for evidence of complicated or metastatic disease, such as endocarditis, suppurative thrombophlebitis, occult abscess or osteomyelitis. Consider Infectious Diseases consultation, echocardiogram, extremity Doppler ultrasound, bone scan, ophthalmologic exam and CT scan of chest/abdomen/pelvis.

Recommendations for Persistently Positive Cultures (Cont’d)

- Suppurative thrombophlebitis should be considered in the setting of a new, large clot and if blood cultures remain positive after line removal or in the setting of appropriate therapy for >72 hours.

- Administer antibiotics for 4 to 6 weeks to patients with persistent fungemia or bacteremia occurring >72 hours after catheter removal (Mermel for S. aureus infection; for infection due to other pathogens), to patients with infective endocarditis or suppurative thrombophlebitis, and to pediatric patients with osteomyelitis (Mermel).
S. aureus Recommendations

- Remove short-term catheters immediately for patients with S. aureus CLI (Mermel, ☐☐☐☐).
- For S. aureus CLI involving long-term catheters, remove the catheter unless there are major contraindications (e.g., there is no alternative venous access, the patient has significant bleeding diathesis, or quality of life issues take priority over the need for reinsertion of a new catheter at another site; Mermel, ☐☐☐☐).
- For methicillin-susceptible S. aureus, treat with nafcillin (cefazolin is an acceptable alternative).
- For methicillin-resistant S. aureus (MRSA) with a vancomycin MIC $<2 \mu g/mL$, use vancomycin. For methicillin-resistant S. aureus (MRSA) with a vancomycin MIC $>2 \mu g/mL$, an ID consultation is recommended.
- Treat patients with uncomplicated CLI due to S. aureus for a minimum of 14 days (Mermel, ☐☐☐☐).

S. aureus Recommendations (cont’d)

- Treat patients for 4-6 weeks if S. aureus CLI is complicated by persistent bacteremia; endocarditis; septic thrombophlebitis; OR metastatic infection (Mermel, ☐☐☐☐).
- Perform echocardiography in all patients with $>1$ positive blood culture with S. aureus and any one of the following criteria: underlying structural heart disease; murmur; peripheral stigmata of endocarditis; or persistently positive cultures.
- If an echocardiogram is performed, perform it at least 5-7 days following onset of bacteremia to minimize the likelihood of a false-negative result (Mermel, ☐☐☐☐).
- Consider Infectious Diseases consultation for all patients with S. aureus bacteremia and a high illness severity of multiple comorbidities (Honda, ☐☐☐☐).

To Initial Culture Phase
- To Preliminary cultures, non-tunneled CVC
- To Preliminary cultures, tunneled CVC
- To Definitive treatment, non-tunneled CVC
- To Definitive treatment, tunneled CVC
**Enterococcus Species Recommendations**

- Remove short-term intravascular catheters infected with enterococci (Mermel, OOO).

- Remove long-term catheters infected with enterococci in cases of insertion site or pocket infection, suppurative thrombophlebitis, sepsis, endocarditis, persistent bacteremia, or metastatic infection (Mermel, OOO).

- Use lock therapy in addition to systemic therapy if the catheter is retained (Mermel, OOO).

- For treatment of uncomplicated CLI due to Enterococcus species in stable patients:
  - Treat with ampicillin if the isolate is susceptible (Mermel, OOO).
    - Gentamicin may be added if the isolate is susceptible to gentamicin or shows gentamicin synergy and if the catheter is retained (Mermel, OOO).

- Use vancomycin if the isolate is resistant to ampicillin but susceptible to vancomycin (Mermel, OOO).
  - Gentamicin may be added if the isolate is susceptible to gentamicin or shows gentamicin synergy and if catheter is retained (Mermel, OOO).

- Use linezolid if the isolate is resistant to ampicillin and vancomycin (VRE; Infectious Disease approval required; Mermel, OOO).
- Treat for 7-14 days from first negative culture in cases of uncomplicated enterococcal CLI (Mermel, OOO).

- For severe or complicated CLI due to Enterococcus species:
  - Add gentamicin to ampicillin or vancomycin if the isolate is susceptible to gentamicin or shows gentamicin synergy (Mermel, OOO).
  - Consult Infectious Diseases if there is high-level gentamicin resistance or for VRE.

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**Enterococcus Species Recommendations (Cont'd)**

- Use vancomycin if the isolate is resistant to ampicillin but susceptible to vancomycin (Mermel, OOO).
  - Gentamicin may be added if the isolate is susceptible to gentamicin or shows gentamicin synergy and if the catheter is retained (Mermel, OOO).

- Use linezolid if the isolate is resistant to ampicillin and vancomycin (VRE; Infectious Disease approval required; Mermel, OOO).
- Treat for 7-14 days from first negative culture in cases of uncomplicated enterococcal CLI (Mermel, OOO).

- For severe or complicated CLI due to Enterococcus species:
  - Add gentamicin to ampicillin or vancomycin if the isolate is susceptible to gentamicin or shows gentamicin synergy (Mermel, OOO).
  - Consult Infectious Diseases if there is high-level gentamicin resistance or for VRE.

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**To Preliminary cultures, non-tunneled CVC**

**To Preliminary cultures, tunneled CVC**

**To Definitive treatment, non-tunneled CVC**

**To Definitive treatment, tunneled CVC**
Coagulase-Negative Staphylococci Recommendations

- If only one culture was positive and the repeat culture drawn prior to the initiation of empirical antibiotics is negative at 48 hours, discontinue antibiotics (Mermel, OOO).
- If the isolate is methicillin-susceptible, use nafcillin.
  o Cefazolin is an acceptable alternative.
  o Use vancomycin for patients with anaphylactic allergies to beta-lactam antibiotics.
- If the isolate is methicillin-resistant, use vancomycin.
- For uncomplicated CLI, treat with antibiotics for 5-7 days if the catheter is removed and for 10-14 days, in combination with lock therapy, if the catheter is retained (Mermel, OOO). Treatment for neonates can be as short as 3 days for uncomplicated CLI when the catheter has been removed (Hemels, OOO).
- Manage CLI due to S. lugdunensis similarly to recommendations above for S. aureus CLI (Mermel, OOO).
Gram-Negative Bacilli Recommendations

- For patients who received combination empiric therapy (e.g., cefepime and gentamicin), de-escalate the initial regimen to a single appropriate antibiotic once culture and susceptibility results are available (Mermel, 2009).

- Treat for 7-14 days from first negative blood culture for uncomplicated gram-negative CLI, or >4-6 weeks for complicated infections.
Candida Species Recommendations

- Remove catheters in cases of CLI due to Candida species (Mermel, 2003).

- Depending on the candida species, use fluconazole or micafungin for treatment. The final culture result from microbiology laboratory will help guide antifungal selection, but please page Infectious Disease service for recommendations.

- Treat for 14 days from first negative blood culture for uncomplicated Candida CLI, or >4-6 weeks for complicated infections.
Other Gram-Positive Organism Recommendations

- Diagnosis of CLI due to Corynebacterium, Bacillus and Micrococcus species requires at least 2 positive results of blood cultures performed on samples obtained from different sites (Mermel, 1). These organisms can be difficult to eradicate with antimicrobial therapy alone.
- For the management of these infections, remove the catheter for patients with a short-term CVC, and for patients with an infected long-term catheter or implanted port, unless there are no alternative intravascular access sites (Mermel, 1).
Replacing the Catheter (if needed)

- The preferred method when a catheter must be replaced is to place the new catheter in a different location. If other vascular sites are unavailable and/or the patient is at increased risk for bleeding diathesis in the setting of CLI not complicated by an exit site or tunnel infection, then attempt exchange of the infected catheter over a guidewire (Mermel, Mermel). In such situations, consider an antimicrobial-impregnated catheter with an anti-infective intraluminal surface for catheter exchange (Mermel, Mermel).

- Ideally, clearance of the CLI should be documented before replacing the catheter. Documenting clearance typically requires a minimum of 48 hours of negative cultures, but some slow growing organisms may require longer. Questions regarding the risks of replacing the catheter during treatment of a CLI may best be addressed by an Infectious Diseases consultation.
### Value Tool: IV Fluconazole

<table>
<thead>
<tr>
<th>DIMENSION</th>
<th>CARE OPTION A</th>
<th>CARE OPTION B</th>
<th>PREFERRED OPTION</th>
<th>ASSUMPTIONS MADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DESCRIPTION OF CARE TREATMENT OPTION</td>
<td>IV Micafungin for empiric therapy when central line infection due to yeast suspected</td>
<td>IV Fluconazole for empiric therapy when central line infection due to yeast suspected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPERATIONAL FACTORS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent adherence to care (goal 80%)</td>
<td>80%</td>
<td>80%</td>
<td>NEUTRAL</td>
<td>With both recommendations, some providers may use alternate agent</td>
</tr>
<tr>
<td>Care delivery team effects</td>
<td>N/A, both drugs are dosed once daily</td>
<td>N/A</td>
<td>NEUTRAL</td>
<td></td>
</tr>
<tr>
<td>BENEFITS / HARMS (QUALITY/OUTCOME)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree of recovery at discharge</td>
<td>Local data indicates that fluconazole</td>
<td>Local data indicates that fluconazole</td>
<td>NEUTRAL</td>
<td></td>
</tr>
<tr>
<td>Effects on natural history of the disease over equivalent time</td>
<td>May cover fluconazole-resistant candida species</td>
<td>May cause elevation of liver enzymes, however very few</td>
<td>OPTION A</td>
<td></td>
</tr>
<tr>
<td>Potential to cause harm</td>
<td>Few adverse effects</td>
<td>May cause elevation of liver enzymes, however very</td>
<td>NEUTRAL</td>
<td></td>
</tr>
<tr>
<td>Palatability to patient/family</td>
<td>Generally not unpalatable</td>
<td>Generally not unpalatable</td>
<td>NEUTRAL</td>
<td></td>
</tr>
<tr>
<td>Population-related benefits</td>
<td>None</td>
<td>May help to decrease spread of resistant candida</td>
<td>OPTION B</td>
<td></td>
</tr>
<tr>
<td>Threshold for population-related benefits reached</td>
<td>N/a</td>
<td>unlikely due to small numbers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COST (Arisimg from Options A or B) - express as cost per day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“ROOM RATE” ($ or time to recovery)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Dx/Rx” costs ($)</td>
<td>$193/day x 3 days empiric therapy = $579/patient</td>
<td>$106 x 3 days = $318</td>
<td>OPTION B</td>
<td>Unclear - up to 40-60 patients/year</td>
</tr>
<tr>
<td>COST (Complications/adverse effects arising from Options A or B) - express as cost per day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“ROOM RATE” ($ or time to recovery)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Dx/Rx” costs ($)</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**STEP 3: APPLY VALUE ANALYSIS GRID**

<table>
<thead>
<tr>
<th>COST</th>
<th>BENEFIT (QUALITY &amp; OUTCOMES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A &gt; B</td>
<td>Make value judgement</td>
</tr>
<tr>
<td>A and B costs are the same</td>
<td>A</td>
</tr>
<tr>
<td>B costs more than A</td>
<td>A</td>
</tr>
</tbody>
</table>

**STEP 4: CREATE VALUE STATEMENT**

**FINAL CSW VALUE STATEMENT**

IV Fluconazole is preferred as empiric therapy for possible fungal central line infection because rates of fluconazole resistant candida at our institution are low, adverse effects are few and it is less costly than micafungin therapy. This approach will also minimize exposure to echinocandins and thereby decrease development of resistance. Key assumptions include the idea that candida albicans and parapsilosis will remain the most frequent species of candida identified at our hospital. This recommendation is based on microbiology data from Seattle Childrens Hospital and University of Washington and the cost dashboard. A cost-minimization approach was applied.
Central Line Infection Approval & Citation

Approved by the CSW Central Line Infection for July 1, 2015

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Surgeon-in-Chief: Bob Sawin, MD


Please cite as:
This pathway was developed through local consensus based on published evidence and expert opinion as part of Clinical Standard Work at Seattle Children’s. Pathway teams include representatives from Medical, Subspecialty, and/or Surgical Services, Nursing, Pharmacy, Clinical Effectiveness, and other services as appropriate.

When possible, we used the GRADE method of rating evidence quality. Evidence is first assessed as to whether it is from randomized trial or cohort studies. The rating is then adjusted in the following manner (from: Guyatt G et al. J Clin Epidemiol. 2011;4:383-94.):

Quality ratings are *downgraded* if studies:
- Have serious limitations
- Have inconsistent results
- If evidence does not directly address clinical questions
- If estimates are imprecise OR
- If it is felt that there is substantial publication bias

Quality ratings are *upgraded* if it is felt that:
- The effect size is large
- If studies are designed in a way that confounding would likely underreport the magnitude of the effect OR
- If a dose-response gradient is evident

Guideline – Recommendation is from a published guideline that used methodology deemed acceptable by the team.

Expert Opinion – Our expert opinion is based on available evidence that does not meet GRADE criteria (for example, case-control studies).

**Quality of Evidence:**
- 🌟🌟🌟🌟 High quality
- 🌟🌟🌟 Moderate quality
- 🌟🌟 Low quality
- 🌟🌟🌟🌟 Very low quality

Guideline
Expert Opinion
Summary of Version Changes

- **Version 1.0 (1/23/2013):** Go live.
- **Version 1.1 (12/17/2013):** Updated “stop sign” inclusion criteria to clarify that hemodialysis catheters are included.
- **Version 2.0 (7/1/2015):** Updated recommendations for empiric and targeted antifungal therapy to recommend fluconazole as empiric therapy for most patients.
- **Version 3.0 (2/23/2016):** CSW value analysis completed including review of the fluconazole recommendation; updated to reflect 2016 IDSA guidelines for treatment of Candidiasis.
- **Version 4.0 (2/1/2018):** Updated the recommendations for treatment of enterococcus. Added more guidance around the issue of suppurative thrombophlebitis.
- **Version 5.0 (3/30/2018):** Updated the recommendations for empiric therapy from pip/tazo to cefepime.
- **Version 6.0 (9/29/2020):** Updated exclusion criteria to include Sickle Cell patients. Corrected email address.
- **Version 7.0 (8/5/2021):** Updated the Initial Blood Culture phase of the algorithm to include blood culture stewardship guidance to reduce unnecessary blood cultures.
Medical Disclaimer

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required.

The authors have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication.

However, in view of the possibility of human error or changes in medical sciences, neither the authors nor Seattle Children's Healthcare System nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such information.

Readers should confirm the information contained herein with other sources and are encouraged to consult with their health care provider before making any health care decision.
Search Methods, Central Line Infection, Clinical Standard Work
Studies were identified by searching electronic databases using search strategies developed and executed by a medical librarian, Susan Klawansky. Searches were performed in July 2012, from 2008 (the year prior to a major IDSA guideline on the topic) to date. The following databases were searched – on the Ovid platform: Medline, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials; elsewhere – Embase, Clinical Evidence, National Guideline Clearinghouse and TRIP. Retrieval was limited to humans and English language. In Medline and Embase, appropriate Medical Subject Headings (MeSH) and Emtree headings were used respectively, along with text words, and the search strategy was adapted for other databases using their controlled vocabularies, where available, along with text words. Concepts searched were central venous catheters, including dozens of alternative phrases; catheter-related infections, including specific bacterial infections; and terms for diagnosis and management, such as anti-infective agents, including specific agents, microbial sensitivity tests, ethanol, device removal, diagnostic techniques and procedures, and subheadings for diagnosis, therapy and drug therapy. All retrieval was further limited to certain evidence categories, such as relevant publication types, Clinical Queries, index terms for study types and other similar limits.

Susan Klawansky, MLS, AHIP
January 3, 2013

Identification

211 records identified through database searching
2 additional records identified through other sources

Screening

207 records after duplicates removed

Eligibility

159 records assessed for eligibility

Included

15 studies included in pathway

Flow diagram adapted from Moher D et al. BMJ 2009;339:bmj.b2535


Bibliography


Additional References