Catheter-Related Thrombosis and Infection: Reducing Controllable Risk Factors

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Disclosures
1. Dr. Nifong has received honoraria and consulting fees from Teleflex
2. Dr. Nifong has received honoraria from AngioDynamics

Learning Objectives
1. Understand the basic pathophysiology and clinical significance of upper extremity thrombosis.
2. Recall the controllable risk factors associated with catheter-related thrombosis.
3. Explain how thrombosis and infection interact in central venous catheters.
4. Know how new technologies will play a role in reducing catheter-related complications.
Venous Thromboembolism

• Incidence of UE-DVT (1-2% that of LE)
  – Primary UE-DVT due to “stress” or ideopathic is rare: 2 per 100,000
  – Secondary UE-DVT was previously considered to be rare, but is now not uncommon in hospitalized patients...

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Hemostasis

Coagulation system
- Activated clotting factors & cofactors
- Thrombin generation
- Thrombin inhibition

Anticoagulant system
- Coagulation inhibitors & cofactors

Fibrinolytic system

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Pathogenesis of Thrombosis

- Rudolph Virchow
  1821 - 1902

- Virchow’s Triad:
  - Stasis
  - Vascular Injury
  - Hypercoagulability

- VTE Risk Factors:
  - PC, PS, AT Deficiency
  - Factor V Leiden
  - Prothrombin G20210A

- Rudolph Virchow
  1821 - 1902
Clinicians are recommended to NOT use either prophylactic doses of LMWH (Grade 1B) or mini-dose warfarin (Grade 1B) to try to prevent catheter-related thrombosis for cancer patients receiving chemotherapy or hormonal therapy or with indwelling central venous catheters.


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Catheter and Thrombosis: Controllable Risk Factor

- Insertion site
  - Femoral vein vs. Subclavian vein vs. Internal Jugular vein vs. PICC
- Catheter type, size, tip location
  - Endothelial damage
    - Traumatic insertion
    - Tip location
  - Catheter size and rigidity
  - Venous stasis
  - Catheter size relative to vein size
  - Catheter material

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CVC-related Thrombosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Detection</th>
<th>Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimochowski</td>
<td>Prospective (acute HD)</td>
<td>Asymptomatic</td>
<td>Venogram</td>
</tr>
<tr>
<td>Schillinger</td>
<td>Prospective (acute HD)</td>
<td>Asymptomatic</td>
<td>Venogram</td>
</tr>
<tr>
<td>Wilkin</td>
<td>Prospective (mitigated)</td>
<td>Asymptomatic</td>
<td>Doppler US</td>
</tr>
<tr>
<td>Theriault</td>
<td>Retrospective (summarized)</td>
<td>Symptomatic</td>
<td>Clinical US or venogram</td>
</tr>
<tr>
<td>Merrer</td>
<td>Prospective (tunneled)</td>
<td>Asymptomatic</td>
<td>Doppler US</td>
</tr>
<tr>
<td>Timsit</td>
<td>Prospective (tunneled)</td>
<td>Asymptomatic</td>
<td>Doppler US</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Li</th>
<th>SC</th>
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<tbody>
<tr>
<td>0%</td>
<td>53%</td>
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<tr>
<td>10%</td>
<td>42%</td>
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<tr>
<td>25.5%</td>
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<tr>
<td>3%</td>
<td>13%</td>
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<tr>
<td>21.5%</td>
<td>1.9%</td>
</tr>
<tr>
<td>41.7%</td>
<td>18.5%</td>
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</table>
PICC-related Thrombosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Detection</th>
<th>Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ng</td>
<td>Prospective</td>
<td>Symptomatic</td>
<td>1.6%</td>
</tr>
<tr>
<td>Grove</td>
<td>Retrospective</td>
<td>Presumed</td>
<td>3.0%</td>
</tr>
<tr>
<td>Chemaly</td>
<td>Retrospective</td>
<td>Presumed</td>
<td>2.5%</td>
</tr>
<tr>
<td>King</td>
<td>Retrospective</td>
<td>Symptomatic</td>
<td>3.9%</td>
</tr>
<tr>
<td>Lobo</td>
<td>Retrospective</td>
<td>Symptomatic</td>
<td>7.8%</td>
</tr>
<tr>
<td>Cowl</td>
<td>Prospective</td>
<td>Asymptomatic</td>
<td>7.0%</td>
</tr>
<tr>
<td>Abdullah</td>
<td>Prospective</td>
<td>Asymptomatic</td>
<td>23.3%</td>
</tr>
<tr>
<td>Allen</td>
<td>Retrospective</td>
<td>Asymptomatic</td>
<td>38.5%</td>
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PICC-related symptomatic SVT versus DVT

  - Retrospective study: All UE venous duplex scans during a 12-month period were reviewed, selecting patients with isolated SVT (213) or DVT (154) and PICCs placed ≤30 days before (1,050)
  - Results:
    - Rates for PICC-SVT (44) were 1.9% for basilic, 7.2% for cephalic, and 0% for brachial vein PICCs
    - Rates for PICC-DVT (54) were 3.1% for basilic, 0% for cephalic, and 2.2% for brachial vein PICCs

Laterality of PICC line placement

  - Retrospective study of 798 PICC placements (568 right-sided and 230 left-sided placement)
  - Results: VTE rate right-sided: 1.23% vs left-sided: 1.30%

  - Retrospective study of 422 consecutive patients with PICC
  - Results: Left-sided PICC line sites posed a greater risk (P=.036)
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Is Upper Extremity Thrombosis Clinically Important?

© Copyright, Gray’s Anatomy of the Human Body

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<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Monreal et al. Thrombosis and Haemostasis 1994</td>
<td>86 patients with PICC or SC catheter-related DVT</td>
<td>VQ scan showed PE in 15.3%</td>
</tr>
<tr>
<td>Lobo B, et al. Journal of Hospital Medicine 2009</td>
<td>777 patients with PICC (128 patients with VTE)</td>
<td>Symptomatic PE in 1% of patients</td>
</tr>
<tr>
<td>Fletcher, et al. Neurocrit Care 2011</td>
<td>439 PICCs from placed in neuro ICU (89 patients with DVT)</td>
<td>Symptomatic PE in 1.3% of patients (13% of patients with DVT)</td>
</tr>
<tr>
<td>Ong B, et al. Australasian Radiology 2006</td>
<td>78 patients with PICC-related DVT</td>
<td>Post-thrombotic sequelae w/25% mild pain, 2% moderate pain, 15% arm edema</td>
</tr>
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<tr>
<th>Treatment</th>
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<tbody>
<tr>
<td>• Conservative management along with catheter removal appropriate for basilic, brachial, and cephalic vein thrombosis</td>
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<tr>
<td>• Recurrence or extension may warrant anticoagulation</td>
</tr>
<tr>
<td>• Catheter removal may lead to PE</td>
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<tr>
<td>• Arterial vein and above requires anticoagulation (3-6 months)</td>
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<tr>
<td>• Recommended to NOT remove catheter if it is still functional and needed</td>
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<tr>
<td>• Initiate with UFH, LMWH, or fondaparinux then maintain with warfarin (INR 2-3) or LMWH</td>
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<tr>
<td>• Thrombolysis is generally NOT recommended but may be indicated for healthy patients (low risk of bleeding) with primary UEDVT with severe symptoms when appropriate expertise is available</td>
</tr>
<tr>
<td>• Surgical intervention is generally NOT recommended but may be indicated for patients with primary UEDVT who fail above therapy</td>
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Risk of Anticoagulation for DVT
Major bleeding risk with warfarin for deep vein thrombosis

- 2,422 patients who received warfarin for more than 3 months
- Approximately 1 in 45 (2.2%) will experience a major bleeding episode
- Approximately 13% of these patients will die from the bleeding

Relationship Between Clot & Infection
- 94 CVC were evaluated after removal

Timsit et al. CVC-related thrombosis in ICU patients. CHEST 1998.
- 208 IJ or SC catheters were analyzed

<table>
<thead>
<tr>
<th>Event</th>
<th>Thrombosis</th>
<th>No Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant CVC colonization</td>
<td>32%</td>
<td>19.4%</td>
</tr>
<tr>
<td>CRBSI</td>
<td>19%</td>
<td>7%</td>
</tr>
<tr>
<td>CR-septicemia</td>
<td>11.6%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

Device-related thrombosis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. with CRBSI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>8 (31%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No</td>
<td>13 (18%)</td>
<td></td>
</tr>
</tbody>
</table>

- 160 IJ or SC tunnelled catheters were analyzed
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- Insertion site
  - Femoral vein vs. Subclavian vein vs. Internal Jugular vein vs. PICC
- Catheter type, size, tip location
  - Endothelial damage
  - Traumatic insertion
  - Tip location
  - Catheter size and rigidity
  - Venous stasis
  - Catheter size relative to vein size
- Catheter material

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- Previous catheter and number of insertion attempts likely indicate endothelial damage:
  - Odds ratio of 5.5 when ≥ 2 insertion
  - Odds ratio of 3.8 with previous central catheter


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- Proximal tip may cause endothelial damage

- 145 patients with oropharyngeal CA with implantable CVC
- Tip confirmed with CXR then with monthly Doppler US
- Tip location divided into five segments

<table>
<thead>
<tr>
<th>Tip Location</th>
<th>Ear</th>
<th>Internal Jugular</th>
<th>Central Vein</th>
<th>Femoral Vein</th>
<th>Subclavian Vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>9</td>
<td>15</td>
<td>43</td>
<td>32</td>
<td>42</td>
</tr>
<tr>
<td>%</td>
<td>6%</td>
<td>10%</td>
<td>29%</td>
<td>22%</td>
<td>29%</td>
</tr>
</tbody>
</table>
Tip location

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kearns et al. JPEN 1996</td>
<td>72 patients with PICC; central tip = in SVC</td>
<td>Central tip 16% Non-central 80%</td>
</tr>
<tr>
<td>Grove &amp; Pevec. JVIR 2009</td>
<td>813 PICC lines; asymptomatic DVT</td>
<td>Central tip 3.6% Non-central 9.3%</td>
</tr>
<tr>
<td>Tesselaar et al. European J of Cancer 2004</td>
<td>245 patients with implantable ports, symptomatic DVT</td>
<td>2.7x higher in SVC versus RA</td>
</tr>
<tr>
<td>Lobo et al. Journal of Hospital Medicine 2009</td>
<td>777 PICC lines; asymptomatic DVT/PE</td>
<td>Non-central tip: OR 2.43 (95% CI 1.15-4.75)</td>
</tr>
</tbody>
</table>

What does this mean clinically?

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifong TP, McDevitt CHEST 2011;140(1):48-53</td>
<td>208 Hickman catheters placed</td>
<td>Symptomatic DVT 10 Fr: 7.0% 12.5 Fr: 21%</td>
</tr>
<tr>
<td>Trerotola SO, et al. Radiology 2000</td>
<td>279 SC and IJ tunnelled catheters (Retrospective)</td>
<td>Symptomatic DVT 9.6-10 Fr: 5.0% 12-12.5 Fr: 12.7%</td>
</tr>
<tr>
<td>Grove &amp; Pevec. JVIR 2000</td>
<td>813 PICC lines (Retrospective)</td>
<td>Symptomatic DVT ≤3 Fr: 0% 4 Fr: 1.0% 5 Fr: 6.6% 6 Fr: 9.8%</td>
</tr>
<tr>
<td>Allen et al. JVIR 2000</td>
<td>354 PICC lines (Retrospective)</td>
<td>Asymptomatic DVT Cephalic: 57% Brachial: 10% Basilic: 14%</td>
</tr>
<tr>
<td>Trerotola et al. Radiology 2010</td>
<td>50 TLP (167 planned 6 Fr tapered) in Brachial or Basilic</td>
<td>Symptomatic Total 20% Extensive 58% (27% extensive)</td>
</tr>
<tr>
<td>Evans et al CHEST 2010</td>
<td>2,014 PICCs in 1,879 patients (Prospective)</td>
<td>Symptomatic DVT 4 Fr: 0.8% 5 Fr: 2.9% 6 Fr: 8.8% p=0.027 p=0.0001 p=0.0006</td>
</tr>
</tbody>
</table>

p=0.0066
Evans et al. Risk of symptomatic DVT associated with peripherally inserted central catheters. CHEST. 2010

What does this mean clinically?

Catheters and Thrombosis: Controllable Risk Factor
- Femoral >> PICC > Subclavian vein ≥ Internal Jugular (lowest for HD)
- Catheter type, size, tip location
- Endothelial damage
  - Traumatic insertion (≥ 2 attempts)
  - Tip location (non-central > atrial-caval junction)
  - Catheter size and rigidity (large > small)
- Venous stasis
- Catheter size relative to vein size
- Catheter material

Prevent Central Venous Catheter Infections (CR-BSI)
- 5 key components proposed by IHI-100K
  - Hand hygiene
  - Maximal barrier precautions
  - Chlorhexidine skin antisepsis
  - Optimal catheter site selection
  - Daily review of line necessity
- + 4 interventions recommended by EPIC 2
  - Education of healthcare workers and patients
  - Selection of catheter: lumens, tunnel, coated
  - Catheter and site care
  - General principles for catheter management
  - CVC insertion checklists

Berenholtz Pronovost
Prevent Central Venous Catheter Infections/CRI – 5 key components proposed by IHI:

- Hand hygiene
- Maximal barrier precautions
- Chlorhexidine skin antisepsis
- Optimal catheter site selection
- Daily review of line necessity

Pronovost 2010

BMJ 2010;340:c309 doi:10.1136/bmj.c309

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3-4X higher than U.S.

1. Do you have a champion at your hospital?
2. Do you have external drivers?
3. Do you track and report outcomes to all stakeholders?
4. Are team members empowered to stop a procedure if sterility is breached?

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Pathogenesis of CRBSI:

Contamination Sources

- Hands of Radical Personnel
- Hub Colonization
- Intraluminal: 10%
- Intracath: 0-20%
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Our Goal

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Infection Protection Technologies

<table>
<thead>
<tr>
<th>Evidence-based recommendation</th>
<th>Environmental Contamination</th>
<th>Skin Flora</th>
<th>Subcutaneous tract (post placement)</th>
<th>Hub/Intraluminal</th>
<th>Hematogenous seeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal Sterile Barrier</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>CHG/SNP</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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Multiple Strategies to Interrupt Infections

Maximal Sterile Barrier
- Cap, mask, gowns, gloves, drapes

Effective Prepping
- CHG/IPA

Care and maintenance
- Education, hand hygiene, catheter & site selection, swabbing

Dressings and Locks
- CHG dressings & Add-on devices, dressing changes, lock/flush solutions
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Target zero: Support best practices

- Level 1: Basic
- Level 2: Optimization
- Level 3: New Technology

Target zero: Support best practices

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The Catheter's Role in Interrupting Pathogenesis

Additional Technologies
- Add layer of risk reduction
- Complement other bundle layers
- Last layer of defense:
  - Lapses in technique
  - Compliance fatigue
  - Not implementing evidence-based practices

Antimicrobial Catheters
- Designed to protect areas other bundle layers can’t touch
  - Subcutaneous tract
  - Internal lumen
  - Hematogenous Seeding

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CDC 2011 – Category 1A recommendation

- Recommendation: use chlorhexidine/silver sulfadiazine or minocycline/rifampin impregnated CVC in patients whose catheter is expected to remain in place > 5 days if CLABSI has not been reduced by a comprehensive strategy:
  - Educating persons who insert and care for catheters
  - Use of maximal sterile barriers
  - Use of a 0.5% chlorhexidine prep with alcohol for skin antiseptic during insertion
- Decision to use chlorhexidine/silver sulfadiazine or minocycline/rifampin impregnated CVC should be based on the need to reduce CLABSI rates, balanced against the concern for the emergence of resistant pathogens and the cost if implementing the strategy
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Catheters and Thromboembolism: Controllable Risk Factors

- Insertion site
  - Femoral >> PICC > Subclavian vein ≥ Internal Jugular (lowest for HD)
- Catheter type, size, tip location
  - Endothelial damage
    - Traumatic insertion (≥ 2 attempts)
    - Tip location (non-central >> atrial-caval junction)
    - Catheter size and rigidity (large > small)
- Venous stasis
  - Catheter size relative to vein size
  - Catheter material

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Platelet Adhesion and Aggregation

- Fibrinogen (GPIIb/IIIa)
- Phospholipid
- Exterior
- Interior
- Subendothelium

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Central Venous Catheters

Catheters provide a thrombogenic surface

- Fibrin Sheath
- Endothelial damage
- Venous stasis

VASCULAR INJURY

STASIS
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**Fibrin Sheath**

  - 55 subclavian veins with CVCs dissected at autopsy  
  - 100% had a fibrin sheath  
  - Materials: polyethylene, Teflon, nylon, siliconized rubber  
  - Additional radiographic studies show rates of 80-90%  
  - Sheath likely forms in first 24 hours  
  - Propagation of fibrin sheath originates from intimal injury at point of entry and at catheter tip

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**Catheter Materials**

- Silicone Catheters: Medical grade silicone rubber has traditionally been considered the gold-standard for long-term vascular access in animals and humans. Its properties include:  
  - High biocompatibility  
  - Relatively non-thrombogenic  
  - Flexible  
  - Soft  
- Polyurethane: Currently the material of choice. Its properties include:  
  - High biocompatibility  
  - Relatively non-thrombogenic  
  - Easier to insert  
  - Sufficiently stiff but then softens in body  
  - Larger internal diameter compared to same silicone French size  
  - Increased flow rate due to increased lumen diameter

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**Platelet Adhesion and Aggregation**

Fibrinogen (GPIIbIIIa)  
Platelet  
Vessel Wall  
Thrombogenic surface  
Exterior  
Phospholipid  
Interior
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THE COAGULATION CASCADE

(Intrinsic Pathway)

(Xa)

(P)

(IIa)

(II)

(II)

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**Pathogenesis of CRBSI**

- **INFECTION**
- **INFECTIOUS AGENT**
- **SUSCEPTIBLE HOST**
- **CHAIN OF INFECTION**
- **ATTACHMENT and COLONIZATION**
- **PORTAL OF ENTRY**

*Meakins JL, Masterson BJ. Prevention of postoperative infection. ACS Surgery. 2003*

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**Coated Catheters**

  - 180 patients (260 catheters) randomized to receive either CVC
    - Heparin coated (132 catheters):
      - Colonization 23.5/1,000 catheter days
      - CR-BSI 3.2/1,000 catheter days
    - CSS
      - Colonization 11.5/1,000 catheter days
      - CR-BSI 2.6/1,000 catheter day

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**Summary**

- **Key Points**
  - CR-BSI and CR-thrombosis are both significant complications of central venous access
  - Prevention is the Goal
  - Technology-driven solutions are required to further reduce the risk to patients
  - Right Care, Right Now (for the) Right Patient
  - Make a Business case issue for Hospital Administrators
  - Quality Care with Improved Outcomes

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Thank you for your attention!