Improving patient safety and outcomes: Prevention of catheter related bloodstream infections

Reid A. Nishikawa, Pharm. D., BCNSP, FCSHP
Director of Research
Coordinator, Clinical Services
Nutrishare, Inc.
reid@nutrishare.com

Questions

- Is the success rate in the treatment of CRBSI acceptable?
- Why are CRBSIs so difficult to treat?
- What is biofilm and what role does it play in the scope of CRBSI?
- What role does fibrin play in CRBSI?
- Why consider catheter lock solutions?

Questions

- Is there a financial incentive to improve the success of treatment of CRBSI?
- Which catheter lock solutions have been used?
- Should non antibiotic lock solutions be considered?
- Are antibiotics alone the best solution in the management of CRBSI or is a combination approach better?

Catheter Related Blood Stream Infections(CRBSI)

Catheter Related Bloodstream Infection (CRBSI)

- Incidence-400,000 CRBSI/y(US) Raad, Nutrition 1997, 13:26S
- 15-35% Mortality
- Extends ICU stay by 20d with cost >$91,000/pt Dimick, Arch Surg, 2001, 136:229
- Emerging of antibiotic-resistant strains of S. epi, S. aureus, Enterococcus, Candida spp
- $5-10 billion additional medical costs

Wenzel, NEJM, 1999, 240:48

CRBSI

Common Clinical Scenario

- Pt on TPN has sn/sx CRBSI, Hickman catheter
- IV ABX started-10d course
- Sx resolve in 2-3d, blood is sterile
- ABX completed
- 4-6 wk later, infusion related fever and chills and bld cx now + for same organism
- OK, WHY???

CRBSI and Treatment Failure

Hematology-Oncology

- CRBSI in adult hem-onc patients, retrospective n=103
- Catheter removal vs ABX Tx
- Mostly Hickman catheters and Coag Neg Staph
- 25% catheter removal
- Tx failure=recurrence within 90d, mortality d/t sepsis within 30 d
- **Results**
  - Recurrence= 52.5%(ABX) vs 4%(catheter removal) p<0.05
  - No difference in mortality

Coyle, J Hosp Infect, 2004, 57:325

CRBSI and Treatment Failure

Hemodialysis/S. aureus bacteremia and ABL

- S. aureus CRBSI in hemodialysis patients tx with ABL + systemic ABX x 3 wk
  - retrospective n=113
- Tx failure=fever after 48h of ABX or recurrent S. aureus bacteremia within 90 d

Maya, Am J Kidney Dis, 2007, 50:289

CRBSI and Treatment Failure

Hemodialysis/S. aureus bacteremia and ABL

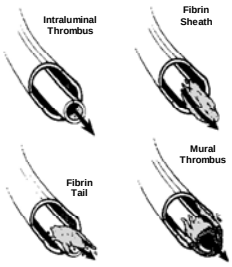
RESULTS

- Catheter removal in 67 pts(59%)
  - Persistent fever n=40
  - Recurrent bacteremia n=27
- Clinical cure n=46(41%)
- Conclusion-Routine ABL may not be appropriate in S. aureus CRBSI??

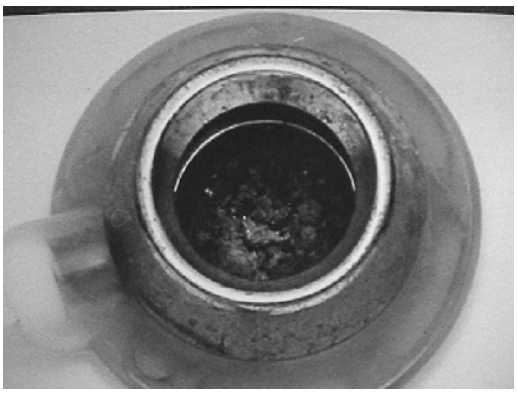
Maya, Am J Kidney Dis, 2007, 50:289

Fibrin:
What Role Does it Play in CRBSI?

Types of Catheter-Related Thrombotic Occlusions



Herbst SL, et al. *Infusion.* 1998;4:S1-S32.



Effect of Bacterial Trapping by Fibrin
Efficacy of systemic ABX in peritonitis

- Gentamicin concentrations
  - PSL 15.84 mcg/ml
  - Peritoneal level 14.75 mcg/ml
  - Fibrin clot level 0.75 mcg/ml
- Conclusions:
  - Entrapment of bacteria by fibrin reduces initial mortality d/t sepsis but favors abscess formation
  - Fibrin protects bacteria from antibiotic penetration

Hau T, Nishikawa R, and Phuangsab A, Surg Gynecol Obstet, 1983, 157:252

Fibrin Sheath
Effect on central venous catheter infection

- Adult Sprague-Dawley rats, n=210
- Implanted catheters(fibrin coated vs non coated)
- 3 grps-A(fibrin) n=85, B(no fibrin) n=85, C(control) n=40
- Tail vein injected bacteria 10^8 S. epi(n=100) or E. cloacae(n=60)

Mehall, Crit Care Med, 2002, 30:908

Fibrin Sheath
Effect on central venous catheter infection

RESULTS

		+catheter culture		
		Roll(%)	Broth(%)	P-value
S. epi	+Fibrin	32	80	<0.01
	-Fibrin	4	20	
E. cloacae	+Fibrin	50	80	<0.01
	-Fibrin	0	12	

Mehall, Crit Care Med, 2002, 30:908

Prophylactic Urokinase in HTPN
Results

	Catheters Replaced	1-time urokinase	Catheter infections	Antibiotic pt-days
Pre Urokinase	0.63±0.99	0.5±0.05	1.0±0.5	34.4±27
Urokinase	0.13±0.33	0±0	0.63±0.7	17±18
P-value	0.05	0.023	0.009	NS

N=8 values reported as n/year

Siepler JK, Nishikawa RA, et al. Gastroent 1999, 112:S321

Prevention of Coag Neg Staph CRBSI
Effect of prophylactic Urokinase

- Hypothesis-Intraluminal fibrin deposition increases the risk of Coag Neg Staph related CRBSI. Prophylactic fibrinolytic therapy might reduce this risk
- Prospective double blind RCT in hematologic malignancy
- Urokinase-5 ml of 5000u/ml vs NS given TIW

Van Rooden, J Clin Oncol, 2008, 26:428

Prevention of Coag Neg Staph CRBSI
Effect of prophylactic Urokinase

	>1+ Bld Cx(%)	**CNS CRBSI(%)**	**CVC thrombosis(%)**
Urokinase	26	1.2	1.3
NS Placebo	42	14.1	9.0
	RR=0.61;95% CI, 0.39-0.94	RR=0.09;95% CI, 0.01-0.50	RR=0.14;95% CI, 0.02-0.82

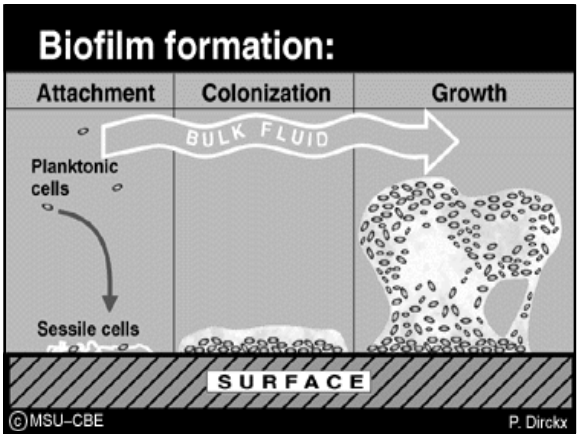
No severe bleeding complication observed

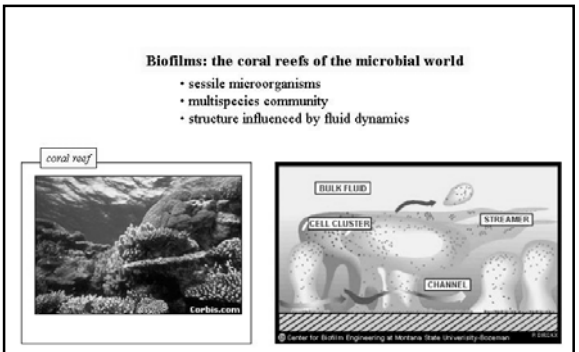
Van Rooden, J Clin Oncol, 2008, 26:428

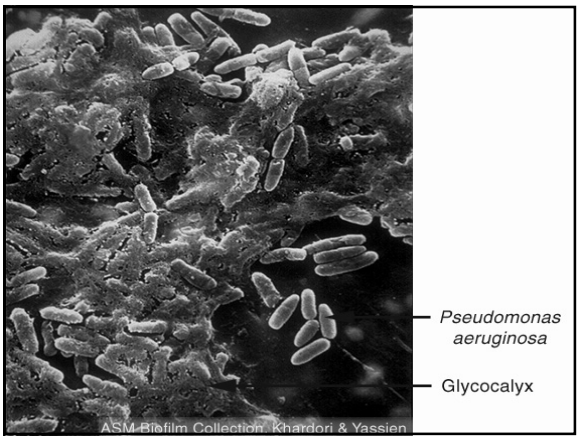
Fibrin and Catheters

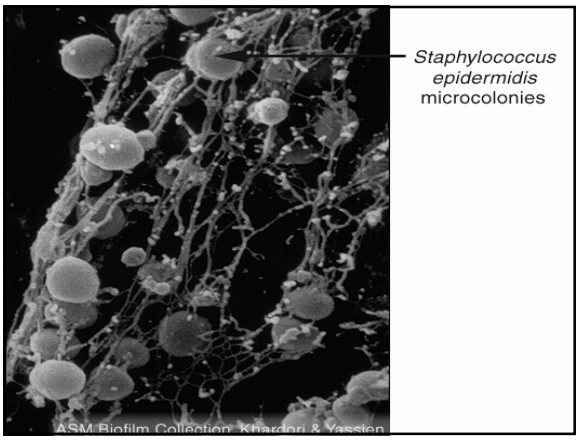
- We do know
  - Fibrin deposition occurs(outside and intraluminal)
  - Bacterial adhere to fibrin
  - ABX penetration of fibrin is poor
- Result=High incidence of ABX failure
- We don't know
  - Frequency
  - Timing
  - dose

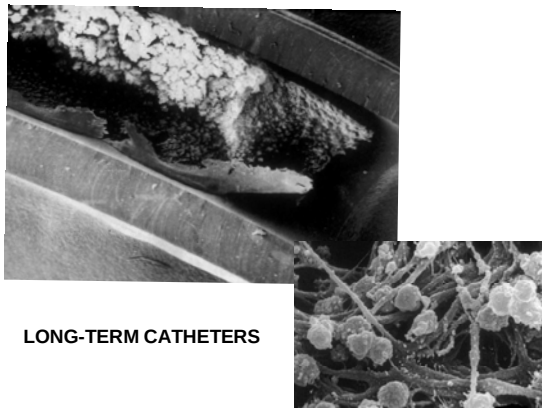
Biofilm, Catheters, and Infection





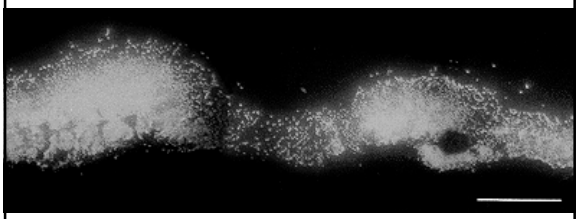






LONG-TERM CATHETERS

Biofilm on a catheter-Acridine orange stain



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Cinepak decompressor
are needed to see this picture.

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Biofilm

Antibiotic Penetration

- In vitro study to assess Vancomycin penetration through S aureus biofilm
- Fluorescently labeled derivative of Vancomycin
  - Confocal laser microscopy
- Results
  - Binding to planktonic bacteria(<5 min)
  - Binding to sessile bacteria(>1h)
  - Will result in gradual exposure to the ABX and potential for resistance

Jefferson, Antimicrob Agents Chemother, 2005, 49:2467

Biofilm

Factors inducing tolerance:PsA

- In vitro study
  - P. aeruginosa biofilms and tobramycin or ciprofloxacin
  - Tob conc. 10 mcg/ml, Cipro conc. 1 mcg/ml
  - 100 h exposure
- Results
  - Insignificant log reductions in bacteria
  - Both antibiotics penetrated the PsA biofilm
  - Oxygen limitation and low metabolic activity inside the biofilm and not penetration cause tolerance

Walters, Antimicrob Agents Chemother, 2003, 47:317

Biofilm

Antibiotic penetration and resistance

- In vitro study to assess Ampicillin and Ciprofloxacin penetration through K. pneumoniae biofilm
- Concentration=10xMIC MIC=(Amp 500 mcg/ml Cipro 0.18 mcg/ml)
- Disk diffusion to measure penetration
- Results
  - Log reduction in CFU of planktonic bacteria similar
  - Log reduction in CFU of sessile bacteria
    - -0.06±0.06(Amp) 1.02±0.04 (Cip)
  - Amp did not penetrate biofilm but Cipro did rapidly(20 min)

Anderl, Antimicrob Agents Chemother, 2000, 44:1818

Biofilm

Persister cells and multi-drug tolerance

- Bacteria produce a small number of dormant persister cells
- Exhibit multidrug tolerance
- Tolerance works by "down regulation" of bacterial growth
- Represents ~1% of bacteria in biofilm
- Also found in yeast
- End result=Multidrug tolerance

Lewis, Curr Top Microbiol Immunol, 2008, 322:107

Ciprofloxacin vs CNS Biofilm Bacteria

	Mean Log Reduction Bacteria			
	10xMIC	100xMIC	1000xMIC	5000xMIC
3h	7%	15%	22%	28%
6h	14%	18%	26%	35%

Ryder M, Nishikawa R, Liu Y, et al, ASM Biofilms 2003
Poster presentation, Victoria, BC

Ciprofloxacin vs PsA Biofilm Bacteria

	Mean Log Reduction Bacteria			
	10xMIC	100xMIC	1000xMIC	5000xMIC
3h	56%	68%	70%	69%
6h	58%	74%	68%	82%

Ryder M, Nishikawa R, Liu Y, et al, ASM Biofilms 2003
Poster presentation, Victoria, BC

Biofilm

Clinical Challenge

- Planktonic vs Sessile cells
- MIC of sessile bacteria=100-1000 x planktonic
- Antibiotic penetration may not explain ABX failure
- Other mechanisms for ABX failure
  - Decreased concentration at deeper layers of the biofilm
  - Nutrient limitation
  - Down regulation of bacterial replication
  - Quorum sensing and transfer of genetic information
  - Persister cells

Summary

- Current use of IV ABX alone results in excessive treatment failure and loss of catheters
- The role of fibrin and biofilm are important factors which effect the success rates of antibiotics alone in the treatment of CRBSI
- We must consider agents to target fibrin and intraluminal colonization associated with catheters.

Summary

- The goal should be to improve success rates in the tx of CRBSI but not cause ADR, drug toxicity or ABX resistance
- Various catheter lock solutions have been investigated to improve the success rates in the treatment/prevention of CRBSI. The data is preliminary but promising.
- Data must be collected to document the long term success of combination therapy for treatment of CRBSI

Reid A. Nishikawa, Pharm. D., BCNSP, FCSHP
Director of Research Coordinator, Clinical Services
Nutrishare, Inc.
reid@nutrishare.com

Learning Objectives

1. Describe how fibrin could increase the risk of CRBSI treatment failure.
2. Describe how biofilm is formed.
3. Describe how biofilm causes tolerance to antibiotics
4. Describe the rationale for combination therapy for the treatment of CRBSI.

Selected References

Anderl JN, Franklin MJ, and Stewart PS, Role of antibiotic penetration limitation in Klebsiella pneumoniae biofilm resistance to ampicillin and ciprofloxacin, Antimicrob Agents Chemother, 2000, 44:1818-24.

Coyle VM, McMullan R, Morris TC, et al, Catheter-related bloodstream infection in adult hematology patients: catheter removal practice and outcome, J Hosp Infection, 2004, 57-325-31.

Donlan R, Biofilms on central venous catheters: Is eradication possible?, Curr Top Microbiol Immunol, 2008, 322:133-61.

Jefferson KK, Goldmann DA, and Pier GB, Use of confocal microscopy to analyze the rate of vancomycin penetration through Staphylococus aureus biofilms, Antimicrob Agents Chemother, 2005, 49:2467.

Lewis K, Multidrug tolerance of biofilms and persister cells, Curr Top Microbiol Immunol, 2008, 322:107-31

Mehall JR, Saltzman DA, Jackson RJ, et al, Fibrin sheath enhances central venous catheter infection, Crit Care Med, 2002, 30:908-12

Opilla MT, Kirby DF, and Edmond MB, Use of ethanol lock therapy to reduce the incidence of catheter-related bloodstream infections in home parenteral nutrition patients, J Parenter Enteral Nutr, 2007, 31:302-5.

Raad I, Hanna H, and Maki D, Intravascular catheter-related infections: Advances in diagnosis, prevention, and management, Lancet Infect Dis, 2007, 7;645-57.

Raad I, Hanna H, Dvorak T, et al, Optimal antimicrobial catheter lock solution, using different combinations of minocycline, EDTA, and 25-percent ethanol, rapidly eradicates organisms embedded in biofilm, Antimicrob Agents Chemother, 2007, 51:78-83.

Van Rooden CJ, Schippers EF, Guiot HF, et al, Prevention of coagulase-negative staphylococcal central venous catheter-related infection using urokinase rinses: a randomized double-blind controlled trial in patients with hematologic malignancies, J Clin Oncol, 2008, 26:241516.

Walters MD, Roe F, Bugnicourt A, et al, Contributions of antibiotic penetration, oxygen limitation, and low metabolic activity to tolerance of Pseudomonas aeruginosa biofilms to ciprofloxacin and tobramycin, Antimicrob Agents Chemother, 2003, 47:317-23

Self assessment questions

1. Fibrin causes antibiotic failure in effectively treat CRBSI as a result of:

a) Enzymatic destruction of the antibiotic
b) Increased clearance of the antibiotic
c) Impaired antibiotic penetration into the fibrin
d) Upregulation of the bacteria

2. Fibrinolytic agents may work synergistically with antibiotics in the treatment of CRBSI by:

a) Increasing the half life of the antibiotic
b) Dissolving fibrin which may harbor bacteria
c) Increase by 10 fold the penetration rate into fibrin
d) Direct bactericidal activity on the bacteria

3) The property of biofilm includes:

a) down regulation of bacterial growth
b) increased rate of antibiotic penetration
c) enhanced bacterial killing from enzymes
d) increased rate of fibrinolytic activity

Ethanol-Lock Therapy for the Prevention of Central Venous Access Device Infection in Pediatric Intestinal Failure Patients

M. Petrea Cober, PharmD, BCNSP,
Daniel H. Teitelbaum, MD,
Debbie Kovacevich, RN, MPH
University of Michigan
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Disclosures

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- Daniel H. Teitelbaum, MD
  - Nothing to disclose
- Debbie Kovacevich, RN, MPH
  - Nothing to disclose

Impact of Venous Access Device Infections

- Infection remains most devastating complication associated with vascular access devices (VADs), particularly with the administration of parenteral nutrition (PN)
- Mortality ranging up to 35% and cost per infection of approximately $56,000
- For home PN patient, potentially requires multiple antibiotic courses at home or in the hospital which affect the patient's quality of life
- Particularly, limited vascular sites in children, so attention given to frequency with which VADs are replaced

Advantages for Ethanol Lock Therapy (ELT) Use

- Effect does not depend on sensitivity to antibacterial agents, may be of particular value for infections with multiresistant organisms
- Highly resistant organism will not be selected, possibly reducing use of broad-spectrum antibiotics

Previous Studies

- Four published retrospective chart reviews to date
  - 3 involving pediatric patients
    - 1 in Hematology/Oncology patients (n = 28)
    - 1 in Hematology/Oncology + Intestinal Failure patients (n = 40)
    - 1 in Short Bowel Syndrome patients (n = 9)
  - 1 involving adult home PN patients (n = 10)
- We wanted to study a pediatric patient population at high risk who would potentially have the greatest benefit from therapy

Objectives

- Primary – To evaluate the use of outpatient ELT for the prevention of central VAD (CVAD) infections in children with a history of severe CVAD infection or limited vascular access sites with our pediatric intestinal rehabilitation clinic
- Secondary – To evaluate the adverse effects from ELT

Methods

- Retrospective chart review
- Inclusion criteria
  - Patients < 25 yo in University of Michigan Children's Intestinal Rehabilitation Program receiving outpatient ELT from July 2006 to April 2008
  - Weight ≥ 5 kg
  - Presence of silicone-based catheter with determined VAD volume
  - Defined as high risk:
    - Two previous CVADs replaced due to infection in the previous 18 months, or
    - Two previous infection in current CVAD which failed to clear with a full antibiotic course or were associated with development of antibiotic resistance, or
    - Limited remaining CVAD access

Preparation and Administration

- 70% ethanol lock therapy (ELT) used
  - 98% ethanol + sterile water for injection (SWI)
  - Stable for up to 14 days
- Minimum dwell time of 2 hours
- Flush before and after PN with 5-10 mL of normal saline
- ELT solution withdrawn
  - To avoid introducing bacteria into the body of the patient after disruption of the biofilm after the initial dose
  - To prevent potential intoxication in pediatric patients

Preparation and Administration

- NOT compatible with heparin or citrate solutions
  - MUST USE NORMAL SALINE FLUSHES
- Compatible with silicone-based VADs, NOT compatible with polyurethane VADs
  - Weakens polyurethane catheters

Patient Demographics

- Total of 15 patients received ELT
  - Male = 67% (10/15)
- Mean age = 5.6 ± 6.9 yo (range: 0.5-21.4 yo)
- Mean weight at initiation of ELT = 19.9 ± 15.4 kg (range: 5.9-52.6 kg)
- Medical Diagnoses
  - Short bowel syndrome = 87% (13/15)
  - Medical intestinal failure = 13% (2/15)

Central VAD Prior to ELT

- Central VAD infection
  - Mean number of infections in last 6 months = 1.9 ± 1.5
  - Mean number of infections in last 12 months = 2.9 ± 2
- Life-threatening VAD infection = 47% (7/15)
- Antibiotic-lock therapy = 33% (5/15)
- Fungal infection = 33% (5/15)
- VRE infection = 27% (4/15)
- Multiple line replacements = 87% (13/15)

Initial ELT placement

- Type of central VAD
  - Single lumen tunneled VAD = 13
  - Double lumen tunneled VAD = 1
  - Implanted port = 1
- Mean volume of ELT = 0.49 mL ± 0.26 mL (range = 0.2 - 1mL)

Study Results

- Mean duration of ELT = 263 ± 190 days (range: 23-652 days)
- 73% of patients remained bloodstream infection free throughout entire study period
  - 3 patients had 1 positive CVAD infection
  - 1 patient had 2 positive CVAD infections
  - 2 additional patients with site infections

Study Results

- Bloodstream infection (BSI) rate
  - Prior to ELT therapy
    - Mean of 8.0 infections/1000 catheter days (range: 0-19.2)
  - After ELT therapy
    - Mean of 1.3 infections/1000 catheter days (range: 0-10.6) ($p < 0.01$)

Potential ELT Adverse Effects

- Thrombosis (n = 1)
- Difficulty withdrawing blood from the CVAD and requiring urokinase administration (n = 3)
- Repair of the CVAD for leakage/tear (n = 20)
  - Prior to ELT therapy
    - Mean of 3.1 ± 5.2 leakages/tear per 1000 catheter days
  - After ELT therapy
    - Mean of 6.4 ± 10 leakages/tears per 1000 catheter days ($p = 0.2$)
- No signs/symptoms of intoxication were observed

Conclusions

- Use of ELT for prevention of CVAD infections in pediatric intestinal failure patients shown to significantly decrease BSI rate
- ELT may be used for extended period of time in outpatient setting to prevent CVAD infection
- Providers should be aware of potential for difficulty withdrawing ELT from catheter and weakening the catheter related to use of ELT

Questions?

Contact Information

- Mary Petrea Cober
  - Email = mcober@mich.edu

Discontinuation of ELT

- 6 patients (40%) are no longer on ELT
  - 1 patient with catheter malfunction and catheter not replaced
  - 4 patients able to wean off TPN and no longer require central venous access
  - 1 patient received liver-small bowel transplant in Nebraska