OTHER INTERVENTIONS TO PROMOTE ANTIMICROBIAL STEWARDSHIP

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NO DISCLOSURES OR CONFLICTS OF INTEREST

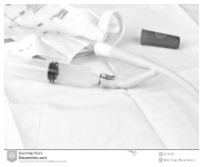
Objectives

- Discuss strategies to decrease the treatment for asymptomatic bacteriuria and to improve the diagnosis of catheter- associated urinary tract infections – a partnership with Infection Prevention
- Review the unintended consequences of using antibiotic loaded cement in the treatment of peri-prosthetic infections
- Outline the impact of false positive blood cultures on patient safety, surveillance of central line-associated blood stream infection, and cost

ANTIMICROBIAL STEWARDSHIP AND ASYMPTOMATIC BACTERIURIA

Definitions

- Catheter-associated urinary tract infection surveillance per National Healthcare Safety Network (NHSN)
  - Indwelling urinary catheter for > 2 days
  - One of the following signs/symptoms
    - Fever >38.0°C
    - Symptoms: suprapubic tenderness, costovertebral angle pain or tenderness, urinary urgency, urinary frequency, dysuria
  - Urinary culture: no more than 2 species of organisms identified, at least one of which is a bacterium of ≥ 100,000 CFU/ml (yeast does not meet definition)



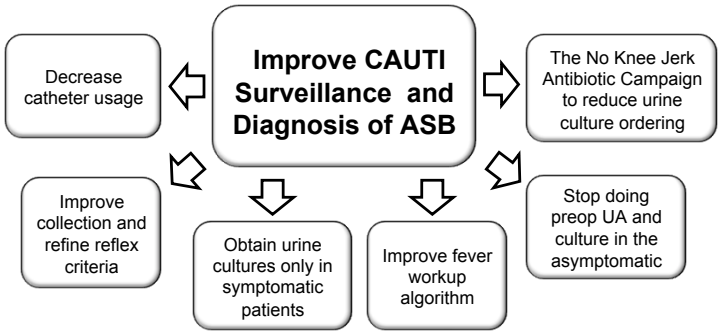
Asymptomatic Bacteriuria (ASB): Defined

- Presence of 1 or more species of bacteria growing ≥10^5 CFU/ml
- Irrespective of the presence of pyuria
- In the absence of signs and symptoms attributable to urinary tract infection
  - Elderly with bacteriuria: sudden altered mental status/ confusion, without local genitourinary symptoms or other systemic signs of infection of sepsis
  - Elderly with bacteriuria who experience a fall
  - Elderly and “sepsis”

Issues with the CAUTI Surveillance Definition

- Fever may be the only "sign" a patient has in the ICU
- Even though there is another more likely explanation for fever, the presence of a "positive" urine culture meets surveillance definition of a CAUTI
- At any give time, up to 100% of patients with an indwelling urinary catheter will be colonized and have asymptomatic bacteriuria
- Is this a true statement or are we being held hostage by a surveillance definition?

"CAUTI is the most common type of healthcare-associated infection, accounting for more than 30% of acute care hospital infections. 13,000 deaths are associated with UTIs each year. There are estimated to be **449,334** CAUTI events per year. Each CAUTI is associated with the medical cost of $758. And, a total of over $340 million spent in health care is attributable to the incident of CAUTI in the U.S. each year."



Decrease Urinary Catheter Usage

- 25% of inpatients receive urinary catheters
- 1/3 of catheter days are unnecessary **"Indwelling urinary catheters: a one-point restraint?" S. Saint, MD**
- 1/3 of physicians are unaware their patient has a catheter 1/3 of the time, there is no order for a catheter: target in the ED and OR
- Use more intermittent catheterization and ensure proper insertion technique

"…Foley catheter-related genitourinary trauma was as common as symptomatic UTI. Moreover…asymptomatic bacteiuria accounted for significantly more antimicrobial treatment than did symptomatic UTI. Elimination of unnecessary Foley catheter use could prevent symptomatic UTI, unnecessary antimicrobial therapy for asymptomatic bacteriuria and Foley catheter-related trauma" J Urol 2012;187:1662-6

Improve Collection and Refine UA Screening Criteria to Reflex to Culture

Finding on UA	Current	Proposed
Nitrite	Reflex to urine culture	Perform microscopic and culture if WBCs ≥ 10
Leukocyte esterase	Reflex to urine culture	Perform microscopic, culture if WBCs ≥ 10
WBCs	Reflex to urine culture if WBCs ≥ 5	Culture if WBCs ≥ 10

Preservatives for Culture and Sensitivity (C&S) Testing: a buffered boric acid formula that maintains urine for up to 48 hours at room temperature (the standard is that urine samples have to be processed within 2 hours or refrigerated) . The preservative helps prevent overgrowth that could result in a false positive culture without causing toxicity to existing pathogens

Wold K. Opern Forum Infect Dis 2017:4:S346
Paulus C. Open Forum Infect Dis 2016:3:396
http://www.thepathologycenter.org/uploads/Lynette-Folder/Urinalysis-with-Reflex-to-Culture.pdf
https://stanfordhealthcare.org/content/dam/SHC/health-care-professionals/medical-staff/medstaff-weekly/20170517-update-to-urinalysis-and-urine-culture-testing.pdf.

Obtain Urine Culture Only in Symptomatic Patients: "when the nurse calls"

Common Myths Regarding the Diagnosis of UTIs

- Myth 1: Urine is cloudy and smells bad → UTI
- Myth 2: Urine has bacteria → UTI
- Myth 3: Urine has a positive leukocyte esterase (for WBCs) → UTI
- Myth 4: Urine contains WBCs → UTI
- Myth 5: Urine has nitrates (for bacteria) → UTI
- Myth 6: Bacteria in a catheterized urine sample → UTI
- Myth 7: Asymptomatic bacteriuria will progress to UTI
- Myth 8: Falls and acute altered mental status changes in the eld → UTI – look for another cause first

Adapted from: Schulz L. J Emerg Med 2016;51:25-30

Clinical Infectious Diseases
IDSA FEATURES

Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America[a]

Lindsay E. Nicolle,[1] Kalpana Gupta,[2] Suzanne F. Bradley,[3] Richard Colgan,[4] Gregory P. DeMuri,[5] Dimitri Drekonja,[6] Linda O. Eckert,[7] Suzanne E. Geerlings,[8] Béla Köves,[9] Thomas M. Hooton,[10] Manisha Juthani-Mehta,[11] Shandra L. Knight,[12] Sanjay Saint,[13] Anthony J. Schaeffer,[14] Barbara Trautner,[15] Bjorn Wullt,[16] and Reed Siemieniuk[17]

- Updated from 2005 guideline
- Reiterates when NOT to obtain urine to detect asymptomatic bacteriuria (ASB) except in special populations
- NEW, addresses:
  - Patients with solid organ transplants
  - Neutropenic patients
  - Reviews evidence for NON-treatment of ASB in pre-surgical patients, especially in orthopedic surgery with implants
- Focuses on the unintended consequences of treatment of ASB: adverse reactions, *C. difficile* infection, and drug resistance

Nicolle LE et.al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. Clin Infect Dis 2019;68:e83-e110

Asymptomatic Bacteriuria (ASB)

- Pyuria accompanying ASB is NOT and indication for treatment
- Randomized controlled trials have demonstrated a LACK of benefit of treatment of ASB in:
  - Premenopausal, non-pregnant women
  - Diabetic women
  - Patients with spinal cord injury
  - Patients with long term indwelling catheters
  - Elderly nursing home or long term care patients

Cosgrove, SE. (2010) Transcript/slides from http://www.medscape.org/viewarticle/731692_transcript
Nicolle LE et.al. Clin Infect Dis 2019;68:e83-e110

What About the Elderly with Bacteriuria?

- Older, functionally or cognitively impaired patients with non-localizing symptoms who may or may not have fever
- Observation data suggest that the relationship between *delirium and bacteriuria* is likely attributable to under host factors and consistent with a high frequency of both events in this populations rather than a true inflammatory or infection related association
- Antimicrobial treatment of ASB did not improve mean behavioral scores in these patients
- In-hospital mortality did not significantly differ in patients who were treated for ASB compared to those not treated

Falls and the Elderly Patient with Bacteriuria?

- Falls and ASB are common in older populations
- Earlier study: 39/80 (48%) who fell on the way to or from the bathroom had pyuria and bacteriuria and was diagnosed to have a UTI – unknown whether these residents were symptomatic
- Later study: 20% (9/45) had fall episodes in nursing home residents with bacteriuria and pyuria present; the remaining 80% had no bacteriuria and pyuria.
  - These studies suggest that most older residents who fall do NOT have ASB
  - Therefore, falls should not immediately trigger suspicion for UTI; other causes are more likely

Rhoads J, et.al. Director 2007;15:22-6
Bowe T, et.al. J Am Geriatr Soc 2013;61:653-4

ASB: The Exceptions to Treat

- Urinalysis is not helpful
- Only a positive culture matters
- Population:
  - Pregnancy
  - Before endourologic surgery – limit doses, penile implants: use recommended preoperative antimicrobial prophylaxis
  - Renal transplant recipients
  - [Febrile neutropenic patients (unable to mount an inflammatory response)]

High Risk: ANC < 100 cells/mm^3; >/= 7 days of neutropenia
- No recommendations for or against screening for ASB
- Standards of care require initiation of broad-spectrum antimicrobials for febrile illness
- Unknown: the frequency of ASB and how often ASB progresses to symptomatic UTI

Horan TC, et al. Am J Infect Control 2008;36:309-32
Cosgrove, SE. (2010) Transcript/slides from http://www.medscape.org/viewarticle/731692_transcript
Nicolle LE. Curr Opin Infect Dis 2014;27(1):90-6
Nicolle LE et.al. Clin Infect Dis 2019;68:e83-e110

Renal Transplant Recipients

- Recommendations
  - Renal transplant recipients who received allograft within 1 month: no recommendations for screening vs. not screening for ASB
  - However, there is evidence against surveillance for ASB > 1 month post transplant
- Caveats:
  - ASB is common following renal transplants
  - Renal transplant recipients with ASB have an increased frequency of symptomatic UTI, including pyelonephritis
  - Risk factors:
    - Female sex
    - Presence of comorbidities
    - Urologic variables
    - Some immunosuppressive regimens
  - Association of early, buy not late graft pyelonephritis with graft loss, pyelonephritis with decreased long term creatinine clearance and late UTI with graft loss

Renal Transplant Recipients

- Symptomatic UTI is the most frequent infection identified in these patients with complications of:
  - Graft loss
  - Acute graft rejection
  - Impaired long-term graft function
- Highest risk: immediate post-transplant period when patient are exposed to intensive immunosuppressive therapy, have indwelling urologic devices and various urologic interventions
- Prophylactic SMX/TMP is standard for 6 months, but bacterial resistance has emerged as a problem

Randomized, Open-Label Comparative Trials: Treatment or Non-Treatment of ASB following Renal Transplant

- Moradi M, et.al. Urol J 2005;2:32-5
  - 88 patients least 1 year after transplant, followed for 9 -12 months; *P mirabilis* infections excluded
  - Outcome of bacteriuric episodes: symptomatic UTI and renal function were similar when treated and non-treated subjects compared
- Origuen J, et.al. Am J Transplant 2016;16:2943-53
  - 112 patients with bacteriuria ≥ 2 months post transplant, followed for 24 months; urine screened every 2 weeks for 1st 3 months, monthly to 1st year, then 1-3 months thereafter
  - Antibiotics were withheld in 49% of ASB; subjects randomized to Rx had no PO options, while 56% of patients randomized to no treatment receive Abx for other indications that were also effective for the bacteriuria.
  - Intention to treat and per protocol
    - Acute pyelonephritis occurred with equal frequency in both group
    - No difference in secondary outcomes of long-term 12-24 months graft function, all-cause mortality, cumulative incidence of lower UTI, acute graft rejection, CDI, colonization or infections due to multidrug resistance bacteria and graft loss at the end of the follow-up period
    - Only 16 (3.6%) episodes pf ASB. (5 treated and 11 untreated) were followed by symptomatic UTI with the same organisms: 6 of 16 were pyelonephritis.

Conclusions

- Treatment of ASB in renal transplant recipients > 2 months after surgery may not prevent pyelonephritis or graft rejection and probably does not improved graft function
- Antimicrobial resistant organisms are common in this population and the high proportion of resistant organisms isolated may not be effectively treated with oral therapy
- Treatment of ASB probably promotes reinfection with organisms increasingly resistant to antimicrobials potentially compromising treatment of symptomatic UTI which is also frequent in these patients

Fever Work-up

- If there is an alternate reason for fever, consider not submitting UA/culture
- From Critical Care:
  - **Premise:** asymptomatic bacteriuria generally should not be treated
  - CA bacteriuria is typically indicative of colonization AND is an infrequent cause of fever or secondary bacteremia
  - **Guidance:** When evaluating fever in critically ill patients, only those patients at high risk invasive infection should be evaluated for a CAUTI:
    - Kidney transplant recipients
    - Patients with evidence of urinary obstruction
    - Neutropenic patients
    - [Pregnant women]
  - **Outcome:** Following the above guidelines, the CAUTI rate decreased from 3/1000 catheter days to 1.9 (p = 0.0003) without adverse outcome

**Mullin KM. Infect Control Hosp Epidemiol 2016;38:1-3.*
O'Grady NP. Crit Care Med 2008;36:1330-1349

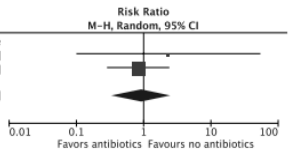
Preoperative Urinalysis/Culture

Theory: remote infection should be treated prior to surgery. Because of the significant morbidity associated with peri-prosthetic joint infections and surgical site infections (SSIs) after cardiothoracic surgery, asymptomatic bacteriuria is treated to prevent hematogenous spread may increase the risk of postoperative SSI.

Treatment of ASB before Non-Endourologic Surgery

Study or Subgroup	Antibiotics Events	Antibiotics Total	No antibiotics Events	No antibiotics Total	Weight	Risk Ratio M-H, Random, 95% CI
Cordero-Ampuero 2013	0	1	0	1		Not estimable
Drekonja 2013	1	26	0	20	10.3%	2.33 [0.10, 54.42]
Sousa 2014	6	154	7	149	89.7%	0.83 [0.29, 2.41]
Total (95% CI)		**181**		**170**	**100.0%**	**0.92 [0.34, 2.53]**
Total events	7		7			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.37$, df = 1 (P = 0.54); $I^2 = 0\%$
Test for overall effect: Z = 0.16 (P = 0.88)



Study or Subgroup	Antibiotics Events	Antibiotics Total	No antibiotics Events	No antibiotics Total	Weight	Risk Ratio M-H, Random, 95% CI
Drekonja 2013	2	11	3	43	54.2%	2.61 [0.49, 13.74]
Sousa 2014	1	154	4	149	45.8%	0.24 [0.03, 2.14]
Total (95% CI)		**165**		**192**	**100.0%**	**0.88 [0.08, 9.79]**
Total events	3		7			

Heterogeneity: $Tau^2 = 2.07$; $Chi^2 = 3.12$, df = 1 (P = 0.08); $I^2 = 68\%$
Test for overall effect: Z = 0.11 (P = 0.92)

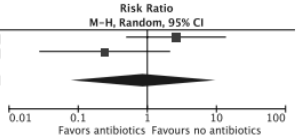


Figure 2. *A*, Risk of prosthetic joint infection in patients treated vs not treated for asymptomatic bacteriuria in patients undergoing orthopedic surgery. *B*, Risk of symptomatic urinary tract infection in the postoperative period in patients treated vs not treated for asymptomatic bacteriuria in patients undergoing orthopedic surgery. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

Nicolle LE et.al. Clin Infect Dis 2019;68:e83-e110

Preoperative Urinalysis/Culture Screening in Orthopedic Surgery

- Enrollment of 2497; ASB = 303 (12.1%)*
- 16.3% women and 5.5% men
- Overall peri-prosthetic joint infection (PJI): 1.7%
  - Infection higher in ASB group (4.3% vs. 1.4%, OR 3.23, p = 0.001)
  - In ASP group, there was no significant difference in PJI rate between treated (3.9%) vs. untreated (4.7%)
  - ***The ASB group had more PJI due to GNR than the non-ASB group; however, there was no correlation between the preop urine isolate and the cause of the PJI***

**Sousa R. CID 2014;59:41-47*
Bouvet C. Bone Joint J 2014;96-B:390-4
David TS. J AM Acad Orthop Surg 2000;8:66-74
Drekonja DM 2013. JAMA Intern Med:173:71-72

Preoperative Urinalysis/Culture Screening in Cardiothoracic Surgery

- 1002 patients met criteria for study; inclusion positive leukocyturia or nitrituria, not culture (only 26 had cultures)
- 96.1% were not treated, 8.3% had postoperative surgical site infection (SSI), compared to 5.1% in the treatment arm (p = 0.39)
- Length of stay did not differ with a hazard ratio of 1.05
- None of the patients who developed a SSI were felt to have hematogenous spread from the urinary tract from bacteria identified preoperatively (de Lange MP. Interact CardioVascu Thorac Surg 2016;22:769-75)

- Study of 840 patients
- 33 (3.9% had asymptomatic bacteriuria; 13 (1.5%) with UTI
- Incidence of SSI was 9.5% (80) patients – 2.3% with mediastinitis
- Multivariate analysis: ASB and URI were not risk factors for SSI, rather tratitional risk factors were found to increase the risk of SSI (Duarte JC. Am J Infect Control 2017; pii:S0196-6553(17)30962-8

Drekonja D.JAMA Intern Med 2013;173:71-2

Effectiveness of an Antimicrobial Stewardship Approach for Urinary Catheter–Associated Asymptomatic Bacteriuria

Changing Clinician's Behavior

2 VA hospitals
- 98- 99% male
- 289,754 bed days
- Overall rate of urine culture ordering decreased from 41.2 to 23.3/1000 bed days
- Overtreatment of ASB fell significantly from 1.6 to 0.6/1000 bed days

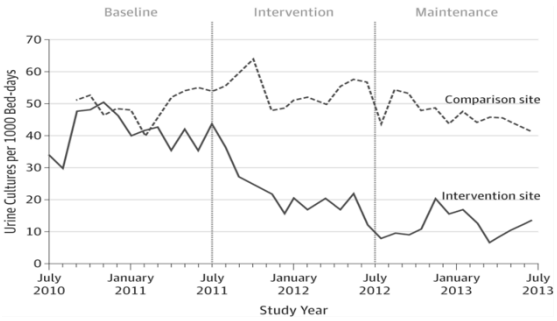


Figure Legend: Monthly Rates of Urine Culture Orders per 1000 Bed-daysShown are the intervention vs comparison sites across the 3 study periods (P < .001).

JAMA Intern Med. 2015;175(7):1120-1127. doi:10.1001/jamainternmed.2015.1878

Date of download: 10/28/2018

Summary

- The management of asymptomatic bacteriuria is an important component of a robust antimicrobial stewardship program
- Urine cultures should only be obtained in symptomatic individuals, except in pregnancy, patients undergoing endourologic surgery, renal transplant recipients with 1 month of transplant, and possibly in patients with prolonged neutropenia
- Alternatives for indwelling urinary catheterization should be implemented for patients who are incontinent and intermittent catheterization should be substituted for patients with urinary retention.

"EXPERIENCE IS SIMPLY THE NAME WE GIVE OUR MISTAKES"

Oscar Wilde

ACUTE KIDNEY INJURY DUE TO SYSTEMIC ABSORPTION OF ANTIBIOTIC LOADED CEMENT AND BEADS

Acknowledgements:
Logan Vasina, PharmD, BCPS
John Engelbert, PharmD, BCPS

Peri-prosthetic Joint Infection (PJI)

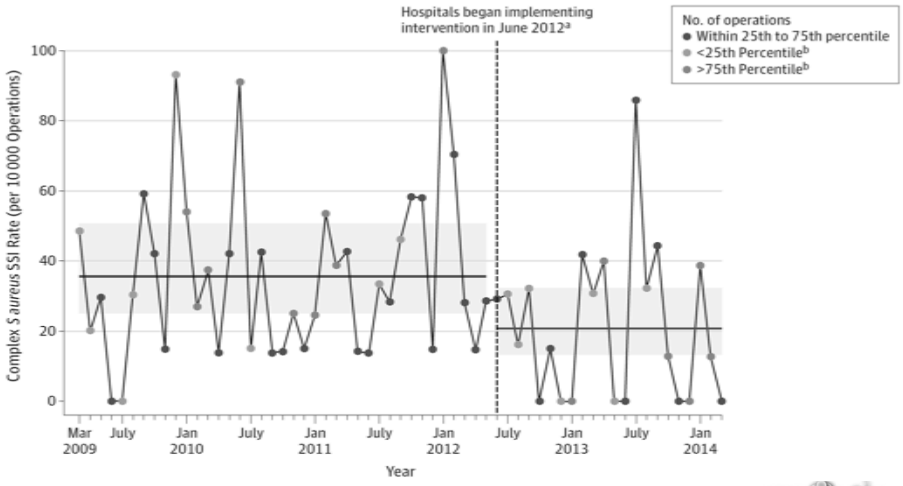
Background

- By 2030, it is projected that the UK and USA will perform 2 million total joint arthroplasties
- PJI results in significant patient morbidity and is estimated to occur about 1% after hip arthroplasties and 1-2% after knee arthroplasties
- An estimated 25% of revisions result from PJIs
- In the USA, the annual hospital cost of infected revisions is estimated to exceed $1.62 billion by 2020
- Prevention = Bundle

Kurtz SM et al. J Arthroplasty, 2008;23:984-91
Kapadia BH et al. The Lancet, 2016;387:386-394
ML Schweizer, et al. JAMA 2015;313:2162-71
Filippone EJ, Yadav A. Cleve Clin J Med 2019:86:263-276

S. aureus Screening, Decolonization, Targeted Prophylaxis, Reduced Complex *S. aureus* Surgical Site Infections by > 40%

20 Centers, 42,000 Surgeries



ML Schweizer, et al. JAMA. 2015;313:2162-71.

Antibiotic Impregnated Bone Cement and Beads

- Antibiotic impregnated bone cement is considered the standard therapy of chronic late prosthetic joint infection (PJI)[1]
- Spacer implanted during a 2-stage revision arthroplasty with success rate 90%
  - Occupies dead space created after the debridement of infected bone and removal of components
  - Ensures antibiotic delivery, stabilize limb, and facilitates re-implantation of the permanent prosthesis 6-8 weeks after removal of the infected prosthesis
  - Administer systemic antimicrobial agents during this period

Clin Infect Dis 2012;55(11):1474–80.

Case Presentation

- 87 y/o Caucasian man, SP heart transplant in March 1993, underwent index left TKA in June 2010 for severe osteoarthritis, complicated by development of a hematoma with elevated INR; SP manipulation under anesthesia for arthrofibrosis; on only cyclosporine for immunosuppression
- Problem List:
  - Type II insulin dependent diabetes mellitus
  - Hyperlipidemia
  - Hypertension
  - Multiple skin cancers
  - SP right TKA

Case Study (cont'd)

- Presents in August 2012 with 1 week history of progressive left knee pain; without a history of trauma
- Diagnosis: peri-prosthetic joint infection
- OR Aug 2012: irrigation and debridement with extensive synovectomy, polyethylene liner exchange (retained implant), placement of absorbable antibiotics loaded beads (Stimulan® with vancomycin and tobramycin)

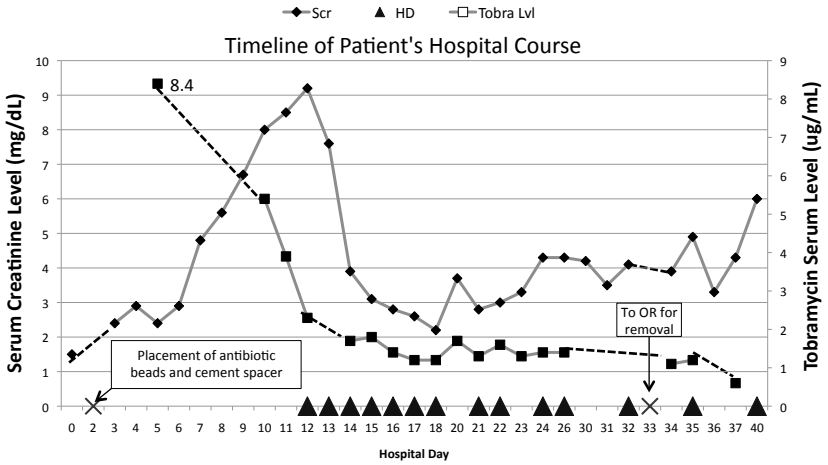
Case Presentation (con't)

- Baseline Cr 1.4-1.8
- Knee aspirate: WBC 96,750 with 86 PMNs, no crystals. Gram stain: many PMNs but no organisms. Culture: β-lactamase producing *S. haemolyticus,* susceptible to oxacillin, clindamycin, and erythromycin
- Discharged to complete parenteral antibiotic therapy followed by suppression with TMP/SMX
- October 2013: progressive pain despite limited arthroscopic debridement and synovectomy earlier

Case Presentation (cont"d)

- Meds: cefazolin, cyclosporine, pantoprazole, pravastatin, furosemide, gabapentin, insulin, (meloxicam, TMP/SMX - home) vancomycin (preop)
- Preop Cr 1.5; no IV contrast procedures; intra-op: few dips into systolic 90's but no use of pressors
- Revision: debridement and removal of all components
  - Implantation
    - PMMA antibiotic spacer (nonabsorbable)
    - Rapid Cure Stimulan® (absorbable) with antibiotics
  - *S. haemolyticus* and *S. lugdunensis* from broth only, susceptible to oxacillin

Acute Kidney Injury Following Revision Arthroplasty Using Tobramycin and Vancomycin Impregnated Bone Cement Spacer and Beads



- *PMMA (non-absorbable) with 3 gm vancomycin/3.6 gm tobramycin x 4 batches; total = 12 gm vancomycin and 14.4 gm tobramycin*
- *$CaSO_4$ (absorbable) with 2 gm vancomycin/ 2.4 g tobramycin x 1 batch*

Antibiotic Loaded Cement and Beads

- "Antibiotics that elute from bone cement do not reach significant concentrations in the systemic bloodstream and therefore do not pose a risk for systemic allergic reactions and/or systemic toxicity in otherwise healthy individuals with normal hepatic and renal function."[1]
- Potential risk factors[2]
  - Higher doses of tobramycin and vancomycin in the spacer
  - Administration of nephrotoxic IV antibiotics: Zosyn/vancomycin, aminoglycoside is
  - Low hemoglobin
  - Intraoperative blood transfusion
  - High BMI
  - Non-steroidal anti-inflammatory agent use
  - Intraoperative hypotension
  - Underlying chronic kidney disease
  - pre-operative heart murmur
  - Use of renin angiotensin aldosterone system blockade
- Several case reports of nephrotoxicity have been reported in the literature; for total knee arthroplasty, the incidence of acute kidney injury 4.8-26%[2]

Orthopedics 2011;34(3): 210-218. Clin Infect Dis 2013;56(1): e1-25. (1)
J Arthroplasty 2012; 27(6):1221-27. Infect Dis Clin Pract 2018:26:291-293. (2)
J Arthroplasty 2013;28:1490-98. J Arthroplasty 2012;27:1221-27. J Arthroplasty 2017;21:3120-25. (3)
Filippone EJ, Yadav A. Cleve Clin J Med 2019:86:263-276 (2)

Type of Bone Cement Utilized

Characteristics	PMMA	Calcium Sulfate
Type	Non-absorbable Non-biodegradeable	Absorbable Biodegradeable
Brand Names	Palacos®, Simplex®	Stimulan®
Therapeutic Uses	Cement Spacer Non-absorbable Beads	Absorbable Beads
- Preparation	- Prepared in OR	- Prepared in OR
Prophylactic Uses	Primary prophylaxis for Prosthetic Joint Infection	Dead space revision, biologic coatings, bone defect
- Preparation	- Premade available	- Prepared in OR
% Release in first 24 hrs	~1%	~10%
Typical Aminoglycoside Dosing	2.4-3.6 g / batch	1.2-2.4 g / batch
Max Number Batches	4 batches	1 batch
Volume	40 g	10-20 g

PMMA = Polymethylmethacrylate
CaSO4 = Calcium Sulfate

What Determines the Elution Characteristics from the Spacers and Beads?

- To ensure adequate eluting concentrations, > 3.5 gm of antibiotics/40 gm cement (PMMA, non-absorbable) is necessary
- Peak values is generally presented at post-op day 1-2, with gradual decline from weeks to months
- **Doses** of > 4.8 gm of tobramycin/40 gm cement increases odds ratio by 5.87 (every gram of ABX increases odds ratio by 1.240)
- **Increase porosity**: combination of vancomycin and tobramycin increases elution of tobramycin by 68% and vancomycin by 103% compared to each antibiotic alone

Same Drug, But Different Release Characteristics

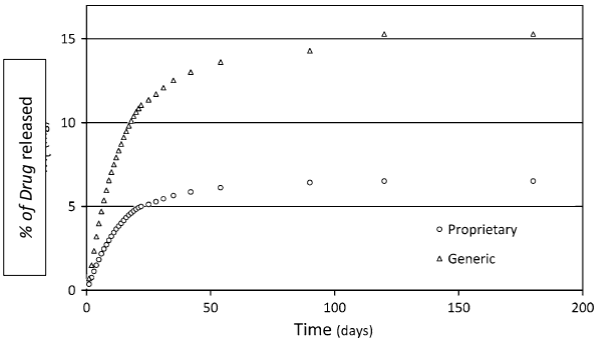


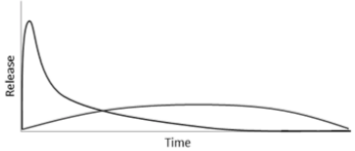
Fig. 2 Cumulative tobramycin release as a function of time showing the release pattern of tobramycin from antibiotic-loaded polymethylmethacrylate. Beads made with generic tobramycin elute more than twice as fast as beads made with proprietary tobramycin.

Clin Orthop Relat Res 2008; 466:1372-76

Factors Affecting Elution From Bone Cement/Beads

- Type of cement (Palacos® vs. Simplex® vs. Stimulan®)
- Antibiotic loaded beads elute more antibiotic than a cement spacer with the same initial concentration (due to increased surface area)

- **PMMA:** slower and longer release (**1%** of abx dose within first 24 hrs)
- **CaSO4:** more porous, increased surface area = greater initial release (**10%** in 24 hours)



- Individual antibiotic elution characteristics:(i.e. tobramycin > gentamicin > vancomycin)
- Heat labile characteristics results in deactivation of antibiotics
- An increase in atmospheric pressure and/or curing temperature during formation of a cement spacer leads to markedly decreased bioavailability of the added antibiotic and/or increases the inactivation of added antibiotics

QUALITY IMPROVEMENT INITIATIVE

Physician to Completed Pre-Operatively

- Designate: treatment or prophylaxis
- Choose type: PMMA and/or calcium sulfate
- Specify number of batches
  - Maximum for PMMA = 4 batches
  - Maximum Calcium Sulfate = 1 batch
- Specify the dose according to whether the patient is high or low risk for acute kidney injury

Type	High Risk Maximum Dose		Low Risk Maximum Dose	
	Tobramycin per batch	Vancomycin per batch	Tobramycin per batch	Vancomycin per batch
PMMA Treatment	2.4gm	1gm	3.6gm	3g
PMMA Prophylaxis	Pre-made 0.5 – 1 gm of tobramycin/gentamicin		Pre-made 0.5 – 1 gm of tobramycin/gentamicin	
Calcium Sulfate Treatment	Do not use without pharmacy oversight		2.4gm (dose >1.2g requires pharm oversight)	1 gm
Calcium Sulfate Prophylaxis	Do not use without pharmacy oversight		1.2gm	

Clinical Infectious Diseases 2012;55(11):1474–80.

Physician to Completed Pre-Operatively

- Identify situations when the biodegradable product is prophylactically used (pharmacy to dose for high risk):
  - Filling in dead space
  - Used as a coating for the implant
  - Used as a filler for bone defects
- Risk assessment based on:

Pharmacist Screening

Pharmacist Screening High versus Low Risk

Pharmacist to Complete Section - Risk Determination (Past Medical History):

- ☐ Y ☐ N Age ≥ 75 years (2 points)
- ☐ Y ☐ N CrCl ≤ 50 ml/min (2 points)
- ☐ Y ☐ N History of Chronic Kidney Disease (CKD) (2 points)
- ☐ Y ☐ N Weight ≤ 55 kg (1 point)
- ☐ Y ☐ N Recent (or current) nephrotoxic drug exposure* (<96 hours) (1 point)

Total Score = _____ ≤1 = low risk or ≥2 = high risk

*Concurrent Nephrotoxin Exposure: Immunosuppressant (e.g. cyclosporine, tacrolimus, sirolimus), NSAIDs, ACE-I/ARB, IV contrast, aminoglycosides

- Keep calcium sulfate in a locked cage with release upon pharmacy approval
- Profile antibiotic dose administered on the MAR
- Monitor levels of systemic aminoglycoside and/or vancomycin on days 2, 5 and 7 or longer to ensure levels are non-sustained at levels > 0.5 mg/dL

ALBC Order Form and Risk Assessment

☐ **A: Cement (PMMA, non-absorbable, non-biodegradeable – Palacos®, Simplex®)**

☐ Tobramycin ____ g ☐ Vancomycin ____ g ☐ Other _____ (Amount per box/batch)

Total # of Boxes (1 box=1 batch): ____ boxes/batches (4 max)

Pharmacist Dose Screening Grid

Dosing Limits per Box/Batch (4 box/batch max)

Indication	High Risk	Low Risk
Treatment	Tobramycin 2.4g/batch Vancomycin 1 g/batch	Tobramycin 3.6g/batch Vancomycin 3g/batch
Prophylaxis	Pre-made Simplex and/or Palacos preparations including 0.5 - 1 g of tobramycin/gentamicin in PMMA	

Total dose tobramycin: _____
Total dose vancomycin: _____
Total dose other: _____
(Ex. Tobramycin 2.4 g per box x4 boxes = 9.6 g)

☐ **B: Absorbable / Biodegradeable Beads (Calcium Sulfate)**

☐ Tobramycin ____ g ☐ Vancomycin ____ g ☐ Other _____ (Amount per box/batch)

Total # of Boxes/Batches: _1_ box/batch (1 max)

Pharmacist Dose Screening Grid

Dosing Limits per Box/Batch (1 box/batch max)

Indication	High Risk	Low Risk
Treatment	Pharmacist to escalate to expert. Refer to Attachments 1 and 2 for Algorithm for Pharmacy Assessment	Tobramycin 1.2 g Vancomycin 1g
Prophylaxis		Tobramycin 1.2 g

Total dose tobramycin: _____
Total dose vancomycin: _____
Total dose other: _____
(Ex. Tobramycin 2.4 g per box x4 boxes = 9.6 g)

Pharmacist Screening

Pharmacist Screening High versus Low Risk

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Total Score = _____ ≤1 = low risk or ≥2 = high risk

*Concurrent Nephrotoxin Exposure: Immunosuppressant (e.g. cyclosporine, tacrolimus, sirolimus), NSAIDs, ACE-I/ARB, IV contrast, aminoglycosides

What Happened to Our Patient

- Discharged to skilled nursing facility with DNR status in November 2013
- Decided on no more dialysis but continued on cefazolin
- Discharged from SNF in December 2013 taking Bactrim suppression that was discontinued by August 2014
- He is age 93 with some impaired left knee mobility, low dose cyclosporine – 23 years post heart transplant
-

Summary

- In patients with comorbidities, acute kidney injury following treatment with antibiotic loaded cement (ABLC) can occur due to increased absorption of and decrease clearance of aminoglycosides
- Mitigation strategies include careful attention to the doses used in ABLC, particularly if PMMA is used with $CaSO_4$ and avoidance of drugs with nephrotoxic potential
- A pre-op pharmacy order form that ensures appropriate doses in ABLC might decrease the risk of AKI in this patient population

"IT DOESN'T REALLY MATTER WHAT THE DENOMINATOR IS WHEN YOU ARE THE NUMERATOR"

CDC Public Relations

BLOOD CULTURE CONTAMINATION AND ANTIMICROBIAL STEWARDSHIP

Can We Do Better?

- In 2005, the College of American Pathologist reported that the average contamination rate from 356 institutions was found to be approximately 3% and was adopted as a performance benchmark in 2007 by the Clinical and laboratory Standards Institute (CLSI)
- Definition: **1 sample** (1 or 2 bottles) was considered contaminated if one of the following organisms was present in ≤50% of all blood culture sets obtained from one patient on the same day: coagulase-negative staphylococci, alpha-hemolytic streptococci, *Micrococcus* species, *Propionibacterium* species, *Corynebacterium* species, and *Bacillus* species.

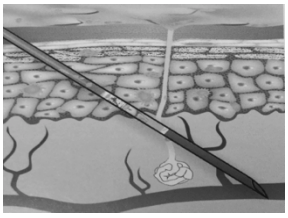
Blood Culture Contamination (BCC)

- Rates: BCC rates differ widely between institutions, frequently; recent survey of 89 hospitals indicated that:
  - 14% of hospitals exceeded 3%
  - 5% of hospitals unaware of rates.
- More than 1 million patients are placed at risk by a false positive blood culture results each year
- False positive blood cultures may fulfill criteria for NHSN's surveillance definition of central line-associated blood stream infection (CLABSI)
  - Sixty percent of the responders reported contaminated blood cultures as a CLABSI.
  - Reporting as a CLABSI can result in decreased funding (Hospital Acquired Condition – HAC)

Garcia RA et.al. Am J Infect Control 2018;46:571-6

Blood Culture Contamination

- Despite skin antisepsis, approximately 20% of bacteria are imbedded within deep layers of the epidermis and dermis.
- Sepsis Campaign: blood cultures should be obtained prior to starting antibiotic therapy and there is a rush to initiate antimicrobial therapy
- Estimated up to 50% of all blood cultures originate in the ED – may be higher due to Sepsis Campaign



Garcia RA. Am J Infect Control. 2015 Nov 1;43(11):1222-37
Makam AN. JAMA Intern Med. 2014 May;174(5):803-6.

A Community Tertiary Care Hospital

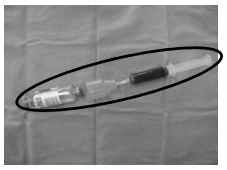
Metric	Results	
Total # of blood cultures	28,000 sets	
# if blood cultures drawn in ED	21,000 sets	
3% contaminated blood cultures	630 bottles	
Estimated extra cost (range)	$2,835,000 – $6,000,000	
Estimated increased length of stay	1260 – 3150 days	
Estimated cost of increased length of stay	$4,829,580 – $12,073,950	

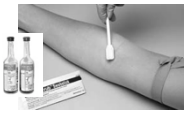
California
State/local government hospitals — $3,068
Nonprofit hospitals — $3,833
For-profit hospitals — $2,189

https://www.beckershospitalreview.com/finance/average-hospital-expenses-per-inpatient-day-across-50-states.html

Recommended Best Practice

- Phlebotomy teams
  - Phlebotomists had a false positive blood cultures rate of 3.1 which was better than the non-phlebotomists (5.6 and 7.4).
  - Comparison of median patient charges between negative and false-positive episodes ($18,752 versus $27,472) showed a $8,720 difference while the median length of stay increased from 4 to 5 days.
  - By utilizing phlebotomists to collect blood cultures in the ED, contamination rates were lowered to recommended levels, with projected reductions in patient charges of approximately $4.1 million per year
  - Baseline contamination rates associated with usual care, sterile kits, and phlebotomy teams were 4.34%, 1.68%, and 1.10%, respectively.





Gander RM. J Clin Microbiol. 2009 Apr;47(4):1021-4
Rupp ME. Clin Infect Dis. 2017 Jul 15;65(2):201-205.
Self WH. Infect Control Hosp Epidemiol. 2014 Aug;35(8):1021-8.
Self WH. Acad Emerg Med. 2014 Mar;21(3):274-82.

- Decrease line draws for blood cultures
- Blood diverting technology

Reduction in Blood Culture Contamination

- False positives increase laboratory costs by approximately 20%, are associated with a nearly 40% increase in antibiotic charges and can extend the length of hospital stay by up to 5 days.
- False positive blood culture rate decreased from 1.78% to 0.22% with use of an Initial Specimen Diversion Device (ISDD).

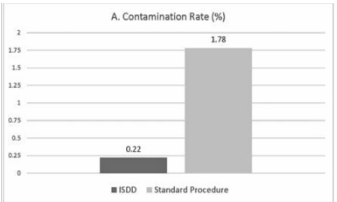
Table 2.

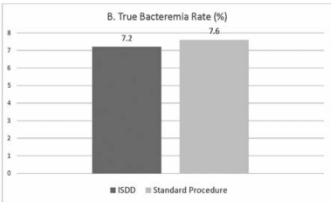
Poisson Regression Analysis of Blood Culture Contamination Rate in the Emergency Department for the Intervention Period (Nov 2014–Oct 2015) Compared to the Preceding and Following 6-Month Periods for All Patients Who Underwent Blood Culture

	Contamination Rate /1000 Blood Cultures		
Observation Period	Observed Rate	Model Estimated Risk vs Intervention (95% CI)	P value
All blood cultures			
Pre 6 mo (N 3454)	33.01	1.356 (1.068–1.723)	.013
Intervention (N 6697)	24.34	Reference	
Post 6 mo (N 3596)	28.09	1.154 (.90–1.48)	.258
Phlebotomist-drawn blood cultures			
Pre 6 mo (N 2684)	26.45	1.305 (.967–1.76)	.082
Intervention (N 5328[a])	20.28	Reference	
Post 6 mo (N 2905)	28.23	1.392 (1.045–1.855)	.024
Nurse-drawn blood cultures			
Pre 6 mo (N 770)	55.84	1.39 (.933–2.071)	.106
Intervention (N1369)	40.18	Reference	
Post 6 mo (N 435)	32.04	0.797 (.444–1.434)	.45

Abbreviation: CI, confidence interval.

[a]Blood cultures from all patients (those enrolled in the study as well as those who underwent blood culture by standard procedures and were not enrolled in the study) were analyzed.





Rupp ME, Clin Infect Dis. 2017 Jul 15;65(2):201-205.

Reduction in Blood Culture Contamination

- Baseline Emergency Department blood culture contamination rates (CBCR) varied between 1.6 and 2.1% (2013-16)
- As a Quality Improvement project, ED department-wide **education** was provided, the **number of staff** drawing blood cultures was limited, and the use of a **blood divertor device** was implemented.
- The CBCR fell to 0.8% over a 3 month trial period
- Using similar DRGs to compare patients with and without contaminated blood cultures (CBCs), a cost of $5200/CBCs was used
- The estimated increased length of stay was 3.2 days for patients with CBCs
- The estimate cost avoidance was $185,000 per year.

Allain, M. Clin Nurs Specialist 2018 May/June; E1-2

Differential Time to Positivity

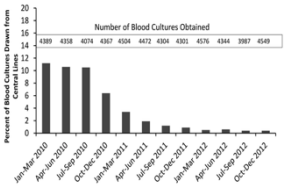
A Useful Method for Diagnosing Catheter-Related Blood Stream Infections

- 191 positive simultaneous central venous catheter and peripheral vein blood cultures were studied
- 108 catheter-related bacteremias (CRBs); 83 had non-CRBs
- CRBs were more frequently caused by staphylococci and less likely to be associated with underlying hematologic malignant conditions, neutropenia, and longer duration of hospitalization
- Differential time to positivity of 120 minutes or more was associated with 81% sensitivity and 92% specificity for short-term catheters and 93% sensitivity and 75% specificity for long-term catheters.

Raad I. Ann Intern Med 2004;140:18-25

Central Line Blood Draws and Contamination

Impact of a new blood culture policy that discouraged drawing blood samples from central lines



Results:

- The proportion of blood samples obtained for culture from central lines decreased from 10.9% to 0.4%.
- The proportion of blood cultures that were contaminated decreased from 84 (1.6%) of 5,274 to 21 (0.5%) of 4,245
- Estimated excess hospital costs of $3,000 per contaminated blood culture yielded an estimated annualized savings of $378,000 (2012 dollars) when compared to pre-intervention period
- Pre-intervention: 3 (30%) of 10 reported CLABSIs were suspected to represent blood culture contamination compared with none of 6 CLABSIs reported 20 months is the post-intervention period

Boyce JM. Infect Control Hosp Epidemiol. 2013 Oct;34(10):1042-7

Summary

- The bench of 3% as being an acceptable blood culture contamination (BCC) rate should be challenged
- BCC is associated with a variety of unintended consequences: patient safety and excessive costs
- Use of protocols to ensure proper disinfection of skin and avoidance of contamination and the use of phlebotomy teams may decrease the BCC rate
- Avoidance of central line draws and implementation of newer technologies of obtaining blood cultures can further reduce the risk of BCC

"THE BELT FASTENED WHILE RUNNING WILL COME UNDONE WHILE RUNNING"

Ethiopian Proverb