Goal

- Review some interesting and possibly practice changing studies in hospital medicine from the 12-18 months

Resources

- Society of Hospital Medicine Annual Meeting 2017
- Journal of Hospital Medicine
- Journal Watch
- ACP Hospitalist
- The Hospitalist
- Annals for Hospitalists
Topics

- Venous Thromboembolism
- Contrast Nephropathy
- Oxygen use in ACS
- Outcomes based on physician age and gender
- Bacteremia
- Five-second rule

Case #1

- 54 year old healthy male is admitted to the hospital for a right lower extremity DVT. No recent travel or surgery. No recent hospitalization.
- ROS negative
- No medications
- No family history of VTE
- No tobacco, alcohol or recreational drug use, malpractice lawyer
- Normal colonoscopy and PSA 3 months prior
- Exam:
  - T 98.2 P 90, BP 134/80, RR 14, Sat 98% RA
  - Comprehensive exam is remarkable only for RLE swelling
- Data: US RLE proximal DVT, Cr 0.8, Hgb 14.2, PTT normal, LFTs normal, UA nl, CXR NAD
- You diagnose him with an unprovoked DVT and start him on rivaroxaban

What additional work-up would you do in the hospital prior to discharge?
A. CT chest, abdomen and pelvis to screen for malignancy
B. Thrombophilia work-up now
C. CT of chest, abdomen and pelvis and a thrombophilia work-up now
D. Discharge the patient on rivaroxaban for a minimum of 3 months with consideration of outpatient thrombophilia work-up
Do not perform thrombophilia testing at the time of VTE diagnosis or during the initial 3-month course of anticoagulant therapy.

Forgo thrombophilia testing when:

- A patient has a provoked venous thromboembolic event
- You do not intend to discontinue anticoagulation (i.e., anticoagulation is indefinite)
- The patient is in the acute (e.g., inpatient) setting
- The patient is on anticoagulants that may render test results uninterpretable
- The patient is pregnant or on oral contraceptives
- Use of alternative patient characteristics and laboratory markers to predict venous thromboembolism recurrence may be an option.
**Thrombophilia Testing**

- Retrospective cohort study
  - July 1, 2014 – December 31, 2014
- Patients > 18 years of age who had thrombophilia testing during an ER or inpatient visit
- 163 patients
  - 1451 thrombophilia tests

**Main Measurement:** Proportion of tests associated with minimal clinic utility
- Discharged before results available
- Test type not recommended
- Testing in situation associated with decreased accuracy
- Duplicate testing
- Testing following a provoked thrombotic event
Testing Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of tests</td>
<td>158</td>
</tr>
<tr>
<td>Number of false positives</td>
<td>22</td>
</tr>
<tr>
<td>Number of false negatives</td>
<td>149</td>
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Results

<table>
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Indication for Testing

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Asthma</td>
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</tr>
<tr>
<td>Sinusitis</td>
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<td>34</td>
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<tr>
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<td>25</td>
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<td>12</td>
</tr>
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<td>10</td>
</tr>
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<td>6</td>
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Results

- 77% of testing met criteria for minimal clinical utility
- 9% of tests were positive
- 1% of patients had anticoagulation initiated because of testing
- 1% of patients had documentation of clear genetic counseling

Discussion

- Limitation: Retrospective, large referral center, relied on provider notes and documentation
- Bottom line: Most testing done inpatient was of minimal clinical utility

Some Reasons Not to Test

- Many thrombophilia tests are inaccurate in the setting of acute VTE and/or anticoagulation
- Results of testing often do not influence management
- Testing in most cases is not cost-effective
- Testing may result in unnecessarily prolonged anticoagulation courses
- Testing may result in unnecessary involvement of inpatient consultants
- A positive test result may lead to unnecessary patient anxiety
How Do We Fix It

• Provider education
• Hard Stops in EMR
• Removing/limiting use of thrombophilia panels
• Requiring specialty consultation prior to testing

Case #1

What additional work-up would you do in the hospital prior to discharge?
A. CT chest, abdomen and pelvis to screen for malignancy
B. Thrombophilia work-up now
C. CT of chest, abdomen and pelvis and a thrombophilia work-up now
D. Discharge the patient on rivaroxaban for a minimum of 3 months with consideration of outpatient thrombophilia work-up

Case #1 Part 2

• Patients is admitted 12 months later for a CAP. He is treated successfully with guideline based therapy and on the day of discharge wants to discuss his rivaroxaban. He has seen and heard a lot on TV and radio about rivaroxaban and bleeding risk. He and his wife are concerned about this risk. After discussion he is adamant about stopping the medication or at a minimum reducing the dose.

Bleeding risk assessment: Low Risk
Which of the following would you recommend?

A. Stop rivaroxaban with no additional therapy
B. Decrease the dose of rivaroxaban to 10 mg daily
C. Stop rivaroxaban and start aspirin 100 mg daily
D. Change rivaroxaban to warfarin with a goal INR 2-3

Study Specifics

- Randomized, double-blind, phase 3 study
- 3396 patients with venous thromboembolism:
  - Rivaroxaban 20 mg daily
  - Rivaroxaban 10 mg daily
  - Aspirin 100 mg daily
- All patients had completed 6-12 months of anticoagulant
- Sponsored by Bayer Pharmaceuticals.
Study Specifics

- **Inclusion**
  - >18 years of age
  - Completed 6-12 months of therapy of guideline-based therapy
  - No interruption of therapy for > 7 days
- **Exclusion**
  - Contraindication to continued anticoagulant therapy
  - Required extended anticoagulant therapy at therapeutic doses or antiplatelet therapy.

Outcomes

- **Primary efficacy outcome**
  - Composite of symptomatic, recurrent fatal or nonfatal venous thromboembolism and unexplained death for which pulmonary embolism could not be ruled out.
- **Secondary Outcomes**
  - Myocardial infarction, ischemic stroke, systemic embolism, venous thrombosis in locations other than the deep veins of the lower limbs, and death from any cause.

Safety Outcomes

- **Primary**
  - Major bleeding
- **Secondary**
  - Clinically relevant non-major bleeding, a composite of major or clinically relevant non-major bleeding, and non-major bleeding that led to study-drug interruption for more than 14 days.
Major Bleeding

- Overt bleeding with:
  - Drop in the Hgb level of 2 g/dl
  - Transfusion of 2 or units of red cells
  - occurred in a critical site
  - contributed to death.

Non-Major Bleeding

- Overt bleeding that did not meet the criteria for major bleeding but required:
  - Medical intervention
  - Unscheduled contact with a physician.
  - Interruption or discontinuation of the study drug
  - Discomfort or impairment of activities of daily living

PATIENTS

<table>
<thead>
<tr>
<th>Event — no. (%)</th>
<th>Placebo</th>
<th>Enoxaparin 30 mg</th>
<th>Enoxaparin 60 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>565 (51.0)</td>
<td>565 (58.3)</td>
<td>577 (51.0)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>381 (34.4)</td>
<td>383 (33.8)</td>
<td>366 (32.4)</td>
</tr>
<tr>
<td>Both DVT and PE</td>
<td>155 (13.6)</td>
<td>179 (15.9)</td>
<td>181 (16.0)</td>
</tr>
<tr>
<td>Non-venous PE</td>
<td>6 (0.5)</td>
<td>2 (0.2)</td>
<td>7 (0.4)</td>
</tr>
</tbody>
</table>

Approximately 40% of patients in each study arm had an unprovoked DVT.
**Bleeding**

<table>
<thead>
<tr>
<th>Study Drug and Dose</th>
<th>Major Bleeding %</th>
<th>Clinically Relevant Non-Major Bleeding %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban 20 mg</td>
<td>0.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Rivaroxaban 10 mg</td>
<td>0.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Aspirin 100 mg</td>
<td>0.3</td>
<td>1.8</td>
</tr>
</tbody>
</table>

**DISCUSSION**

- NNT to prevent recurrent VTE in comparison to aspirin
  - 33 with 20 mg dose
  - 30 with 10 mg dose
- No statistically significant increase in risk of major or non-major bleeding
Limitations

- Excluded patients with indications for ongoing anticoagulation so unsure of benefit of lower dose rivaroxaban in this population

Current Guidelines

- Unprovoked DVT
  - 3 months if high bleeding risk (IB)
  - Extended therapy (no scheduled stop date) if low or moderate bleeding risk (2B)
  - Aspirin recommended if stopping anticoagulant therapy

Which of the following would you recommend?

A. Stop rivaroxaban
B. Decrease the dose of rivaroxaban to 10 mg daily
C. Stop rivaroxaban and start aspirin 100 mg daily
D. Change rivaroxaban to warfarin with goal INR 2-3
Take Home Point

- Consider low dose rivaroxaban as an option when stopping anticoagulation in patients with DVT
- Especially those with an unprovoked event

Case #2

- A 64 year old female with a PMH of Hypertension and G3bA1 CKD presented to the ER with acute onset of pleuritic chest pain and shortness of breath. Non-massive hemoptysis. She did undergo right total knee arthroplasty 3 weeks ago.
- Physical Exam: T 99.4 HR 108, RR 22, BP 104/60, O2 Sat 92% on RA
- CHEST: CTA bilaterally
- CV: Regular, S1 and S2, no M/R/G, no elevated JVP
- EXT: No edema or asymmetry
- Wells score = 6
- CR 1.6, eGFR 44, CXR NAD

Case #2

- What is most appropriate next step in the management of this patient?
  A. CT angiography
  B. Anticoagulation and V/Q Scan on Monday when tech is available
  C. D-Dimer
Contrast Nephropathy

- Risk ranges from 1-20%
- Reasons for discrepancy
  - Varying definitions of contrast induced nephropathy
  - Differences in rates of contrast nephropathy for procedures vs. CT
  - Differing characteristics of patients populations
  - Routine use of low-osmolar contrast vs. prior use of high-osmolar contrast

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Study Specifics

- Single-center retrospective cohort study
- 17,934 ED visits for patients who underwent:
  - Contrast-enhanced CT
  - CT without contrast
  - No CT
- 5-year period (2009 to 2014)

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Risk of Acute Kidney Injury After Intravenous Contrast Media Administration

Jeremiah S. Herson, MD, PhD; Michael P. Danis, MD, MPH; Derek M. Pine, MD; Stacia K. Rubenstein, MD, PA-C; Matthew F. Touijer, BS; Richard E. Rothman, MD, PhD; Gui-Y. Han, MS, PhD

*Corresponding Author. E-mail: jherson@cumc.columbia.edu*

http://dx.doi.org/10.1016/j.annemergmed.2016.11.021
Study Specifics

• Logistic regression modeling and odds ratios with and without propensity-score matching
• Independent association between contrast administration and primary and secondary outcomes.

Outcomes

• Primary outcome
  – Incidence of AKI
• Secondary Outcomes
  – New chronic kidney disease, dialysis, and renal transplantation at 6 months

Inclusion Criteria

• 18 years and older
• CT with or without contrast enhancement
• Serum Cr level measured in the 8 hours before CT
• A second Cr level measured 48 to 72 hours after CT
Exclusion Criteria

- Serum Cr level less than 0.4 mg/dL
- Serum Cr ≥ 4.0 mg/dL
- Insufficient serum Cr level data
- A history of renal transplant or ongoing or previous dialysis
- An ED visit in the 6 months before the study start date
- A CT scan performed in the 6 months preceding the index ED visit
- A contrast-enhanced CT performed within 72 hours of ED departure

Definitions

- **Contrast Nephropathy**
  - Increase in serum creatinine level ≥ 0.5 mg/dL
  - ≥25% increase over baseline serum Cr level
  - Timing 48-72 hours after CT

- **AKI**
  - KDIGO Guidelines

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272,791 patient visits without CT scan on 113,602 patients

Excluded
1. CT scan at other vix (13,578)
2. No initial SC (11,817)
3. No follow-up SC (31,975)
4. ED encounter in 168 days prior to start date of study (11)
5. History of dialysis/renal transplant (448)
6. Initial SC ≤ 0.3 or ≥ 4.0 mg/dL (355)
7. SCCT < 72 hours after ED departure (906)

Final Inclusion
17,931 patient visits 16,802 patients

7,361 CT scans with contrast
5,499 CT scans without contrast
5,234 patients without CT

80,729 patient visits with CT scan on 54,740 patients

Excluded
1. No initial SC (10,830)
2. No follow-up SC (9,937)
3. CT Scan in the prior 6 months (4,734)
4. ED encounter in 168 days prior start date of study (499)
5. History of dialysis/renal transplant (482)
6. Initial SC ≤ 0.3 or ≥ 4.0 mg/dL (479)
7. SCCT < 72 hours after ED departure (430)
No difference in Risk of AKI between contrast and non-contrast enhanced CT

Only 18 patients with a GFR <45 underwent a contrast enhanced CT

Limitations

- Did not account for nephron-protective or nephron-toxic interventions performed after the patient left the ER
- Most patients with GFR >45
- Significant selection bias
  - ER doctors less likely to order CT in those they felt were at high risk

http://dx.doi.org/10.1016/j.annemergmed.2017.06.041
Outcomes

• Primary Outcome
  – Development of AKI in individuals receiving contrast enhanced CT compared with those who had a contrast enhanced CT

• Secondary Outcomes
  – Renal replacement therapy
  – All cause mortality

| Incidence | 2.1-26% |
Results

• NO difference in the rates of renal insufficiency, need for dialysis, or mortality between patients receiving contrast-enhanced CT versus those receiving non-contrast CT

Limitations

• Observational data
• Most retrospective
• Selection bias
• Heterogeneity of included studies
  – Type of contrast
  – Setting
  – Patient population
  – Definitions of AKI
Strengths

- Large dataset
- Multiple patient populations
- Given the unlikelihood of a randomized controlled trial this is likely the best data we will get

Key Point

- Only included patients undergo CT with contrast NOT other contrast procedures (angiography)

ACR Guide on Contrast Media

- At the current time, there is very little evidence that IV contrast material is an independent risk factor for AKI in patients with eGFR ≥30 mL
- Therefore, if a threshold for CIN risk is used at all, 30 mL/min/1.73m² seems to be the one with the greatest level of evidence
Take Home Points

• We may have overestimated the risk of post-contrast AKI
• No real cutoff for GFR
  – Data and ACR suggest those with GFR <30 may be at greatest risk
  • Radiology. 2013 Sep;268(3):719-28
• Individual patient risk and the indication for the test should be your guide
  – Suspect PE in patient with GFR 45 → CTA angiogram

Case #2

• What is most appropriate next step in the management of this patient?
  A. CT angiography
  B. Anticoagulation and V/Q Scan on Monday when tech is available
  C. D-Dimer

Case #3

• 72 year old present with 4 hours of chest pain. Pain relieved with 3 NTG
• O2 saturation 98% on RA
• EKG: NSR, NS ST-T wave changes
• Troponin 2.4
Case #3

- Should this patient be given supplemental oxygen?
  A. Yes
  B. No
  C. Maybe

Oxygen Therapy in Suspected Acute Myocardial Infarction
Robin Hofmann, M.D., Stefan K. Jørgen, M.D., Ph.D.,
Tomas Jendeborg, M.D., Ph.D., Bent Lindahl, M.D., Ph.D.,
David Elinge, M.D., Ph.D., Nils Witt, M.D., Ph.D., Gabriel Antikak, M.D.,
Mats Fiek, M.D., Ph.D., Jaakko Alliksdottir, M.D., Ph.D.,
Lennart Nilsson, M.D., Ph.D., Annica Ram-Fischer, M.D., Ph.D.,
Elvira Omerovic, M.D., Ph.D., Thomas Kellen, M.D., David Sparr, B.Sc.,
Ulf Ekelund, M.D., Ph.D., Richard Linder, M.D., Ph.D.,
Mattias Ekstrom, M.D., Ph.D., Jörg Lucern, M.D., Urban Haag, B.Sc.,
John Peres, M.D., Ph.D., Ole Øst, M.D., Ph.D., Johan Hertel, M.D., Ph.D.,
and Laila Svensson, M.D., Ph.D., for the DETOX-SWEDEHEART Investigators*
Trial Specifics

• Registry-based, multiple center, open label randomized clinic trial
• Patient with suspected MI with an O2 saturation > 90%
  – Supplemental oxygen 6 liters per minute for 6-12 hours
  – Ambient air
• Primary endpoint:
  – Death from any cause within one year of randomization

Trial Specifics

• Inclusion criteria
  – >30 year of age
  – Symptoms suggestive of MI for <6 hours
  – O2 sat of 90% or higher
  – ECG indicating ischemia or elevated troponin levels
• Exclusion
  – Ongoing oxygen therapy
  – Presentation with cardiac arrest
Results

Key Point

• No beneficial effect of oxygen treatment with respect to all-cause mortality at 1 year
There is no evidence from randomised controlled trials to support the routine use of inhaled oxygen in people with AMI, and we cannot rule out a harmful effect.

Other Data

- **AVOID trial STEMI**
  - Larger myocardial infarcts in patients assigned to oxygen group
  - Circulation 2015;131:2143-50

- **SOCCER Trial**
  - Oxygen had no effect on infarct size
  - Eur J Emerg Med November 13, 2016 Epub
Take Home Point

- Newer data suggest that oxygen therapy in non-hypoxemic patients with AMI does not improve outcomes

Provider and Outcomes

- Women physicians had lower 30 day mortality and readmission rates
Provider and Outcomes

- Older physicians had higher mortality than patients cared for by younger physicians
- Exception: Physicians treating high volumes of patients
  - >201 admissions per year
  - 1.08 admission per day if working a 7 on and 7 off model

Case #3

- 64 year old admitted for cellulitis on IV cefazolin who has been afebrile for 48 hours spikes a T to 102.1
- Blood cultures on admission were negative
- He has normal food consumptions and no shaking chills
- Should be get blood cultures on this patient?
Our Reflex

Study Specifics

- Prospective cohort study at VA medical center
- Included all hospitalized patients on a medical service for whom a blood culture was obtained
- Main Outcomes:
  - Rate of true positive blood cultures
  - Predictors of true positive blood cultures
Results

<table>
<thead>
<tr>
<th>Indication</th>
<th>LR of a True Positive Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>0.6 (0.2-1.7)</td>
</tr>
<tr>
<td>Fever and Leukocytosis</td>
<td>1.1 (0.5-2.4)</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>1.1 (0.3-4.0)</td>
</tr>
<tr>
<td>Fever and Other Indications</td>
<td>1.1 (0.5-2.4)</td>
</tr>
<tr>
<td>Follow-up of Previous Positive Culture</td>
<td>3.4 (1.8-6.5)</td>
</tr>
</tbody>
</table>
## Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>LR for True Positive Blood Culture</th>
<th>LR for False Positive Blood Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>0.1 (0.0-1.9)</td>
<td>1.8 (0.8-4.1)</td>
</tr>
<tr>
<td>Bacteremia/Endocarditis</td>
<td>3.7 (2.5-5.7)</td>
<td>0.5 (0.1-3.0)</td>
</tr>
<tr>
<td>UTI</td>
<td>2.5 (1.7-3.2)</td>
<td>0.9 (0.3-3.4)</td>
</tr>
<tr>
<td>Non-infectious Diagnosis</td>
<td>0.3 (0.0-1.8)</td>
<td>2.3 (1.1-4.6)</td>
</tr>
</tbody>
</table>

## Recent Antibiotic Exposure

<table>
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<th>Recent Antibiotic Exposure</th>
<th>LR for True Positive Blood Culture</th>
<th>LR for False Positive Blood Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>0.4 (0.2-0.8)</td>
<td>0.6 (0.3-1.2)</td>
</tr>
<tr>
<td>No</td>
<td>2.1 (1.6-2.7)</td>
<td>1.6 (1.0-2.5)</td>
</tr>
<tr>
<td>No with Fever</td>
<td>2.4 (1.2-4.0)</td>
<td>0.8 (0.2-3.6)</td>
</tr>
<tr>
<td>No with fever and leukocytosis</td>
<td>5.6 (1.8-18.2)</td>
<td>0.4 (0.1-2.6)</td>
</tr>
</tbody>
</table>

## Putting It All Together

- **Increased likelihood of TRUE positive**
  - Follow-up of previous positive cultures
  - Diagnosis of bacteremia/endocarditis
  - Lack of prior antibiotic exposure
- **Decreased Likelihood of TRUE positive culture**
  - Previous exposure to antibiotics
A Few Scenarios

• No antibiotics, fever and leukocytosis
  – Likelihood ratio 5.6
  – Assuming a true positive rate of 3.6% the probability of a positive culture would be 17.3%

• Treated for pneumonia already on antibiotics
  – LR 0.4
  – Probability of a true positive culture 1.5%

Limitations

• Based on physician chosen indication which may not correlate with actual clinical picture
• No evaluation of harm of not ordering a blood culture
• Did not assess the value of a true negative blood culture
• VA hospital
• Patients on general medical ward

Our Reflex Might Be Wrong

CAVEAT: DON'T FORGET ABOUT CMS CORE MEASURES FOR SEVERE SEPSIS
CMS Measures for Severe Sepsis

- Measure serum lactate
- Obtain BLOOD CULTURES prior to antibiotics
- Administer Antibiotics
- Repeat serum lactate if initial >2

Take Home Point

- Yield of blood cultures in the inpatient setting is low
- In the end you have to weigh the low true positive rate against the consequence of missing a blood stream infection and/or a core measure
Study Specifics

- Prospective multicenter observational study
- Three hospitals in a large Japanese city
- 1943 patients age 14-96 who have blood cultures drawn from April 2013 to August 2014
- Excluded patients with anorexia-inducing conditions

Study Specifics

- Looked at meal consumption immediately prior to the blood culture
  - Normal defined as >80%
- Looked for history of shaking chills

Bacteremia group:
1) Higher T, HR, RR, and CRP
2) Shaking chills = 23% vs. 4.9%
3) Low food consumption = 78% vs. 48.6%
Results

- Pre-test probability of true bacteremia was in all patients – 2.4%
- Pre-test probability of bacteremia in those with shaking chills and low food consumption – 47.7%
Take Home Points

- Shaking chills and low food consumption were associated with a higher probability of true positive blood cultures
- Simple bedside assessment that may increase the yield of blood cultures in hospitalized patients

Case #4

- In patients with S. Aureus bacteremia which of the following measures improve mortality?
  A. Appropriate antibiotics
  B. Echocardiography
  C. ID Consultation
  D. All of the above

Study Specifics

- Retrospective observational cohort study
- All patients admitted to the VA hospital who had S. aureus bacteremia from 2003-2014
- 36,868 patients in 124 hospitals
  - 19,325 MRSA
  - 17,543 MSSA

Results

- Echo, ID consultation and appropriate antibiotics therapy all reduced mortality
Combining ID consultation, echo and appropriate antibiotics markedly reduced mortality (OR 0.33)

Discussion

• Definitely some limitations with VA population and retrospective observational study
• However compelling data to suggest these process improve overall mortality
Take Home Point

- The following measures should likely be standard in S aureus bacteremia
  - Appropriate antibiotics
  - Echo
  - ID consult

The Study

- Four surfaces
  - Tile, Stainless steel, wood and carpet
  - Surfaces with inoculated with 1 ml of fluid containing Enterobacter aerogenes
- Four foods
  - Watermelon, gummy candy, bread, bread with butter
- Contact times
  - <1 s, 5 s, 30 s, 300 s
Bottom Line

• Don’t trust the 5 second rule especially with watermelon

What Did We Learn

• Think at least twice before doing a thrombophilia work-up in the hospital
• Consider low dose rivaroxaban after stopping full anticoagulation for DVT
• Recognize that the risk of contrast nephropathy in patients with GFR >30 is not as high as we might think
• Do not routinely give oxygen to non-hypoxemic patients admitted with ACS
• Choose your physician carefully
• Do not routinely reflex to culture in patients who “spike” while hospitalized
• Consider echo and ID consultation in addition to appropriate antibiotics in patients with S. aureus bacteremia
• Do not rely on the 5 second rule