Project ECHO: Intermountain Healthcare HOSPITALIST MEDICINE

Oral antibiotics for Endocarditis, Osteomyelitis: MRSA bacteremia, emerging antibiotic approaches

Brandon Webb, MD
Division of Infectious Diseases and Clinical Epidemiology, Intermountain Healthcare
Clinical Assistant Professor (Affiliated), Stanford Medicine
IMC and LDS Hospitals

Case #1 – Presented by Charlie Ayers, MD

- 68 yo woman with depression and HLD was in a restrained MVA and was admitted to Trauma at IMC with rib fractures and a splenic subcapsular hematoma. She was discharged to a SNF after an uneventful course.
- She was brought back to the IMC ER 5 days later in respiratory distress with altered mental status. In the ER she was febrile with 24% bands on her diff. A RUL infiltrate was seen on CXR. She was given vancomycin, ceftriaxone, and azithro.
- She was admitted to the ICU with shock, respiratory failure, and acute kidney injury.
- Blood cultures grew gram positive cocci, identified by pcr as MRSA.
- **Antibiotics were changed to ceftaroline and daptomycin.**

Case #1

- Diagnoses:
  - MRSA Bacteremia, persistent, with positive cultures for 5d
  - Spontaneous cervical epidural abscess with discitis/vertebral osteomyelitis
- Course:
  - Taken to the OR on day 5 for evacuation of C6 – C7 epidural abscess
  - Cultures became negative on day 6
  - Received 6 days of ceftaroline/daptomycin
  - Was transitioned back to vancomycin on day 8
  - Completed 6 weeks of IV vancomycin and followed up in ID clinic.

Disclosures

The speaker has no significant financial conflicts of interest to disclose.

Objectives

At the conclusion of this session, participants will:

- recognize a new antibiotic strategy for complicated MRSA Bacteremia
- analyze the evidence supporting the use of this strategy
- recognize situations in which oral antibiotics may be used in the treatment of blood stream infections, osteomyelitis, joint infections, and endocarditis.

Background

Staphylococcus aureus bacteremia is perhaps the prototypical infectious disease condition

MRSA bacteremia (MRSAB) is associated with poorer outcomes, mortality up to 30%[1]

Vancomycin has been the mainstay of therapy for 3 decades

Unlike sepsis, PE, heart failure, no improvement in MRSAB outcomes has been observed since the 1990's

Better treatment is needed to improve MRSAB treatment

van Hal SJ et al. *Clinical microbiology reviews.* 2012;25:362-386.

Vancomycin

Vancomycin has recognized limitations:

- Slow cidal activity, magnified in high-inoculum settings
- Heteroresistance
- Nephrotoxicity
- Limited tissue distribution

All of these factors have been proposed as possible contributors to poorer outcomes in MRSAB compared to MSSAB

Newer Agents

Daptomycin (Cubison)

- Cyclic lipopeptide approved for treatment of MRSA bacteremia and endocarditis.
- IDSA-guideline recommended alternative first-line therapy
- In the original Phase III study, 44% of daptomycin treated patients achieved the primary endpoint compared to 32% of vancomycin

Ceftaroline

- Novel fifth-generation cephalosporin with high-affinity for penicillin-binding protein 2a conveying potent activity against MRSA
- Ceftaroline has been shown in multiple studies to be effective in MRSAB, both as primary monotherapy and salvage after vancomycin failure

Combination Data

Early effective therapy is associated with improved outcomes

Daptomycin plus beta-lactams results in synergistic decrease in kill time due to enhanced membrane depolarization

- Even observed when the beta-lactam lacks activity against MRSAB; capable of restoring daptomycin susceptibility

Daptomycin plus ceftaroline associated with enhanced, highly bactericidal activity *in vitro*.

Modeling simulations suggest synergistic effect is realized within first 4-8 days of treatment

Clinically, multiple studies confirm efficacy of this combination as a salvage, best if started within 72h in complicated cases

Geriak et al. AAC May 2019 63(5):e02483-18

40 patients with with MRSAB at Henry Ford, San Diego and Rhode Island

Randomized within 72 hours of diagnosis to daptomycin 6 to 8 mg/kg every 24 hours plus ceftaroline 600 mg IV every 8 hours or vancomycin or daptomycin monotherapy.

The combination therapy was administered for a median 8 days.

Groups were very similar in demographics, comorbidities, severity and Pitt bacteremia score.

An endovascular source was noted in roughly half of patients, with a soft-tissue source identified in the other half.

Geriak et al. AAC May 2019 63(5):e02483-18

The study was terminated early due to mortality difference:

6/23 (26%) of patients in the monotherapy group experienced in-hospital mortality

0/17 patients in the combination group

This effect was isolated to patients with complicated (endovascular infection).

This study will not be replicated due to loss of equipoise.

Assessment

Financial impact is of greatest interest:

- Direct drug costs for this regimen ($622.59 per day) are clearly greater than for vancomycin (est. $75 per day with monitoring)
- Overall financial impact would be heavily influenced by outcomes benefit including length of stay
- Adverse events and compliance would also be important

Infectious Diseases- Antibiotic Stewardship
Joint Endorsed Preferred Practice:

Daptomycin 6 to 8 mg/kg every 24 hours plus ceftaroline 600mg IV every 8 hours as initial therapy for complicated* MRSAB

Early de-escalation to monotherapy after clearance of bacteremia.

* Complicated bacteremia: Any of the following: 1) Severe sepsis or septic shock, 2) endovascular site of infection, 3) involvement of indwelling prosthetic material, including valves, vascular grafts, joints and cardiac devices (but excluding venous catheters that are removed) 4) metastatic sites of infection including septic pulmonary emboli, 5) osteoarticular infection including osteomyelitis, septic arthritis or tenosynovitis, 6) vertebral osteomyelitis/discitis or epidural abscess, 7) deep or complex soft tissue infection such as myositis, iliopsoas abscess, perinephric abscess, etc.

Project ECHO® Intermountain Healthcare Utah

Intermountain® Healthcare

Proposal Details

1. No change in initial empiric vancomycin therapy
2. Infectious Disease consultation and switch to daptomycin PLUS ceftaroline as soon as MRSAB is confirmed by molecular or PBP2a testing.
3. Initial recommendations to initiate therapy may originate with Antimicrobial Stewardship, contingent on ID consultation
4. All other management, including an emphasis on source control, to remain per standard of care for S. aureus bacteremia.
5. Strong recommendation to transition to monotherapy, agent per clinician choice (including vancomycin), once blood cultures are negative for at least 48 hours.

Proposed Exclusions

1. MRSAB secondary to primary MRSA pneumonia (excluding septic emboli) or meningitis.
2. History of serious adverse drug event to either daptomycin or ceftaroline.
3. History of severe beta-lactam hypersensitivity or hypersensitivity to cephalosporins.
4. *In vitro* resistance to either daptomycin or ceftaroline
5. Consider exclusion if lack of drug availability leads to a delay of >72 hours and at the time of drug availability the patient no longer classifies as complicated.

Case #2 – Presented by Kory Anderson, MD

- 67 yo man with recent large MCA stroke treated with thrombectomy complicated by respiratory failure and AKI in Las Vegas.
- Admitted to McKay Dee Hospital with recurrent respiratory failure and worsening kidney injury requiring dialysis. A dialysis catheter was placed.
- The catheter became infected. He suffered 5 days of MRSA bacteremia.
- The catheter was removed and replaced.
- He was treated with vancomycin and received a total 6 weeks.
- Should he have received ceftaroline/daptomycin?

Case #3 – Presented by Jeff Miller, MD
Transition to Oral Antibiotics for a Blood Stream Infection

- 81 yo man with multiple comorbidities including diabetes with chronic foot wounds and dementia was admitted with altered mental status and sepsis.
- He was empirically started on vancomycin and ertapenem.
- Source identified was a UTI, and vancomycin was stopped.
- Blood and urine cultures grew Enterobacter cloacae sensitive to fluoroquinolones and trimethoprim/sulfa.
- Repeat blood cultures were negative, and he was transitioned to oral Bactrim.
- Total course completed was 7 days.

Oral Antibiotics

Clinical Infectious Diseases

Seven versus fourteen Days of Antibiotic Therapy for uncomplicated Gram-negative Bacteremia: a Non-inferiority Randomized Controlled Trial

RCT of 604 adults with GNR bacteremia:

- Afebrile and clinically stable by day 5
- Had source control

→ Randomized to 7 vs. 14 days of antibiotics

→ Primary outcome: Composite of all-cause mortality, clinical failure, re-admission, LOS>14d (at 90 days)

Yahav et al, Clin Infect Dis 2018. Dec 11 Epub.

Project ECHO® Intermountain Healthcare Utah

Intermountain® Healthcare

Yahav et al.

Patient Characteristics and Results

Characteristics

- Groups well balanced (25% ICH)
- Bacteria:
  - 90% Enterobacteriaceae (19% ESBL)
  - 8% Pseudomonas
- Source:
  - Urinary 68%
  - Intra-abdominal 12%
  - Unknown source 8%
  - Resp 4%, CVC 6%, SSTI 1%

Results

- No difference in primary composite outcome or individual components
- No difference based on source (urinary or not) or resistance (MDR or not)
- Patients in 7-day group had quicker return to baseline (2 vs 3 days, p=.01)
- No difference in adverse effects, *C diff*

Yahav et al, Clin Infect Dis 2018. Dec 11 Epub.

Project ECHO® Intermountain Healthcare Utah

Intermountain® Healthcare

Yahav et al.

- PO antibiotics for part of the course: 64% of short, 81% of long group
- IV to PO transition not standardized

IV Antibiotics

- 54% Cephalosporin
- 22% BL/BLI
- 12% Aminoglycoside
- 5% Fluoroquinolone
- 6% Carbapenem

PO Antibiotics

- 74% Fluoroquinolones
- 18% beta-lactams
- 8% TMP-SMX

Yahav et al, Clin Infect Dis 2018. Dec 11 Epub.

Project ECHO® Intermountain Healthcare Utah

Intermountain® Healthcare

Tamma et al.

What's New? → Oral Step Down Rx for GNR Bacteremia

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia

Retrospective study of 1478 adults with Enterobacteriaceae bacteremia:

- Clinically stable
- Able to take PO
- Had source control

→

- By day 5: oral step-down therapy vs continued IV therapy
- Both groups got 14d

→

Primary outcome: 30-day all-cause mortality

Tamma et al, JAMA IM 2019, Jan 22 Epub.

Project ECHO® Intermountain Healthcare Utah

Intermountain® Healthcare

Tamma et al.

Characteristics

- Propensity matched cohort (45% ICH)
- Bacteria:
  - 80% *E coli* and *Klebsiella*
  - 12% *Enterobacter*
- Source:
  - Urinary 40%
  - GI tract 20%, Biliary tract 14%
  - Central line 18%
  - Respiratory 4%
  - SSTI 3%

Results

- No difference in mortality or recurrent bacteremia
- Oral step-down therapy group had shorter LOS (5 vs 7 days, p<.001)

Tamma et al, JAMA IM 2019, Jan 22 Epub.

Project ECHO® Intermountain Healthcare Utah

Intermountain® Healthcare

Oral Antibiotics for BSI

Situations where IV to oral antibiotic transition for BSI is never best practice:

1. Staphylococcus aureus bacteremia
2. Endovascular infection
3. High risk for endovascular infection (unknown source, history of IE, indwelling cardiac devices, structural valve disease)
4. High-grade *gram-positive* bacteremia (e.g. persistent on more than one day)
5. Uncontrolled source
6. Impaired gastrointestinal absorption or unable to safely or compliantly take oral medications
7. If best-practice management of a concomitant site of infection requires initial intravenous antibiotics (e.g. septic arthritis).
8. Absolute neutrophil count currently <500
9. If clinical stability criteria have not been met

Oral Antibiotics for BSI

Situations where IV to oral step down to complete an appropriate course of antibiotics *may be appropriate:**

***ONLY APPROPRIATE IF: 1) *NO* criteria from list A are met, 2) the patient has met clinical stability criteria and 3) the case has been discussed with ID or Antibiotic Stewardship provider**

1. Intra-abdominal, pleural, soft-tissue and *select* osteoarticular infections with definitive surgical source control
2. Uncomplicated gram-negative BSI where the following criteria are met: 1) susceptibility to a highly bioavailable agent (fluoroquinolone, TMP-SMX, cephalexin, amoxicillin) and 2) no contraindications to these agents are present (hypersensitivity, QTc prolongation, drug-drug interractions, etc).
3. Bacteremic streptococcal pneumonia (pneumococcal, alpha- and beta-hemolytic streptococci)
4. Uncomplicated line-associated BSI after line removal
5. Anaerobic BSI

Case #4 – Presented by Taki May, MD

- 30 yo female with heroin and methamphetamine abuse presented in Las Vegas with MSSA bacteremia and left AMA.
- Admitted to Dixie with recurrent bacteremia with a tricuspid vegetation and cultures grew MSSA and MRSA.
- Dx: Tricuspid valve endocarditis with both MRSA and MSSA
- Completed one week of ceftaroline/dapto, then transitioned to oral linezolid after demanding to leave the hospital.
- Did not leave AMA, but refused initiation of opiate replacement and referral to rehab environment.
- Completed total course 6 weeks with oral linezolid doing well on follow up.

POET Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

RCT of 400 adults with:
- Left sided endocarditis
- Stable condition
- Gram (+) organisms

→

- IV for 10d → then PO vs. IV
- Had normal GI function
- Seen in clinic 2-3 times/wk

→

Primary outcome (composite, 6 mo):
- all-cause mortality
- cardiac surgery
- embolic events
- relapsed bacteremia

Iversen et al, NEJM 2019, 380:415.

Project ECHO® Intermountain Healthcare Utah

Intermountain® Healthcare

POET Study

Patients

- Groups well balanced
- Mean age 67, 77% men
- Only 35% had a comorbidity (few immunocompromised)
- PWID 1%
- Valve surgery in 38%

Valves

- Prosthetic valve 27%
- Aortic 54%, Mitral 34%
- Veg size >1cm in 5%
- Mod-severe regurg 10%

Microbiology

- Streptococci 49%
- E. faecalis 24%
- MSSA 22% (no MRSA)
- Coag neg Staph 6%

Iversen et al, NEJM 2019, 380:415.

Project ECHO® Intermountain Healthcare Utah

Intermountain® Healthcare

POET Study

Both groups: 17 days of IV antibiotics

IV group: + 19 days IV

Oral group: + 17 days PO

- Combination therapy for all
- Most common regimens:
  - **Strep**: amox + (rifampin or moxi)
  - **E. faecalis**: amox + (moxi or linezolid)
  - **MSSA**: (diclox or amox) + rifampin
  - **CONS**: linezolid + rifampin

Iversen et al, NEJM 2019, 380:415.

Project ECHO® Intermountain Healthcare Utah

Intermountain® Healthcare

POET Study

- No difference in composite endpoint (12% in IV group, 9% in oral group) or components
- No difference by organism, surgery or not, involved valve, or valve type
- Shorter LOS: LOS after randomization 19d in IV group vs. 3d in PO group (p<.001)
- Outcomes at 3.5 years: no delayed treatment failure, NO patients lost to follow-up

Iversen et al, NEJM 2019, 380:415. Bundgaard H et al. N Engl J Med 2019, 380:415.

OVIVA Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

RCT of 1054 adults with bone or joint infection

- No SAB, endocarditis, native septic arthritis
- "Likely to comply w/ Rx"

→

- Within 7d of surgery or Abx start → IV vs. PO for 6 wks
- Follow-on oral Abx in both groups

→

Primary outcome:

Definitive treatment failure at 1 year

Li et al, NEJM 2019, 380:425.

Project ECHO® Intermountain Healthcare Utah

OVIVA Study

Patients

- Groups well balanced
  - Diabetes 20%
  - Immunosuppressed 15%
  - No PWID
- Infections
  - Hardware 61%
  - Surgical debridement 92%
  - Lower limb 81%, upper limb 10%, vertebral 7%

Microbiology

- Staph aureus 38%
  --10% MRSA, 90% MSSA
- Coag neg Staph 27%
- Streptococcus 15%
- Pseudomonas 5%
- Other GNRs 17%
- Culture negative 16%
- Polymicrobial 18%

Li et al, NEJM 2019, 380:425.

Project ECHO® Intermountain Healthcare Utah

Intermountain® Healthcare

OVIVA Study

- No difference in definitive treatment failure between groups (15% in IV group, 13% in oral group)

- PO group also had:
  - Fewer catheter related complications (1% vs 9%)
  - Shorter LOS (11 vs 14 days)

Li et al, NEJM 2019, 380:425.

Thank you Dr. Webb!

References

Dafna Yahav, Erica Franceschini, Fidi Koppel, Adi Turjeman, Tanya Babich, Roni Bitterman, Ami Neuberger, Nesrin Ghanem-Zoubi, Antonella Santoro, Noa Eliakim-Raz, Barak Pertzov, Tali Steinmetz, Anat Stern, Yaakov Dickstein, Elias Maroun, Hiba Zayyad, Jihad Bishara, Danny Alon, Yonatan Edel, Elad Goldberg, Claudia Venturelli, Cristina Mussini, Leonard Leibovici, Mical Paul, Bacteremia Duration Study Group, Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial, Clinical Infectious Diseases, Volume 69, Issue 7, 1 October 2019, Pages 1091–1098, https://doi.org/10.1093/cid/ciy1054

Geriak, Matthew et al. "Clinical Data On Daptomycin Plus Ceftaroline Versus Standard Of Care Monotherapy In The Treatment Of Methicillin-Resistant Staphylococcus Aureus Bacteremia". Antimicrobial Agents And Chemotherapy, vol 63, no. 5, 2019. American Society For Microbiology, doi:10.1128/aac.02483-18.

Tamma PD, Conley AT, Cosgrove SE, et al. Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia. JAMA Intern Med. 2019;179(3):316–323. doi:10.1001/jamainternmed.2018.6226

Project ECHO® Intermountain Healthcare Utah

Intermountain® Healthcare

Additional Resources

- van Hal SJ et al. *Clinical microbiology reviews.* 2012;25:362-386
- Hassoun A, et al. *Critical care.* 2017;21:211
- Holubar M, et al., Infectious disease clinics of North America. 2016;30:491-507.
- Fowler VG, et al. The New England journal of medicine. 2006;355:653-665.
- Zasowski EJ, et al. Antimicrobial agents and chemotherapy. 2017;61.
- Liu C, et al. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2011;52:285-292.
- Casapao AM, et al. Antimicrobial agents and chemotherapy. 2014;58:2541-2546.
- Arshad S, et al. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2017;57:27-31
- Iversen et al, NEJM, 380:415.
- Li et al, NEJM 2019, 380:425.