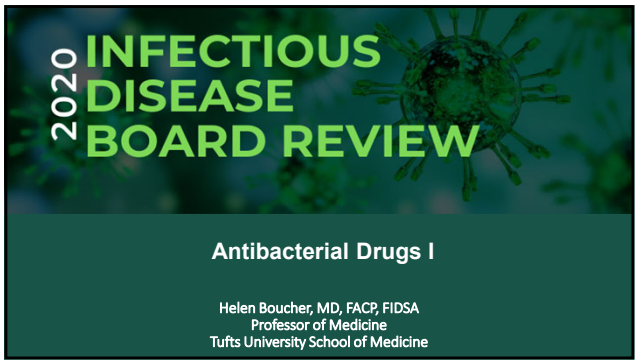
55 – Antibacterial Drugs

Speaker: Helen Boucher, MD



CASE

- 64 year old woman with diabetes mellitus, hypertension, coronary artery disease, osteoarthritis, depression, and recently diagnosed MRSA skin infection on her leg presents with 24 hours of fever, chills and shakes
  - Presented with abscess that was drained; linezolid prescribed 5 days earlier
  - 24 hours ago: chills, malaise and tremors
  - No diarrhea, abdominal pain, skin rash
- Current medications: lantus insulin, linezolid, hydrochlorothiazide, aspirin, metoprolol, sertraline, tramadol. No allergies.

3

Exam

- T 101.6F, BP 146/88, HR 100, RR 20, Sat 97%RA
- HEENT, chest clear, CV, abdomen normal
- Leg with 5 cm wound with pink granulation tissue, scant purulent drainage on dressing; no tenderness, surrounding erythema, warmth or edema
- Neuro: alert and oriented to person, place and time; CN II-XII intact, motor and sensory intact; 3+ bilateral patellar reflexes, resting tremor worse in legs, + clonus
- Labs wbc 7.5, 72%p, 20%l, 5 mono, 2 eo, 1 baso, hct 39, plt 160, Na 145, K 3.9, Cl 96, CO2 20, BUN/Cr 30/1.4 (baseline)

Progress: Neurology consult pending

4

ARS

In addition to blood cultures, chest x-ray, urine analysis and culture, you recommend

A. STAT blood glucose
B. Discontinuation of linezolid
C. MRI of the leg
D. Brain imaging and lumbar puncture

5

Serotonin Syndrome Related to Linezolid

- Linezolid is a MAO inhibitor, interacts with SSRIs, tramadol and other rx to cause serotonin syndrome
  - Lawrence et al. CID 2006; 42: 1578

Other answers:

- Addition of parenteral dalbavancin –reasonable if failure of therapy of the ABSSSI was considered
- MRI of the leg - failure of source control might be considered
- Brain imaging and lumbar puncture – reasonable for concern of brain infection

6

55 – Antibacterial Drugs

Speaker: Helen Boucher, MD

Case

- 74 year-old man admitted for elective surgery for metastatic cancer of unknown primary
- Presented 6 months earlier with persistent cough. Chest x-ray showed a solitary lung lesion and chest CT confirmed a lung nodule. Lung wedge resection was nondiagnostic. MRI showed two brain lesions in the cerebellum and left temporal lobe. Lung needle biopsy was non-diagnostic. He was referred to Neurosurgery to discuss treatment options for brain metastasis
- Exam notable for unsteady gait. MRI: increase in size of the temporal lesion, new ring-enhancing lesions in cerebellum with surrounding edema
- Dexamethasone started and he was admitted for brain biopsy

7

Case

- Past medical history: hypertension, CAD
- No smoking, alcohol, drug use. No pets. Travel to California, Arizona, Europe
- Family history – father + colon cancer
- Medication: dexamethasone; NKDA
- T 37C, BP137/84, HR94, RR16, O2 SAT 100%.
- Neuro - unsteady gait, muscle strength 5/5 throughout, normal DTR
- Wbc 13.2, 95%polys, hct 31.7, platelets 495, BUN 13/Creat 0.62

8

ARS#

Which of the following is the best initial therapy?

A. meropenem and TMP/SMX
B. pyrimethamine and sulfadiazine
C. chemotherapy and radiation
D. vancomycin and cefepime

9

Nocardiosis

- Gram-positive bacterial infection caused by aerobic actinomycetes in the genus *Nocardia*
- Epidemiology: 2/3 immunocompromised, 1/3 immunocompetent
- Pneumonia, brain abscess, lymphadenitis
- Can disseminate to virtually any organ, particularly the central nervous system
- Tends to relapse or progress despite appropriate therapy
- Different *Nocardia* species/strains have different susceptibility patterns
  - Send for species ID and susceptibility testing
- Treat with 2-3 drugs pending susceptibility
  - TMP-SMX
  - Carbapenem (imi/meropenem)
- Also linezolid, amikacin, third-generation cephalosporins, minocycline, extended spectrum fluoroquinolones (eg, moxifloxacin), tigecycline, and dapsone

10

Case

A 38 year old male lobsterman presents with a 4 day history of worsening erythema, warmth and pain in his middle finger. A biopsy of the site reveals small, slightly curved, gram-positive, catalase negative bacillary organisms

11

ARS

Which of the following is the most likely organism causing this infection?

- *Vibrio vulnificus*
- *S. pyogenes*
- *S. anginosus* group
- *Erysipelothrix rhusiopathiae*

12

Erysipeloid "Whale Finger"

Erysipelothrix rhusiopathiae

- α-hemolytic, gram positive (though loses staining readily – may look gram neg), catalase negative
- Confused with listeria, arcanobacterium (but they are β-hemolytic)
- Found in environment – soil, grow readily in slime layers on fish
- Swine = major reservoir
- Occupational exposure highest risk

Treatment:

- Susceptible to b-lactams, quinolones, clindamycin
- Resistant to vancomycin, TMP-SMX, aminoglycosides

13

Case

- 22 year old man with substance use disorder presents to OPAT clinic on day 24 of parenteral oxacillin for MSSA bloodstream infection. He feels well but notes decreased appetite over the last few days. No nausea, vomiting, diarrhea, rash, fever, chills or sweats. No problem with the PICC line or difficulty infusing
- Exam unremarkable; PICC site without erythema, drainage, warmth, redness or palpable cord
  - White blood cell count 8, normal differential
  - normal electrolytes, BUN/Cr 18/0.6, urine analysis normal
  - ALT 250, AST 142, Alk phos 117, T Bili 1.3
  - Hepatitis B surface antigen negative
  - Hepatitis C RNA not detected, HIV negative

14

ARS#

- Which of the following agents is best to replace oxacillin:

1. Ceftaroline
2. Daptomycin
3. Linezolid
4. Cefazolin
5. Vancomycin

15

Outcomes in MSSA Bacteremia B-Lactam Versus Vancomycin

	B-Lactam N = 44	Vancomycin N = 28	P - value
Infection-related Mortality	5 (11%)	11 (39%)	0.005

Risk Factors for Failure (multivariate anal)		
Vancomycin Tx	6.5 (1.4-29.4)	

- Higher mortality in ceftriaxone-treated B-lactam patients
- No difference in mortality between patients who received initial vanco and those who had vanco switched to B-lactam (33% vs. 41%, p 0.7)

Lodise et al. AAC 2007; 51(10): 3731-33

16

Outcomes in MSSA Bacteremia Cefazolin Versus Vancomycin

	Cefazolin N = 46	Vancomycin N = 77	P - value
12 Week Failure	13%	31%	0.02

Risk Factors for Failure (multivariate anal)		
Vancomycin Tx	3.53 (1.15-13.45)	0.04
Reten HD cath	4.99 (1.89-13.76)	0.001

- Cefazolin patients older and had more metastatic infections at baseline
- Only 9% of vancomycin patients had allergies to PCN/cephalos

Stryjewski et al. CID 2007; 44: 190-6

17

For MSSA, use a β-lactam

MAJOR ARTICLE

Comparative Effectiveness of Beta-Lactams Versus Vancomycin for Treatment of Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections Among 122 Hospitals

Jennifer S. McDaniel,[1,2,3] Eli N. Perencevich,[1,2,3] Daniel J. Diekema,[2,4,5] Loreen A. Herwaldt,[2,4,5] Tara C. Smith,[1,4] Elizabeth A. Chrischilles,[1] Jeffrey D. Dawson,[6] Lan Jiang,[7] Michihiko Goto,[2,3] and Marin L. Schweizer[2,3,5]

- β-lactams associated with 35% lower mortality
- Vancomycin is clearly inferior for MSSA bacteremia

McDaniel et al, Clin Inf Dis 2015;61:361-67

18

55 – Antibacterial Drugs

Speaker: Helen Boucher, MD

Case

- 45 year old woman admitted for cholecystitis has MSSA bloodstream infection related to thrombophlebitis at IV site
- TTE showed normal valves
- Started on parenteral cefazolin with plan to treat for 4 weeks
- At 2nd week OPAT visit (cefazolin day 14)
  - Exam unchanged
  - White blood cell count 8.4, hemoglobin 6.7
  - normal electrolytes, BUN/Cr 32/1.0
  - AST 23, ALT 16, Alk phos 55, T Bili 1.8, LDH 459, haptoglobin < 8

19

ARS Question # 1

After discontinuing cefazoin, you recommend:

A. Piperacillin-tazobactam
B. Ampicillin-sulbactam
C. Meropenem
D. Moxifloxacin

20

Cephalosporin Toxicity

- Hypersensitivity reactions , rash
- GI disturbances
  - Nausea, vomiting, diarrhea (+/- C. difficile)
  - GB sludge or pseudocholecystitis with ceftriaxone
- Hematologic toxicity (class effect)
  - Eosinophilia
  - Hemolytic anemia, positive Coomb's test
- Hepatotoxicity
- Nephrotoxicity (interstitial nephritis)
- Neurotoxicity – tremor, confusion, seizure, encephalopathy
  - Worse with renal failure

21

45 year old man from Miami
Painful lesion not responsive to cephalexin

Diameter: 3cm

22

ARS Question

In addition to incision and drainage, which of the following is the best oral therapy?

A. Doxycycline
B. Delafloxacin
C. Tedizolid
D. TMP/SMX

23

TMP-SMX for *S. aureus* ABSSI

- For skin/skin structure infections:
  - Resistance among CA-MRSA: 0-17%
  - ?Poor coverage of Group A Strep
  - Clinical data for use in skin infections
    - TMP/SMX superior to placebo with I&D
    - Success common with outpatient Rx

1. d'Oliveira RE, et al. *Microb Drug Resist.* 2003;9:87-91
2. Iyer S, Jones DH. *J Am Acad Derm.* 2004;50:854-858.
3. Miller LG, et al. *Clin Infect Dis.* 2007;44:483–492.
4. Ruhe JJ, et al. *Clin Infect Dis.* 2007; 44:777-784.
5. Duong M, et al. *Ann Emerg Med.* 2010;55:401-407
6. Schmitz GR, et al. *Ann Emerg Med.* 2010; 56:283-287.
7. Frei CR, et al. *J Am Board Fam Med.* 2010;23:714-719.
8. Fridkin SF, et al. *New Engl J Med.* 2005;352:1436-1444.
9. Frazee BW, et al. *Ann Emerg Med.* 2005;45:311-320.
10. Miller LG, et al. *Clin Infect Dis.* 2007; 44:471–82
11. Talan et al *N Engl J Med* 2016; 374:823-832

24

Antibiotic Therapy for Small MRSA Abscesses

- 1220 patients with abscess 2-5 cm diameter, 45% MRSA, all had I&D
  - TMP-SMX (320 mg/1600 mg 2x/d) better than placebo
- > 780 patients with abscess ≤5 cm (45 % ≤2 cm), 49% MRSA, all had I&D
  - TMP-SMX or clindamycin better than placebo
- Systematic review/meta-analysis > 2400 patients with drained abscess
  - Lower failure in patients who received antibiotics vs placebo (7% versus 16%); odds ratio for cure 2.3 (95% CI 1.7-3.1)
  - Antimicrobial therapy may also decrease the risk of recurrent skin abscess

Talan et al. N Engl J Med. 2016;374(9):823. Daum et al. N Engl J Med. 2017;376(26):2545. Gottlieb et al. Ann Emerg Med. 2019;73(1):8. Epub 2018 Mar 9

25

Unresponsive Female with a Red Arm

- 61 year old female admitted to an outside hospital with unresponsiveness
- Blood glucose >1000 mg/dl and hypotensive on admission
- Noted to have desquamating L hand with L arm erythema, swelling, and bullae
- Placed on pressors and transferred for further care

26

Unresponsive Female with a Red Arm

- Past Medical History
  - Diabetes mellitus, HTN
- Vitals: BP109/48 on levophed, HR 71 RR 31 Temp 37.9F, 98% on 40% Fio_2
- Exam: intubated/sedated
  - Erythematous furuncles on abdomen, bilateral lower extremities, L arm
    - Patchy erythema, tense edema
    - Hand with erythema, bullae
- Pertinent labs: BUN/creat 17/0.8, wbc 37k

27

Unresponsive Female With DM Presented With Shock, Glucose > 1000

28

Unresponsive Female With DM, Presented With Shock, Glucose > 1000

29

Intra-operative

30

Hospital Course

Operative findings
- Muscles and tendons intact
  - No bulging noted
- Return to the OR the next day
  - Incision extended to the digits
  - Gross purulence
- Blood cultures negative
- Tissue and wound cultures grew *S. aureus*
  - Susceptible to vanco, clindamycin, gent, rifampin, Tetracycline, TMP/SMX, linezolid
  - Resistant to penicillin, oxacillin, erythro
    - CA-MRSA

31

Hospital Course - Progress

- Repeated surgical debridement
- Extubated HD #10

- Additional history
  - Animal/insect contact: dog at home with fleas
    - Pt bathed dog and developed small itchy bites

32

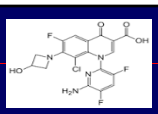
ARS Question #3

The best therapy includes

A. Delafloxacin
B. Vancomycin
C. Linezolid
D. TMP/SMX

33

Delafloxacin



- Broad spectrum anionic fluoroquinolone
- FDA approved ABSSI
- Potential advantages:
  - First FQ with MRSA activity (not effective vs GC)
  - Oral bioavailability
  - Accumulates in acid pH (intracellular)
  - Efficacy in obese patients
- Safety – > 2100 subjects studied prior to pivotal ABSSSI trials
  - MILD GI effects most common
  - No QTc Prolongation observed
  - Phototoxicity not observed
  - No effect on LFTs or glucose
  - No tendon rupture cases to date

Saravolatz LD and Stein GE. Clin Infect Dis. 2018

34

Antibiotic Challenges Case

57 year old man with endstage non-ischemic cardiomyopathy, valvular heart disease, hypothyroidism, diabetes
- Cardiogenic shock
- Left Ventricular Assist Device (LVAD)
- Listed for transplant

35

Case (continued)

Two months later…
- Pain and drainage from driveline exit site
- History of trauma 3 days prior
- Exam 10cm surrounding cellulitis, purulent drainage
- Gram stain 4+ polys, many gram-positive cocci in clusters
- VAD wound culture + MRSA
- Vancomycin initiated

36

37

Case (continued)

- Imaging with CT + enlarging collection surrounding the aortic limb of the VAD with ? sternal osteomyelitis; new, progressive subcutaneous fat stranding and skin thickening along abdominal wall at DL exit site with internal mesenteric fat stranding
  - Cellulitis vs mesenteritis
- Blood cultures + MRSA
- Progress
  - Difficulty administering and obtaining vancomycin levels in ambulatory patient with VAD
  - Fluctuating vancomycin levels and renal function

38

ARS Question
Which of the following is the best therapy for this ambulatory patient?

A. Oral Linezolid
B. IV Daptomycin
C. Oral TMP/SMX
D. IV Dalbavancin
E. IV Ceftaroline

39

Linezolid and Tedizolid

	Linezolid	Tedizolid
FDA approval	ABSSSI, PNA, VRE; NOT BSI (Black Box Warning)	ABSSSI
Dosing	600mg twice daily IV/oral x 10 days	200mg once daily IV/oral x 6 days
Activity	Similar spectrum to include MRSA, VRE, *Nocardia* spp, Mycobacteria	
MRSA Pneumonia	Superior to vancomycin?	Study vs linezolid complete
Safety	Bone marrow (platelets)	? More safe than linezolid
	Serotonin syndrome, lactic acidosis, peripheral/optic neuritis	Not studied in neutropenic patients

40

Daptomycin for *S. aureus* Bacteremia and Right IE

SAB/IE Study Issues
- Design - dapto alone vs. combo/init low dose gent
- Vanco MIC_{90} 0.5µg/ml – higher in many centers in 2008

Daptomycin 6mg/kg iv daily - ? Higher doses
- Follow CPK – espec CrCl < 30 ml/min or high dose
  - Not for pneumonia
    - Inactivated by pulmonary surfactant → failed pneumonia studies
    - Seems to be OK for septic pulmonary emboli
  - Resistance on therapy
  - Use with caution with retained foreign body/undrained abscess

Benvenuto et al. *Antimicrob Agents Chemother.* 2006;50:3245
Cunha BA et al. *Heart Lung.* 2006;35:207-11; Boucher and Sakoulas CID 2007

41

TMP/SMX for MRSA BSI/Endocarditis

Conflicting data vs. vancomycin
- Old study showed longer duration of SAB, potentially worse outcomes with TMP/SMX for MSSA SAB
- More recent retrospective matched cohort study of patients with MRSA BSI treated with TMP/SMX or vancomycin
  - Similar duration MRSA SAB
  - Numerically fewer relapsed MRSA SAB
  - Similar mortality, renal toxicity

Option for salvage MRSA therapy

Markowitz N et al. *Ann Intern Med.* 1992;117:390-398
Goldberg E et al. J Antimicrob Chemother. 2010;65:1779

42

55 – Antibacterial Drugs

Speaker: Helen Boucher, MD

31 year old homeless woman with substance use disorder and history of recurrent MRSA skin infections presents with a 12cm diameter thigh abscess. She reports active IV drug use this AM

No medications, no known allergies

- T 102, BP 96/58, P 110, RR 18, Sat 96% room air
- Nontoxic appearing. o/p with dry mucosa, no thrush, chest clear, CT tachy + S1, S2, abdomen – normal bowel sounds, soft, nontender; extremities, left leg with 12cm diameter fluctuant area on anterior thigh; 22 cm diameter overlying erythema, with warmth and induration; exquisitely tender to palpation; visible track marks over arms and legs. Neuro + fine tremor

43

Laboratory data:

- wbc 14k, 88%P, 8L, 4mono
- Na 134, K 3.4, Cl, Hco2, BUN/Cr 29/1.2
- AST 34, ALT 48, Alk P 122, T bili 1.2
- Rapid HIV negative
- X-ray of leg – no fracture, no gas
- Blood cultures obtained
- Patient declines hospital admission, will allow incision and drainage

44

ARS#

Which of the following is most appropriate for this patient?

1. Vancomycin
2. Ceftaroline
3. Dalbavancin
4. Daptomycin

45

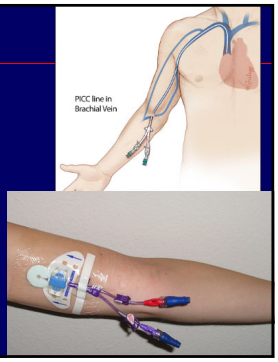
Long-acting Lipoglycopeptides

	Dalbavancin	Oritavancin
FDA approval	ABSSSI vs vanco then linezolid	ABSSSI vs vanco
Dosing	1000 mg followed by 500 mg one week later or 1500 mg once (30 minute infusion) Dose adjustment if CrCL < 30 mcg/mL	1200 mg once (3 hour infusion) No dose adjustment (minimal renal excretion)
Activity	Some hVISA/VISA strains *VanB* VRE only	Some hVISA/VISA strains *VanA* and *VanB* VRE
BSI/osteo	Case series	Few cases
Susceptibility	Inferred from vancomycin	Inferred from vancomycin
Safety	? Liver dysfxn	? Liver dysfxn osteo
Coag interference	No	Falsely elevated aPTT first 24-48 hrs Increased warfarin exposure

46

Why consider oral antibiotics?

- Less intravenous access complications
- Reduced frequency of hospital follow-up appointments
- Fewer restrictions in activities of daily living and return to work



POET *S. aureus* Patients

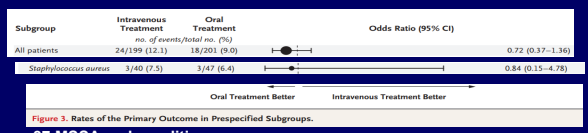


Figure 3. Rates of the Primary Outcome in Prespecified Subgroups.

- 87 MSSA endocarditis
- Most common oral regimens:
  - Dicloxacillin + rifampin (N=15)
  - Amoxicillin + rifampin (N=13)
- Take-home for SAB oral step-down therapy: apply to MSSA only, no extracardiac complications

Iversen et al, NEJM 2018, doi:10.1056/NEJMoa1808312

48

Case

- 30 year old healthy teacher presents with 1cm abscess on the left thigh, no systemic illness
- PMHx menorrhagia
- Meds: oral contraceptive, ferrous sulfate
- Afebrile, exam otherwise normal
- ER MD performs incision & drainage, advises abstaining from shaving
- Tetanus booster administered
- You are asked to recommend further therapy

49

ARS Question

You prescribe doxycycline for acute bacterial skin infection. You advise

A. Taking doxycycline with food
B. Avoiding sun exposure
C. Taking doxycycline with morning medications
D. Discontinuing oral contraceptive

50

Tetracycline Absorption/Adverse Effects

- Absorption in the proximal small intestine and the stomach
  - Doxycycline is 95% bioavailable with or without food, whereas
  - Tetracycline bioavailability reduced x 50 percent if taken with food
- Absorption of tetracyclines decreased with administration of chelating multivalent cations (ie, aluminum, calcium, iron, magnesium)
- Adverse effects:
  - Gastrointestinal (N/V), hepatotoxicity rare but fatal
  - Photosensitivity
  - Tooth discoloration
  - Teratogenic
  - Vertigo - minocycline
  - Death - tigecycline black box warning
  - Heme (rare), minocycline associated lupus

51

Case

- 42 year old healthy man presents in February with cough, T38C, wheezing
- Rapid flu test positive; SARS CoV-2 PCR negative
- Discharged home
- 5 days later returns to ER with T 39C, dyspnea, oxygen sat 90% RA
- CXRay + dense RLL infiltrate
- Sputum gram stain 4+ polys, 4+ G+ cocci in clusters
- WBC 21,000, 96% polys, creat 1.2, Lactate 2.4
- Sputum /blood cultures sent

52

ARS Question

In addition to supportive care, the best therapy includes:

A. Linezolid
B. Ceftriaxone
C. Azithromycin
D. Daptomycin

53

Treatment of Community-Acquired Bacterial Pneumonia (CABP)

<u>Outpatient</u>

Healthy – macrolide or doxycycline

(+) comorbidity or risk factor for drug-resistant S. pneumoniae (DRSP):

Respiratory quinolone

β-lactam + macrolide

<u>Inpatient, non-ICU</u>

Respiratory quinolone

β-lactam + (macrolide or quinolone)

54

55 – Antibacterial Drugs

Speaker: Helen Boucher, MD

Empirical CABP Coverage in ICU

No Pseudomonas	Beta-lactam + macrolide/quinolone
	PCN allergy: quinolone + aztreoman
Pseudomonas?	anti-Pseudomonal beta-lactam + quinolone
	anti-Pseudomonal beta-lactam + AG + azithro/levo
	PCN allergy: aztreonam + AG + levo
MRSA?	add vancomycin or linezolid to above

IDSA Guidelines 2007 (revision pending): https://academic.oup.com/cid/article/44/Supplement_2/S27/372079

55

Risk factors for MRSA in CABP

- Gram-positive cocci in clusters on sputum Gram stain
- Known colonization with MRSA
- Risk factors for colonization with MRSA (eg, end-stage renal disease, contact sport participants, injection drug users, those living in crowded conditions, men who have sex with men, prisoners)
- Recent influenza-like illness
- Antimicrobial therapy (particularly with a fluoroquinolone) in the prior three months
- Necrotizing or cavitary pneumonia
- Empyema

56

Risk Factors for DRSP in CABP

- Age >65 years
- Beta-lactam, macrolide, or fluoroquinolone therapy within the past three to six months
- Alcoholism
- Medical comorbidities
- Immunosuppressive illness or therapy
- Exposure to a child in a daycare center
- Healthcare exposure (LTC)
- Recent tx/repeated course of therapy with beta-lactams, macrolides, or FQ = risk for pneumococcal resistance to the same class of antibiotic - use an agent from an alternative class

57

Abx Options for MRSA Pneumonia

- Vancomycin
- Linezolid/Tedizolid
- Clindamycin (D test negative)
- Ceftaroline
- Omadacycline
- Lefamulin
- Delafloxacin

58

FOCUS
Ceftaroline CABP FDA Analysis/Early Endpt

	Ceftaroline	Ceftriaxone	Tx Diff (95% CI)
Day 4 response	69.5%	59.4%	10.1 (-0.6, 20.6)
S. pneumo	54/74 (73.0%)	42/75 (56.0%)	16.9 (1.4, 31.6)
S. aureus	14/24 (58.3%)	17/31 (54.8%)	0.7 (-24.7, 26.2)

*MITT included pts who received study drug, had baseline pathogen isolated. Success required BOTH clinical stability and symptom improvement.

File et al. CID 2011, File et al. CID 2012, www.fda.gov

59

Ceftaroline
Safety and Monitoring

- Rash, GI disturbances – like other cephalosporins
- Hematologic toxicity (class effect)
  - Eosinophilia
  - Positive Coomb's test
- Hepatotoxicity – LFT abnormalities 1-7%
- Neurotoxicity – tremor, confusion, seizure, encephalopathy
  - Worse with renal failure

60

New Tetracyclines

	Omadacycline	Eravacycline
FDA approval	ABSSSI, CABP	cIAI, not cUTI (failed studies)
Dosing	200 mg loading dose over 60 min day 1, 100mg IV over 30 min or 300mg orally once daily No dose adjustment for renal/hepatic impairment	1mg/kg IV q 12h (over 60 minutes) Dose adjustment with hepatic impairment
Activity	Broad spectrum: Gram-pos including MRSA, VRE; Gram-neg including ESBL, CRE (not all); anaerobes	
Issues	Limited activity vs carbapenem-resistant *K. pneumoniae*	High MIC *Pseudomonas*, *Burkholderia* spp.
Safety	GI, rash, ?heart rate	GI, rash

61

Lefamulin CABP
FDA Analysis/Early Endpt (ITT)

	Lefamulin N = 276	Moxifloxacin+/- LZD N = 275	Tx Diff (95% CI)
Day 4 response	87.3%	90.2%	-2.9 (-8.5, 2.8)
S. Pneumo	82/93 (88.2%)	91/97 (93.8%)	ND
S. aureus	10/10	4/4	ND

File et al. CID 2019

62

Case

- 73 year old man with prostate cancer, presented after rapid deterioration at home (<24hrs): feeling unwell, nausea and coffee-ground vomiting, followed by lethargy/difficulty speaking; intubated
- Never smoker, rarely drinks alcohol
- Never used IV drugs
- Lives with his wife at home
- Retired engineer

63

Case

- BP 102/73 (on levophed), HR 72, Tm 100.1 Tc 98.7, RR 16 Sat 95% on FiO2 40%
- General: Intubated, unresponsive
- HEENT: Anisocoria, left pupil fixed and dilated, right responds to light, no conjunctival hemorrhage, minimal stiffness in the neck
- Chest clear
- Heart : S1 S2 RRR, no murmur
- Abd: normal bowel sounds, soft NT ND
- Ext: no joint swelling, no stigmata of endocarditis

64

Case (continued)

- WBC 13.7, Hb 10 Plt 150
- BUN 20, Cr 0.8, LFTs normal
- Lactate 1.2
- CXR RLL infiltrate
- Brain MRI Early subacute, nonhemorrhagic, cerebral as well as cerebellar hemispheric microembolic infarcts most probably ascribable to a central embolic source
- CSF WBC 975 (neutrophils 85%), RBC 192, Glucose <5, Protein 540
- Blood Cx + *S. pneumoniae*, penicillin MIC 2 mcg/ml, ceftriaxone MIC < 0.5 mcg/ml

65

ARS Question
You recommend which of the following:

A. Penicillin
B. Ceftriaxone
C. Vancomycin
D. Moxifloxacin

66

S. pneumoniae Penicillin Breakpoints

	Minimum Inhibitory Concentration (MIC) (mcg/mL)		
	Susceptible (S)	Intermediate (I)	Resistant (R)
Updated	≤2	4	≥8
Previous	≤0.06	0.12-1.0	≥2

The susceptible breakpoint for meningitis caused by *S. pneumoniae* remains unchanged (≤ 0.06 mcg/mL)

Weinstein et al. CID 2009

67

Case (continued)

You recommend therapy with ceftriaxone 2g IV every 12 hours

- He improves clinically
- On day 9 of therapy, you are called back as the patient has developed profuse watery diarrhea with abdominal cramping
- BP is normal, abdomen + normal bowel sounds, soft
- Wbc 30,000 with left shift
- BUN/Cr 65/1.8
- Lactate normal
- Stool positive for *C. difficile* toxin

68

ARS Question
The best therapy includes

A. Oral metronidazole
B. Oral vancomycin
C. Oral fidaxomicin
D. Fecal microbiota transplant
E. Intravenous Bezlotoxumab

69

Antibiotics Associated with *C. difficile*

Frequently associated
- Fluoroquinolones
- Clindamycin
- Cephalosporins (broad spectrum)
- Penicillins (broad spectrum)

Occasionally associated
- Macrolides
- Trimethoprim-sulfamethoxazole

Rarely associated
- Aminoglycosides
- Tetracyclines
- Metronidazole
- Vancomycin

70

Thank You!

- Henry Masur
- Sue Cammarata
- G. Ralph Corey
- Sara Cosgrove
- Mike Dudley
- Mike Dunne
- David Gilbert
- Susan Hadley
- Kenneth Lawrence
- Evan Loh
- Paul McGovern
- Federico Perez
- Debra Poutsiaka
- George H. Talbot
- Our patients and their families

71