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MANAGEMENT OF MRSA AND C. DIFFICILE INFECTIONS IN HOSPITALIZED PATIENTS
Case #1

- A 55 yo obese man is admitted for dehydration secondary to vomiting – presentation consistent with gastroenteritis. IV access is difficult so an IJ central line is placed in the ED. Three days after admission, the patient is febrile. Blood cultures are obtained. By the next day, 2/2 positive Gram positive cocci in clusters – then identified as *Staphylococcus aureus*. Sensitivities pending.
Case #1: What would you do next?

1. Remove line, vancomycin
2. Remove line, daptomycin
3. Remove line, vancomycin, repeat blood cultures
4. Remove line, vancomycin, repeat blood cultures, TTE
5. Remove line, vancomycin, repeat blood cultures, TTE, request I.D. consult
6. Remove line, vancomycin, repeat blood cultures, TEE
7. Remove line, repeat blood cultures, TEE, request I.D. consult
Principles of Management:

- Source control/removal of devices – short and long term catheters should be removed with *S. aureus* bacteremia. Without removal, risk of non-response, metastatic infection, relapse.

Principles of Management:

- Repeat blood cultures should be obtained until clearance – influence both prognosis and management (which antibiotic and duration of therapy)

Hawkins et al, Arch Intern Med 2007;167:1861-7

Fowler et al, Arch Intern Med 2003;163:2066-72
Principles of Management:

- Echocardiography
  - Endocarditis present in 5 – 25% of patients with S. aureus bacteremia, depending on study
  - Risk factors include valvular disease, h/o endocarditis, IDU, community acquisition, hemodialysis, persistent bacteremia, permanent cardiac device, osteomyelitis
    - Absence sensitive enough to rule out endocarditis?
  - Practice varies considerably regarding whether echocardiography routinely obtained and whether TTE or TEE

Kern, Curr Opin in Infect Dis 2010;23:346-58
Fowler et al, J Am Coll Cardiol 1997;30:1072-8
Principles of Management:

- Studies in 1990s showed limited sensitivity of TTE compared with TEE for diagnosis of endocarditis
- Image quality has improved
- TTE often used as first line when suspicion low – high negative predictive value, especially when normal
- If echocardiography not done routinely, suggest low threshold to order
Principles of Management:

- Should an I.D. Consult be obtained for all cases of *S. aureus* bacteremia?
  - At least 4 studies address
  - Findings: decreased mortality for patients who received Infectious Diseases Consultation and greater adherence to recommended management principles

Principles of Management:

- Duration of therapy for MRSA bacteremia?
- Uncomplicated bacteremia: 2 weeks IV therapy
  - No endocarditis
  - No implanted prostheses
  - Negative blood cultures after 2-4 days therapy
  - Defervescence within 72 hrs of starting therapy
- Complicated bacteremia (i.e. not uncomplicated) without endocarditis 4-6 weeks IV therapy
- Endocarditis (right or left sided) 6 weeks IV therapy

Case #1 continued:

- You started vancomycin with weight-based dosing at 15 – 20 mg/kg every 12 hours with a target trough 15 – 20 mcg/mL. (Could have given a loading dose of 25 mg/kg x 1.) The line has been pulled, and a TTE is normal. Repeat blood cultures are pending. The organism is identified as MRSA with a vancomycin MIC = 1 mcg/mL.
Case #1:

- What do you do next?
  1. Continue vancomycin, check trough level
  2. Switch to daptomycin
Daptomycin vs. Vancomycin

- Randomized trial showed that daptomycin is not inferior to vancomycin for treatment of S. aureus bacteremia and endocarditis

- Case-control study of S. aureus bacteremia, vancomycin MIC > 1 mcg/mL, suggested better outcomes (lower mortality) for daptomycin-treated patients (59) compared with vancomycin treated patients (118)
Case #1 continued:

- The vancomycin trough is initially low, and you adjust dose until trough is 18 mcg/mL. The patient remains intermittently febrile, and blood cultures are persistently positive for MRSA. A TEE is normal. No foci of seeding are detected clinically. Blood cultures drawn on day #10 of therapy show MRSA with a vancomycin MIC = 2 mcg/mL and a daptomycin MIC = 0.5 mcg/mL.
Case #1 continued:

- What do you do next?
  1. Increase vancomycin dose further
  2. Continue vancomycin, add gentamicin
  3. Switch to daptomycin 6 mg/kg daily (+/- rifampin)
  4. Switch to daptomycin 8 – 10 mg/kg daily (+/- rifampin)
  5. Switch to daptomycin 15 mg/kg daily
  6. Switch to tigecycline
Persistent MRSA bacteremia

- Median time to MRSA clearance 7 – 9 days
  - When to call vancomycin failure?
- Options
  - High dose daptomycin + either gentamicin, rifampin, linezolid, TMP-SMX, or a beta-lactam antibiotic


- Other options: telavancin (not currently available?), ceftaroline
Case #2

- A 67 yo woman with diabetes is admitted to the floor with recurrent left lower extremity cellulitis. There is no purulence and nothing to drain. In addition to recommending elevation of her leg, which regimen do you prescribe?
Case #2:

1. Vancomycin
2. Vancomycin plus ceftriaxone
3. Vancomycin plus cefepime
4. Vancomycin plus clindamycin
5. Vancomycin plus cefepime plus clindamycin
6. Cefazolin
Cellulitis

- Cellulitis and cutaneous abscesses caused by aerobic Gram positive organisms
  - Streptococci and *S. aureus*
- No need for Gram negative or anaerobic coverage unless e.g. critically ill, necrotizing fasciitis, other unusual circumstance
  
  Jenkins et al, Arch Intern Med 2011;171:1072-9
- Role of community MRSA in cellulitis is unclear
  - *S. aureus* predominant organism with purulent skin and soft tissue infection; community MRSA plays a major role
Case #2 continued:

- Your patient with cellulitis responded well to treatment with vancomycin. No blood cultures were obtained. She is ready for discharge 72 hours after admission. What regimen will you prescribe at discharge (7 day course adequate for many patients)?
Case #2 continued:

1. Linezolid
2. TMP-SMX
3. Doxycycline
4. Clindamycin
5. Amoxicillin
San Francisco General Hospital S. aureus susceptibilities for 2011 (non-urine isolates)

<table>
<thead>
<tr>
<th></th>
<th>MSSA (n=586)</th>
<th>MRSA (n=499)</th>
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<tbody>
<tr>
<td>Clindamycin</td>
<td>82%</td>
<td>70%</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>88%</td>
<td>91%</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>89%</td>
<td>40%</td>
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Case #3

- A 50 yo woman is admitted for a COPD exacerbation. Treatment includes levofloxacin and prednisone. She is slow to improve, but on day #5 she seems ready for discharge. However, the nurse informs you that the patient now has profuse diarrhea with 4 episodes in the last 12 hours. She remains afebrile and her wbc is 11K. You send her stool for Clostridium difficile testing, which returns positive. You start therapy with
Case #3

1. Metronidazole 500 mg po three times daily
2. Vancomycin 125 mg po four times daily
3. Vancomycin 500 mg po four times daily
4. Vancomycin 1 g IV every 12 hrs
5. Cholestryramine 4 g po four times daily
6. Fidaxomicin 200 mg po twice daily
Cost

- Vancomycin pulvules 125 mg cost ~ $31 per pill: treatment cost $124 per day (cost may be less in some settings)
- Fidaxomicin average wholesale price ~ $135.00 per pill: treatment cost $270 per day
- Metronidazole cost ~ $.73 per pill: treatment cost $2.19 per day
More Severe *C. difficile*

- Oral vancomycin probably preferred over metronidazole for severe disease (or long courses)
  - Contributing factors: age > 60, fever, low albumin, WBC>15,000, pseudomembranous colitis, in ICU
  - Better clinical response but no difference in relapse
- Fidaxomicin?
Fidaxomicin

- New macrocyclic antibiotic; inhibits RNA polymerase
- Narrow spectrum of activity – very specific for *C. difficile*
- Approved by the FDA in 2011
- NEJM study fidaxomicin vs. vancomycin: lower relapse rate (15% vs. 25%) but only in those without NAP1/BI/027 strain
  
  *Louie et al, N Engl Med 2011;364:422-31*

- Improved rates of clinical cure if taking concomitant antibiotics (90% vs. 79%) and lower rates of relapse (17% vs. 29%)
  
  *Mullane et al, Clin Infect Dis 2011; 53:440-47*
Fidaxomycin

- Multicenter, randomized, double blind study in Europe, Canada, and U.S.
- Fidaxomycin vs. vancomycin for 10 days
- Primary endpoint clinical cure: 87.7% vs. 86.8% in modified intention to treat population (509 patients total)
  - With severe infection, 76.2% vs. 70.5% clinical cure (NS)
- Recurrence 12.7% vs. 26.9% overall (p < .001)
  - 9.2% vs. 27.4% non-BI/027 strain (p < .001)
  - 22.2% vs. 38% BI/027 strain (NS)

Case #4

- You are treating a 75 year old man in the ICU who was admitted with severe community acquired pneumonia. He initially improves but later develops first diarrhea and then ileus, a WBC of 35,000, a distended abdomen, and hypotension. Stool is positive for \textit{C. difficile} toxin. How would you treat this patient medically?
Case #4

1. Metronidazole 500 mg per NGT q 8h
2. Vancomycin 125 mg per NGT q 6h
3. Metronidazole 500 mg IV q 8h
4. Fidaxomicin 200 mg per NGT q 12h
5. Vancomycin 500 mg per NGT q 6h
6. Vancomycin 500 mg per NGT q 6h + metronidazole 500 mg IV q 8h + vancomycin 500 mg in 250 mL NS as retention enema (x 1hr) q 6h
Case #5

- Your patient from case #3 responded well to 10 days of treatment with metronidazole. However, 6 days after discontinuing therapy, her symptoms returned. Her primary treated her a second time with oral metronidazole, with good response while on therapy. Unfortunately, her symptoms recurred once again several days after discontinuation. She is readmitted to the hospital. How would you treat her now?
Case #5

1. Metronidazole again
2. Vancomycin – 14 day course
3. Fidaxomicin
4. Vancomycin – 14 day course at usual dose, then taper
5. Vancomycin – 14 day course, followed by rifaximin
6. Fecal bacteriotherapy
C. difficile Relapse

- Initial treatment success ~ 90% but relapse in 15-30% of cases
- After 2\textsuperscript{nd} relapse, consider:
  - Tapered, pulse dose vancomycin
  - Fidaxomicin
  - Prolonged course probiotics
  - Rifaximin, nitazoxanide, or cholestyramine chaser
  - IVIG
  - Chronic, low dose, suppressive vancomycin
  - Fecal bacteriotherapy
- Future – monoclonal antibodies against toxins A & B?  
“Stool Transplant”

- AKA intestinal microbiota transplantation (IMT)
- Results reported for more than 300 patients
- IMT given by enema, colonoscope, or nasojejunal (NJ) tube in most
- Majority received stool donation from a family member, spouse/partner
- Normal saline most commonly used to prepare suspension
  - About half given immediately
- Success rate > 90% - some received more than one infusion

Gough et al, Clin Infect Dis 2011;53:994-1002
Fecal bacteriotherapy

- Donor screening?
  - HIV, hepatitis (A, B, C), bacterial stool culture, *C. difficile*, stool ova and parasites, giardia
- A number of GI practices are performing this procedure
Case #6

- When a patient presents with diarrhea and other signs/symptoms suggestive of CDI, you should order a separate stool culture test to check for *C. difficile*.

  1. True
  2. False
C. difficile testing

- Toxigenic culture – not widely available
- Cell culture cytotoxicity neutralization assay - labor intensive, takes 48 hours
- Enzyme immunoassays (EIA) – limited sensitivity and specificity
- Nucleic acid amplification testing – high sensitivity and specificity, cost
- Sequential testing by algorithm
  - Screen for glutamate dehydrogenase antigen (GDH) [highly sensitive] and toxins A and B by EIA
  - Both negative or both positive – report result
  - One negative, one positive – further testing, e.g. NAAT
C. difficile testing

- Carriage of *C. difficile* - < 3% for healthy adults in community
- Carriage ~ 20% (or higher) in hospitalized or long-term care facility patients
- Test only those with symptoms
  - At least 3 loose stools in 24 hours
  - Stool conforms to the cup
- No need to re-test if using sensitive test – guided by clinical change
  - NAAT detects toxin B gene
- “Test of cure” not recommended
Infection Control – in a nutshell

- Contact isolation in the hospital
  - How long? Variable. At least until diarrhea resolves. Perhaps until discharge.
- Wash hands with soap and water
- Bleach cleaning

- Outpatient – dedicated toilet, if possible; hygiene; cleaning – consider dilute bleach; hand washing
Does Doxycycline Protect Against Development of Clostridium difficile Infection?

Sarah B. Doernberg,¹ Lisa G. Winston,¹ Daniel H. Deck,² and Henry F. Chambers¹

Clin Infect Dis 2012;55:615-20

• SFGH inpatient adults June 2005 – December 2010

• Compared those who received ceftriaxone + doxycycline to those who received ceftriaxone alone

• 2734 hospitalizations: 1668 no doxy, 1066 with doxy

• Outcome: CDI within 30 days of doxycycline receipt
Doxycycline and *C. difficile*

- CDI incidence 8.1 / 10,000 patient days in those receiving ceftriaxone alone
- CDI incidence 1.7 / 10,000 patient days in those who received ceftriaxone and doxycycline
- In multivariable model adjusted for age, gender, race, comorbidities, length of stay, pneumonia diagnosis, surgical admission, duration of ceftriaxone and other antibiotics, for each day of doxy receipt CDI risk was 27% lower (95% CI for HR 0.56 – 0.96)
Risk factors in hospital

- Prospective Canadian study: 4143 patients
- Stool samples or rectal swabs obtained from consecutive patients on admission, weekly, and with diarrhea
- Older age, antibiotics, PPI associated with infection
- Previous hospitalization, chemotherapy, PPI, H2 blocker, antibodies against toxin B associated with colonization
- NAP 1 strain more common in those with infection (63%) than with colonization (36%)

Loo et al, N Engl Med 2011;365:1693-703