Monday, October 25, 2016
10:15 a.m. to 11:45 a.m.
Great Hall 4

Moderator: Douglas L. Jennings, Pharm. D., FCCP, FAHA, AACC, BCPS, AQ-Cardiology
Clinical Pharmacy Manager-Heart Transplant and Mechanical Circulatory Support, New York Presbyterian Columbia University Medical Center, New York, New York

Agenda

10:15 a.m.  Ivabradine For Heart Failure: A “Funny” Alternative or Serious Drug Therapy?
Sheryl L. Chow, Pharm. D., FCCP, BCPS, AQ-Cardiology
Associate Professor, Western University of Health Sciences, Los Angeles, California

10:35 a.m.  Digoxin and Heart Failure: The End of an Era?
Steven P. Dunn, Pharm. D., BCPS
Pharmacy Clinical Coordinator, Cardiology, University of Virginia Health System, Charlottesville, Virginia

10:55 a.m.  Emerging Concepts in the Management of Clostridium difficile-Associated Diarrhea
P. Brandon Bookstaver, Pharm. D., BCPS, AQ-ID
Associate Professor and Vice Chair, South Carolina College of Pharmacy, University of South Carolina, Columbia, South Carolina

11:15 a.m.  Short-Course Antimicrobials for Systemic Infections: How Low Can We Go?
David T. Bearden, Pharm. D.
Clinical Professor and Chair, Department of Pharmacy Practice; Clinical Assistant Director, Department of Pharmacy Services, Oregon State University/Oregon Health and Science University College of Pharmacy, Portland, Oregon

11:35 a.m.  Question and Answer Session

Conflict of Interest Disclosures
David T. Bearden: no conflicts to disclose
P. Brandon Bookstaver: Speaker’s Bureau: (Rockpointe, FeeCe.com), Grants: (Allergan, Plc)
Sheryl L. Chow: Consultancies: (Relypsa), Speaker’s Bureau: (Amgen, Novartis)
Steven P. Dunn: no conflicts to disclose
Douglas L. Jennings: no conflicts to disclose

Learning Objectives
1. Explain how I-f, or “funny” channel inhibition relates to heart failure symptoms and outcomes.
2. Evaluate the literature describing the use of ivabradine in patients with heart failure.
3. Recommend a clinical role for ivabradine in the management of heart failure.
4. Review the pitfalls of digoxin therapy in heart failure.
5. Define the risk of mortality in digoxin-treated patients.
6. Clarify the role for digoxin in the management of heart failure.
7. Discuss the clinical utility of C. difficile ribotyping.
8. Define the role of metronidazole as a first-line therapy.
9. Outline the role of pharmacists in fecal bacteriotherapy.
10. Analyze the evidence base for shortening antimicrobial courses
11. Outline the benefits/risks of short course antibiotic therapy.
12. Define the role of antimicrobial stewardship in the implementation of abbreviated antibiotic course.

**Self-Assessment Questions**

Self-assessment questions are available online at [www.accp.com/am](http://www.accp.com/am)
Ivabradine for Heart Failure: A “funny” alternative or a serious drug therapy?

American College of Clinical Pharmacy
Hollywood, FL
October 25, 2016

Sheryl L. Chow, PharmD, FCCP, FAHA, FHFA, BCPSAQ-Cardiology
Associate Professor
College of Pharmacy
Western University of Health Sciences

Conflict of Interest
• Speakers Bureau: Novartis, Amgen, and American Heart Association
• Consultant: Relypsa

Ivabradine Mechanism of Action

Objectives
• Explain how If channel inhibition relates to heart failure symptoms and outcomes
• Evaluate the literature describing use of ivabradine in patients with heart failure
• Recommend a clinical role for ivabradine in the management of heart failure

Ivabradine Pivotal Study – SHIFT
Systolic Heart failure treatment with the If inhibitor ivabradine Trial

SHIFT Study Design

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Primary and Secondary Endpoints

Primary Endpoints
- Composite of the first occurrence of either CV death or hospital admission for worsening HF
- CV death (component of the primary composite endpoint)
- Hospitalization for worsening HF (component of the primary composite endpoint)

Secondary Endpoints
- eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.
- MI, myocardial infarction; NYHA, New York Heart Association.
- CV, cardiovascular.

Key Inclusion and Exclusion Criteria

Inclusion Criteria
- Male/female ≥ 18 years
- NYHA Class II, III, or IV and in stable condition for 4 weeks
- LVEF ≥ 35%
- Sinus rhythm with resting HR ≤ 70 bpm (resting EKG)
- Hospital admission for worsening HF within previous 12 months

Exclusion Criteria
- Recent MI (<2 months)
- Ventricular or atrioventricular pacing operative for 40% or more of the day
- Permanent atrial fibrillation or flutter
- Sick sinus syndrome, sino-atrial block, second and third degree atrioventricular block
- Symptomatic hypotension
- Severe or uncontrolled hypertension

Reasons Failure to Reach Beta-Blocker Target Dose or Not Receiving Beta-Blocker

Patient Disposition

3,286 Ivabradine
6,558 randomized
3,290 placebo

Median follow-up duration: 22.9 months
Ivabradine Titration

- Starting dose: 5 mg twice daily
- Titration Period: D14 & D28
- Follow-up Period: Every 4 months

- < 50 bpm or patient experiencing signs or symptoms related to bradycardia: 2.5 mg twice daily
- 50 to 60 bpm: 5 mg twice daily
- > 60 bpm: 7.5 mg twice daily

Treatment was discontinued if heart rate remained below 50 bpm or symptoms of bradycardia persisted after dose reduction.

Difference in Heart Rate Reduction Between Groups Was Early and Sustained Throughout Study

CV Death at Any Time

Effect of Ivabradine on Outcomes in Patients by Baseline Heart Rate (median 77 bpm)
Effects of ivabradine in NYHA Class or Heart Failure Symptoms in SHIFT

- Small but significant improvements were observed in NYHA functional class and patient- and physician-assessed change in heart failure symptoms

<table>
<thead>
<tr>
<th>NYHA classification</th>
<th>Improvement (%)</th>
<th>Ivabradine</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class ≤ II</td>
<td>26%</td>
<td>24%</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>NYHA class ≥ III</td>
<td>28%</td>
<td>26%</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association; SHIFT = Systolic Heart Failure Treatment with the Calcium Channel Blocker Ivabradine; End-stage heart failure

What Was the Effect of Ivabradine on Left Ventricular End-Systolic Volume Index?

Primary Endpoint:
- Change in LVEF from baseline to 8 months

<table>
<thead>
<tr>
<th>Included set (n = 413)</th>
<th>Excluded (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivabradine (n = 320)</td>
<td>Placebo (n = 307)</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction
Effect of \( \Delta \) = estimate minus placebo.

For adjusted \( \Delta \) = baseline KCCQ, beta = 0.018, P < 0.001; KCCQ at 12 months was assessed, adjusted for \( \Delta \) = baseline KCCQ, beta = 0.842; Placebo (n = 203) versus Ivabradine (n = 842) Placebo.

How treatments are evaluated for ACC/AHA/HFSA Guidelines

<table>
<thead>
<tr>
<th>Class (Strength) of Recommendation (COR)</th>
<th>Level (Quality) of Evidence (LOE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (benefit &gt;&gt; risk)</td>
<td>Level A: Evidence from more than 1 randomized clinical trial or meta-analyses of high-quality randomized clinical trials, or 1 or more randomized clinical trials corroborated by high-quality registry studies</td>
</tr>
<tr>
<td>Class IIa (benefit &gt; risk)</td>
<td>Level B (NEW): Evidence from 1 or more randomized clinical trials or meta-analyses of moderate quality randomized clinical trials</td>
</tr>
<tr>
<td>Class IIb (benefit &gt; risk)</td>
<td>Level B-NN (NEW): Evidence from 1 or more well-designed non-randomized studies, observational studies, or registry studies, or meta-analyses of such studies</td>
</tr>
<tr>
<td>Class III (harm &gt; risk; benefit)</td>
<td>Level C-D: Consensus of expert opinion based on clinical experience</td>
</tr>
</tbody>
</table>


Potential Candidates for Ivabradine Therapy

Patients with stable symptomatic chronic heart failure with LVEF ≤ 35% in sinus rhythm receiving standard therapy with resting heart rate ≥ 70 bpm

- Taking maximally tolerated doses of beta-blockers
  - Common reasons for not taking maximally tolerated dose
    - Hypotension
    - Fatigue
    - Dizziness
- Contraindicated to beta-blocker use
  - Common reasons for not receiving any dose
    - COPD
    - Hypotension
    - Severe Asthma
Summary

- Ivabradine is the first-in-class, HCN channel blocker that lowers heart rate.
- Indicated to reduce risk of hospitalization for worsening HF in patients with stable symptomatic CHF with LVEF ≤ 35%, who are in sinus rhythm with resting HR ≥ 70 bpm.
- Maximally tolerated beta-blockers
- Contraindication to beta-blockers
- Current guideline updates provide a moderate recommendation (Class IIa; LOE B-R) based on SHIFT data.
- Further study needed in other populations?
Digoxin and Heart Failure: The End of an Era?

Steven P. Dunn, PharmD, BCPP (AG Cardiology), FAHA
Pharmacy Clinical Coordinator, Heart & Vascular
University of Virginia Health System
Assistant Professor of Medicine, UVA School of Medicine
Charlottesville, Virginia
October 2016

Learning Objectives

• Review the pitfalls of digoxin therapy in heart failure.
• Define the risk of mortality in digoxin-treated patients.
• Clarify the role for digoxin in the management of heart failure.

Conflict of Interests

• No relevant conflicts
• I do have foxglove in my garden

The Digoxin Era

• Digoxin has been in use for cardiac disease for more than 200 years
• Medical utility of foxglove first identified by Withering

“...the proposal for digitalization... There was no dyspnea on lying flat... The lungs were entirely clear.”
--Dr. Howard G. Bruenn on treating President Franklin D. Roosevelt

Lower serum digoxin concentration associated with improved mortality

Withering describes the use of foxglove in heart failure

DIG
No mortality benefit to digoxin in HF; reduces rehospitalization

Digoxin analyses in atrial fibrillation

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Guideline Recommendations

- 2013 ACC/AHA: Class IIa, LOE C: “Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF”
- 2010 HFSA: “Digoxin may be considered to improve symptoms in patients with reduced LV EF who have signs and symptoms of HF and are receiving standard therapy” [SOE B/C]
- 2016 ESC: “Digoxin may be considered in patients in sinus rhythm with symptomatic HF rEF to reduce the risk of hospitalization…”
- 2013 CCS: “We recommend digoxin in patients in sinus rhythm who continue to have moderate to severe symptoms, despite optimized HF therapy to relieve symptoms and reduce hospitalizations” [Strong Recommendation]
The DIG Trial

<table>
<thead>
<tr>
<th>Concomitant Therapies (%)</th>
<th>Digoxin (n=3397)</th>
<th>Placebo (n=3403)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>81.2</td>
<td>82.2</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>94.1</td>
<td>94.8</td>
</tr>
<tr>
<td>Nitrates</td>
<td>42.1</td>
<td>43.1</td>
</tr>
<tr>
<td>Other vasodilators</td>
<td>5.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>MRA's</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Bi-ventricular pacing/ICD</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Digoxin Headwinds

- **(Un)ease of use; potential for toxicity**
- Lack of overall survival benefit in heart failure patients
- Increase in mortality in digoxin treated patients with atrial fibrillation?
- Alternatives to digoxin in selected patients

Digoxin in Atrial Fibrillation

- **AFFIRM Trial – A Tale of Two Analyses**
  - Whitbeck et al.
    - Analyzed digoxin use in multivariate Cox proportional hazard ratio
    - All-cause mortality: HR 1.41, 95% CI 1.19-1.64
    - CHF patients only: HR 1.41, 95% CI 1.09-1.84
  - Gheorghiade et al.
    - Analyzed digoxin use in propensity matched cohorts
    - Digoxin not associated with all-cause mortality (HR 1.06, 95% CI 0.83-1.37) or cardiovascular mortality (HR 1.13, 95% CI 0.79-1.63)

Alternatives to Digoxin

- The DIG trial was conducted prior to modern-day HF therapies:
  - Beta-blockers, MRA’s, device therapy
  - Ivabradine was FDA approved in 2015 and has been in use in Europe since 2005
    - Slows atrioventricular node, reducing sinus heart rate
Ivabradine – SHIFT trial

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>IVA (%)</th>
<th>PLB (%)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or HF hospitalization</td>
<td>24</td>
<td>24</td>
<td>0.73</td>
<td>0.0001</td>
</tr>
<tr>
<td>HF death</td>
<td>3</td>
<td>5</td>
<td>0.74</td>
<td>0.054</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>16</td>
<td>21</td>
<td>0.74</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CV death, HF hospitalization, or admission for nonfatal MI</td>
<td>25</td>
<td>30</td>
<td>0.74 (0.64-0.89)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Role of Digoxin in Heart Failure

- Digoxin is no longer first-line therapy in patients with heart failure
- Digoxin use should likely be relegated to specialized HF or EP clinics
- Digoxin may be useful as secondary therapy in patients with continued symptoms or intolerant/contraindicated for first-line therapy (especially beta-blockers)
- Ivabradine may be a better choice but potentially unaffordable for many
- Digoxin as add-on therapy for atrial fibrillation and normal LVEF is in question
- Digoxin still has a role in heart failure patients with atrial fibrillation
  - Ivabradine will NOT slow RVR from atrial dysrhythmia
- Other cardiac indications:
  - Congenital
  - RV inotropic support (patients with LVADs, pulmonary hypertension)

Digoxin - Pearls for Use

- Excellent role for pharmacists in heart failure clinics
- Screen for renal function
- Examine drug-drug interactions carefully involving p-glycoprotein (amiodarone)
- Use a nomogram (Bauman-DiDomenico Nomogram - Arch Intern Med. 2006 Dec 11;166(22):2539-45) or calculator (DigCalc – available on Apple App Store and Google Play)
- Most HF patients will require 125 mcg/day or less – maintain digoxin trough concentration of 0.5-1 ng/ml
- Don’t check concentrations within 4-6 hours after taking a dose

Digoxin – Future Directions?

- Don’t count out a drug that’s been in use for over 200 years!
- DIGIT-HF:
  - HFrEF III/IV or HFrEF II and EF <20% with or without AF
  - Primary endpoint: Composite of mortality and HF hospitalization
- RATE-AF:
  - HFrEF NYHA II or greater and permanent AF
  - Primary endpoint: Patient reported Quality of Life
Emerging Concepts in the Management of Clostridium difficile-Associated Diarrhea

P. Brandon Bookstaver, PharmD, FCCP, FIDSA, BCPS, AAHIVP
Associate Professor & Director of Residency Training
Infectious Diseases Pharmacist
College of Pharmacy, University of South Carolina & Palmetto Health Richland
Columbia, SC

October 25, 2016

Conflicts of Interest

• *Clostridium difficile* infection Speaker for Rockpointe Inc. on educational grant funded by Merck & Co., Inc.

Learning Objectives

• Discuss the clinical utility of *C. difficile* ribotyping

• Define the role of metronidazole as a first-line therapy

• Outline the role of pharmacists in fecal bacteriotherapy

Audience Question

How many of your institutions are doing *C. difficile* ribotyping?

• A) On all positive CDI tests

• B) By request only

• C) Not available at my institution

• D) Ribo who?

Clostridium difficile: Pathogenicity Locus & Typing Methods

- Restriction endonuclease analysis (eg BI)
- Pulsed-field gel electrophoresis (eg North American pulsed-field type 1, NAP1)
- Toxinotyping – Toxin type I to XXXIV
- Ribotyping – >200 ribotypes identified

B1/NAP1/027 --- aka Ribotype 027

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Antibiotic Resistance in RT027

<table>
<thead>
<tr>
<th>PCR Ribotype</th>
<th>MEZ</th>
<th>Cldm</th>
<th>Minfloxac</th>
<th>Rifampin</th>
</tr>
</thead>
<tbody>
<tr>
<td>027</td>
<td>0.02</td>
<td>32</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>

- What about metronidazole or vancomycin resistance?
- MIC50 and MIC90 values reportedly higher for metronidazole in RT-027, but limited resistance (MIC>2mg/ml) reported globally.

Recurrence & RT-027

- Figueroa I, et al. used strains from patients included in original Phase 3 RCT for fidaxomycin vs. vancomycin.
- Higher rate of recurrence with RT-027 with same strain (re-lapse).
- Advantages of fidaxomycin for reduced recurrence rates compared to vancomycin was mitigated in RT-027 strains.
- Richardson C, et al. in a Canadian population, RT-027 appeared significantly associated with recurrence compared to other Rfs.
- One limitation to interpretation is that sporadic burden appears higher in hospital acquired cases in epidemics, which are both associated with RT-027.
- Other strong predictors such as concurrent antibiotics too.

Ribotyping Options

- Fluorescent ribotyping, modified capillary gel electrophoresis, multilocus variable-number tandem-repeat analysis.
- Commercial product: Cepheid Xpert C. difficile Epi assay.
- tcdB, cdt, and single-base deletion in tcdC.
- Sensitivity: 96-99.7% and specificity: 93-98.6%.

Severity of Disease & Severe Clinical Outcomes Association with RT-027

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>RT027 vs. Association Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walk J, et al. Clin Infect Dis 2014</td>
<td>14% RT-027(U of Michigan)</td>
<td>Severe disease: 1.90 (0.83 – 3.23) &amp; 1.35 (0.83 – 2.14) in derivation &amp; validation data sets, respectively</td>
</tr>
<tr>
<td>See I, et al. Clin Infect Dis 2014</td>
<td>28.4% RT-027 (CDC EIP)</td>
<td>Severe disease: 1.74 (1.36-2.24) &amp; Severe outcomes: 1.66 (1.09-2.54) increased 14-day mortality</td>
</tr>
<tr>
<td>Aitken SL, et al. ICHE 2015</td>
<td>24% RT-027 (Houston)</td>
<td>Severe disease: 1.27 (0.83-1.94) &amp; Severe outcomes: 1.28 (0.87-1.90)</td>
</tr>
</tbody>
</table>

Summary Assessment of Outcomes & Ribotyping

- RT-027 consistently associated with the following:
  - Disease in older patients.
  - Hospital acquired infections/outbreaks.
  - In episodes/clusters, RT-027 associated with severe diseases/outcomes.
  - Other Rfs (eg RT-078) equally virulent.
  - Some Rfs (014-020) significantly less virulent.
  - Clinical outcomes such as concurrent antibiotics & organ dysfunction consistent correlation with negative outcomes.

So, what should we do?

- Ribotyping as a rapid diagnostic test directly from stool is limited to a single test currently.
- Advantages:
  - Infection control & hospital epidemiology (outbreaks)?
  - Research purposes.
- Questions:
  - Would this impact treatment decisions? Would you utilize vancomycin?
  - Would you treat a recurrent episode differently? Or utilize concurrent antibiotics differently?

- My perspective: Clinical and host factors are more consistently predictive of negative outcomes in CDI; thus ribotyping at your institution should not be a [the] priority diagnostic tool. If using or plan to obtain, please collaborate/engage in epidemiologic, clinical and outcomes research – it’s still needed.
Audience response
Where does metronidazole fit in your CDI protocol at your institution?
- A) First-line therapy for majority of patients regardless of severity of illness
- C) One of the above options plus typical first recurrence.
- D) Infrequently used at my institution except in specific instances.

Metronidazole for Clostridium difficile-Associated Disease: Is It Okay for Mom?

Examining Clinical Cure Rates: Vancomycin vs. Metronidazole
- Meta-analysis of studies examining metronidazole versus vancomycin
- Quality of evidence:
  - 3 High quality
  - 6 Moderate quality

Metronidazole PK Concerns
- Average fecal concentrations following metronidazole 400mg PO q8 hours (or 500mg IV q8) in early disease/watery stools = 9 mcg/g
- Hydroxymetabolite ~12 mcg/g
- As stool becomes more formed what happens to metronidazole fecal concentrations?
- Confirmed in healthy volunteers
- Majority of metronidazole absorbed in upper GI tract; as inflammation decreases, movement into gut lumen is reduced

Clostridium difficile Infection
United States Guideline Comparison

Examining Clinical Cure Rates: Vancomycin vs. Metronidazole
- Meta-analysis (described previously)
- Retrospective cohort of VAMC 2005 – 2012 of + CDI (any severity)
- 8 week recurrence rates: V: 15.8% vs. M: 16.7%, p=0.32
- 30-d mortality: V: 8.6% vs. M: 12.4%, RR=0.69 (0.59-0.80)

Resistance concerns w/ Metronidazole?
- Resistance / reduced susceptibility (MIC>4 mcg/mL) to metronidazole has sporadically been reported

**Testing methods create significant variation in susceptibility testing results**
Ex: E-test tend to underestimate MIC values for metronidazole and C. difficile
Other potential concerns of metronidazole therapy: ADEs, DDIs and VRE

- CNS toxicity – overall rare; primarily manifesting as cerebellar dysfunction (77%) or altered mental status (33%)
- Median duration 54 days; 11% among those <72 hours of tx.
- Drug-drug interactions
  - ETOH-based solutions
  - Warfarin
- VRE colonization associated with up to 50% of CDI cases
  - Lack of correlation with drug therapy
  - Increases during therapy, reduced by 2 weeks post-completion


Summary Comparison: Metronidazole vs. Vancomycin

<table>
<thead>
<tr>
<th>Variable</th>
<th>Metronidazole</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-Moderate</td>
<td>Guideline recommended; supported by evidence</td>
<td>Supported by evidence, recent RCT, VA cohort and meta-analysis, suggesting superiority in all cases</td>
</tr>
<tr>
<td>Severe Disease</td>
<td>Inferior to vancomycin</td>
<td>Superior to metronidazole, supported by evidence as 1st line</td>
</tr>
<tr>
<td>Recurrence rates</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>VRE colonization /impact gut</td>
<td>Infrequent ADE (NAG), warfarin, DDI/AD</td>
<td>Frequent ADE &gt;500-1000 times MIC, no direct clinical link to success/failure</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Fecal conc. &gt;8mg/kg; reduced fecal concentrations as disease improves; no direct clinical link to failure</td>
<td>Fecal conc. &gt;500-1000 times MIC, no direct clinical link to success/failure</td>
</tr>
<tr>
<td>Resistance</td>
<td>Sporadic; no direct link to clinical failures</td>
<td>Rare; highly dependent on testing methods</td>
</tr>
<tr>
<td>Cost</td>
<td>$5</td>
<td>$5 (if using IV formulation); $55 if using capsules</td>
</tr>
</tbody>
</table>

Audience Response

How many of your institutions are actively doing fecal microbiota transplants?

What is your current role in FMT at your institution?

- A) None, but I think they’re cool
- B) None, and I think they’re grossss
- C) Significant involvement – I assisted in protocol development
- D) Very significant involvement – I assisted in protocol development and assist with performing the FMT (eg screening, packaging, etc)

Fecal Microbiota Transplant - The ultimate “probiotic” since 1958 -

- Healthy related or unrelated donor stool transplanted via ND/enema/colonoscopy to patient with recurrent/relapsing CDI

- What is required?
  - Hospital protocol
  - IND not required if used for CDI

- Resource page: https://www.idsociety.org/FMT/

Fecal Microbiota Transplant: Rates of cure without relapse at 10 weeks

First Infusion of Donor Feces (N=16) Focus Overall (N=10)

- Vancomycin (N=13)
- FMT-related ADE: Belching: (3/10), 9%

- First Infusion of Donor Feces (N=16) Focus Overall (N=10)

- Vancomycin (N=13)
- FMT-related ADE: Belching: (3/10), 9%
Commercial Product vs. Local Prep

Screening of potential donor...or the donor could be you?

<table>
<thead>
<tr>
<th>Serum Labs</th>
<th>Stool Specimen</th>
<th>Other Donor Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>C. difficile toxin B (PCR)</td>
<td>≥ 18 y/o</td>
</tr>
<tr>
<td>HBV (anti-HCV Ab)</td>
<td>C. difficile toxin A &amp; B (PCR)</td>
<td>No antibiotics for 3 months</td>
</tr>
<tr>
<td>HAV (IgM)</td>
<td>MDRO Gram*</td>
<td>No auto-immune disease or DMARD tx.</td>
</tr>
<tr>
<td>HLA</td>
<td>No chronic pain d/o</td>
<td></td>
</tr>
<tr>
<td>ICVirus*</td>
<td>No malignancy</td>
<td></td>
</tr>
<tr>
<td>HIV2-1*</td>
<td>*Obesity</td>
<td></td>
</tr>
<tr>
<td>HPV*</td>
<td>*Current PPI use</td>
<td></td>
</tr>
<tr>
<td>*Food intake/allergens</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Available at: https://www.gastro.org/research/Joint_Society_FMT_Guidance.pdf

Billing & Coding

• Commercial Payers
  • 44705: Preparation of fecal microbiota for instillation, including assessment of donor specimen
• CMS Beneficiaries
  • GG455, Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen
  • No payment available for screening labs

Get your hands dirty

Summary of Pharmacist’s Role in FMT

1) Identifying potential patients for FMT
   • Best achieved by knowing the evidence

2) Ensuring/helping to develop hospital protocol
   • Available routes to deliver FMT at your institution
   • Local prep versus commercial product
   • Donor bank versus individual related or unrelated donors (what to screen for)
   • Billing codes

3) Prepping the product

4) Logging patient outcomes for future requirements from FDA or for scholarly purposes

Emerging Concepts in the Management of Clostridium difficile-Associated Diarrhea

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Short-Course Antimicrobials for Systemic Infections: How Low Can We Go?

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Conflict of Interests
• None

Learning Objectives
• Analyze the evidence base for shortening antimicrobial courses
• Outline the benefits/risks of short course antibiotic therapy
• Define the role of antimicrobial stewardship in the implementation of abbreviated antibiotic course

Duration of Therapy
Limited science behind the numbers...
... GAβHS pharyngitis...

The Good... and Bad of Shortened Therapy

Potential Positives
• Less selective pressure
• Dead bugs don’t mutate – hit hard, stop early
• Less cost

Potential Negatives
• Poorer clinical response
• Relapse/Reinfection
• Readmissions

Does this translate to severe infections?

Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial
• 401 VAP patients
  • No mortality difference (18.8% short vs 17.2%)
  • No LOS or ICU LOS difference
  • Caution for non-fermenting GNR (e.g., Pseudomonas sp)
  • 40.6% recurrence vs 25.4%

Reconfirmed in 2015 Cochrane Review


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Intraabdominal Infections

- Randomized 518 patients with adequate source control
  - Standard abx: 2d post clinical improvement (fever, WBC, ileus)
  - Short course: 4 ± 1d
- No outcome differences
  - Surgical Site Infect (6.6% short vs 8.8%)
  - Recurrence (15.6% short vs 13.8%)
  - Death (1.2% short vs 0.8%)
- Secondary analysis with sepsis unchanged

Bacteremia

- Difficult to compare sources
- 24 trials examined
- No differences in
  - Clinical cure (86.5% vs. 95.9%)
  - Microbiological cure (100% vs 93.8%)
  - Survival (88.2% vs 89.6%)

Community Acquired Pneumonia

- Are the IDSA/ATS Guidelines Safe?
- Randomized Controlled Trial, 312 patients
- Intervention at Day 5 to consider stopping per guidelines

10d vs 5d of treatment
No outcome differences

Community Acquired Pneumonia

- Antibiotic time-out at 48h, including duration if extended
- Audit and Feedback
- Automatic stop orders

Antimicrobial Stewardship Implications

CDC Core Elements
- "Antibiotic time-out" at 48h, including duration if extended
- Audit and Feedback
- Automatic stop orders

Targeted duration reductions
- Choose an indication with data (e.g., Intraabdominal)
- Get baseline data
- Educate
- Audit and prepare for windows (e.g., at d3 begin conversation)
- Follow up and report

Can Biomarkers Save Us?

- C-reactive protein & Procalcitonin
  - Unclear utility
  - Send out labs PCT
  - Further data needed

No clinical outcome differences with +3d excess therapy
Current State of Short Durations

- IAI – 4d post source control
- VAP – 7-8d (more for Pseudomonas controversial)
- Hospitalized CAP – 5d
- Bacteremia & Sepsis?

Stay tuned...


3-6 days = 10 days?

Continued questions
- Can we go <7 days?
- Biomarker improvement
- Clinical factors favoring shortening
- Differential antibiotic effects

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