Learning Objectives

1. Identify the risks of overuse of benzodiazepine therapy and its impact on patients with alcohol withdrawal
2. Describe the mechanism of action and rationale for use of clonidine as adjunctive therapy in alcohol withdrawal

Alcohol Withdrawal Syndrome (AWS)

- Significant cause of morbidity and mortality
  - 17.9 million Americans have alcohol dependence
  - Up to 33% of intensive care unit (ICU) admissions are at risk of alcohol withdrawal

Alcohol Withdrawal Syndrome (AWS)

Background

Chronic Alcohol Use
GABA Agonism and NMDA Antagonism
Compensatory Neurotransmitter Changes
Abrupt Cessation ➔ AUTONOMIC OVERACTIVITY

Current Practice

Background

Benzodiazepines (BZD) are the treatment of choice
No studies have demonstrated efficacy of one BZD over others
Choice is dependent on patient specific factors
No difference in symptom-triggered versus fixed-dose strategies
Oversed can lead to respiratory depression, sedation, mechanical ventilation, and potentially ICU admission
Which of the following is/are potential side effect(s) of benzodiazepines?

A. Respiratory depression
B. Hypertension
C. Sedation
D. A and C

Alpha-2 Agonists

Background

• Rationale for evaluation of use as adjunct therapy
• May be beneficial as adjunct therapy by decreasing the sympathetic surge, ultimately, decreasing BZD requirements

Effect of Clonidine on Sympathetic Activity

• Randomized, double blind, parallel group trial in 20 patients who met defined criteria for chronic alcoholism who presented with AWS

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP/HR</td>
<td>Significantly lower in the clonidine group</td>
</tr>
<tr>
<td>Symptoms</td>
<td>No major differences between the groups in withdrawal intensity ratings</td>
</tr>
<tr>
<td>Plasma NE/Epi</td>
<td>Sustained fall in clonidine group</td>
</tr>
</tbody>
</table>

Adjunctive Dexmedetomidine for AWS

• Single center, retrospective, controlled, cohort study evaluating the impact of early dexmedetomidine (DEX) on critically ill patients with AWS

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative 12-hour BZD requirement change</td>
<td>-20 mg vs -8.3 mg, p = 0.0455</td>
</tr>
<tr>
<td>Post minus pre after DEX exposure</td>
<td></td>
</tr>
<tr>
<td>Length of ICU stay</td>
<td>87 hours vs 54 hours, p = 0.23</td>
</tr>
<tr>
<td>Incidence of mechanical ventilation (MV)</td>
<td>8% vs 9%, p = 1.0</td>
</tr>
<tr>
<td>Duration of MV</td>
<td>31 hours vs 49 hours, p = 0.23</td>
</tr>
</tbody>
</table>
Alpha-2 Agonist Comparison

<table>
<thead>
<tr>
<th></th>
<th>Dexmedetomidine</th>
<th>Clonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action</td>
<td>5-10 minutes</td>
<td>30-60 minutes</td>
</tr>
<tr>
<td>Duration of action</td>
<td>60 minutes</td>
<td>4 to 6 hours</td>
</tr>
<tr>
<td>Cost</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Formulation</td>
<td>Intravenous</td>
<td>Oral, transdermal</td>
</tr>
<tr>
<td>NMH restrictions</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Common adverse effects</td>
<td>Hypotension, bradycardia</td>
<td>Hypotension, rebound hypertension</td>
</tr>
</tbody>
</table>

Northwestern Memorial Hospital (NMH) Practice

<table>
<thead>
<tr>
<th></th>
<th>Alcohol withdrawal protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No NMH protocol</td>
</tr>
<tr>
<td></td>
<td>Provider preference</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Dexmedetomidine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Restricted to mechanically ventilated patients</td>
</tr>
<tr>
<td></td>
<td>Indication is unaddressed by P&amp;T committee</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CIWA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rarely used in the ED</td>
</tr>
<tr>
<td></td>
<td>Lack of data</td>
</tr>
<tr>
<td></td>
<td>Time constraints</td>
</tr>
</tbody>
</table>

Study Rationale

- Gaps in literature
  - Clonidine was previously studied as monotherapy
  - Dexmedetomidine demonstrated BZD sparing effects
- Some ED physicians have begun using clonidine as an alternative to dexmedetomidine for adjunctive therapy
  - Rationale
    - ICU admission not required
    - Cost effective

Study Question

Does the administration of adjunctive clonidine in the emergency department for alcohol withdrawal decrease the benzodiazepine requirements?

Northwestern Memorial Hospital
Chicago, Illinois

- 894-bed Academic Medical Center Hospital
- Primary teaching affiliate of Northwestern University Feinberg School of Medicine
- Calendar Year 2016
  - Inpatient Admissions: 43,933
  - Emergency Room Visits: 87,893

Study Design

- Single center retrospective cohort study
- Alcohol withdrawal patients admitted to NMH ED
- Study arms:
  - BZD monotherapy [control group]
  - BZD plus adjunctive clonidine [intervention group]
- Matched at ratio of 3:1 based on rapid emergency medicine score
- Statistical analysis:
  - Continuous data analyzed using T-test
  - Categorical data analyzed using Chi-Square test
  - All statistical analysis performed using IBM SPSS v23
Rapid Emergency Medicine Score (REMS)

- Predictor of in-hospital mortality for nonsurgical patients in the emergency department
- Derivative of the APACHE II

### Predictor
- **Age**
- **Systolic blood pressure**
- **Diastolic blood pressure**
- **Heart rate**
- **Respiratory rate**
- **Glasgow coma score**
- **Oxygen saturation**

### REMS Score In-Hospital Mortality

<table>
<thead>
<tr>
<th>REMS Score</th>
<th>In-Hospital Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>0%</td>
</tr>
<tr>
<td>3-5</td>
<td>1%</td>
</tr>
<tr>
<td>6-9</td>
<td>3%</td>
</tr>
<tr>
<td>10-11</td>
<td>4%</td>
</tr>
<tr>
<td>12-13</td>
<td>10%</td>
</tr>
<tr>
<td>14-15</td>
<td>17%</td>
</tr>
<tr>
<td>16-17</td>
<td>38%</td>
</tr>
<tr>
<td>18-19</td>
<td>45%</td>
</tr>
<tr>
<td>20-21</td>
<td>56%</td>
</tr>
<tr>
<td>22-23</td>
<td>66%</td>
</tr>
<tr>
<td>24-26</td>
<td>100%</td>
</tr>
</tbody>
</table>


Study Population

- **Inclusion Criteria**
  - Patients 18 years or older who received at least 24 hours of BZD for alcohol withdrawal who present to the NMH emergency department
- **Exclusion Criteria**
  - Trauma
  - Primary diagnosis was not alcohol withdrawal
  - Discharged directly from the emergency department

Outcome Measures

- **Primary Endpoint**
  - 12 hour cumulative BZD requirements in lorazepam equivalents (LE)
- **Secondary Endpoints**
  - Total BZD requirements
  - Admission to the ICU
  - ICU and hospital days
  - Hypotension

Lorazepam Equivalents

<table>
<thead>
<tr>
<th>Benzodiazepine Conversions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg oral lorazepam</td>
</tr>
<tr>
<td>0.25 mg oral clonazepam</td>
</tr>
<tr>
<td>0.5 mg oral alprazolam</td>
</tr>
<tr>
<td>0.5 mg intravenous lorazepam</td>
</tr>
<tr>
<td>5 mg intravenous diazepam</td>
</tr>
<tr>
<td>10 mg oral chlordiazepoxide</td>
</tr>
</tbody>
</table>


Baseline Characteristics

<table>
<thead>
<tr>
<th>Results</th>
<th>Intervention group (n=11)</th>
<th>Control group (n=33)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50 (38-52)</td>
<td>47 (40-54)</td>
<td>0.62</td>
</tr>
<tr>
<td>Sex, male (n, %)</td>
<td>9 (82)</td>
<td>28 (85)</td>
<td>0.99</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73 (67-78)</td>
<td>77 (69-89)</td>
<td>0.09</td>
</tr>
<tr>
<td>REMS</td>
<td>6 (3-10)</td>
<td>6 (3-8)</td>
<td>0.62</td>
</tr>
<tr>
<td>Maximum SBP</td>
<td>185 (143-206)</td>
<td>167 (146-194)</td>
<td>0.28</td>
</tr>
<tr>
<td>Maximum DBP</td>
<td>101 (92-119)</td>
<td>99 (81-109)</td>
<td>0.52</td>
</tr>
<tr>
<td>Maximum HR</td>
<td>132 (112-138)</td>
<td>120 (107-130)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Results reported in median (IQR) unless otherwise noted.

Clonidine Use

Results

- Median cumulative clonidine in the ED
  - 100 mcg
  - Range: 100-300 mcg

- Continuation of clonidine after admission
  - 10/11 patients (91%)

- Median clonidine days
  - 3 days
  - Range: 1-4 days

Benzodiazepine Requirements

Results

<table>
<thead>
<tr>
<th></th>
<th>Intervention group (n=11)</th>
<th>Control group (n=33)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 hour cumulative BZD*</td>
<td>16 (3-19)</td>
<td>7 (4-13)</td>
<td>0.90</td>
</tr>
<tr>
<td>24 hour cumulative BZD</td>
<td>21 (16-30)</td>
<td>18 (11-34)</td>
<td>0.44</td>
</tr>
<tr>
<td>Total cumulative BZD</td>
<td>31 (21-48)</td>
<td>45 (26-71)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Results reported as milligrams of lorazepam equivalents in median (IQR)

*Primary outcome

Results

<table>
<thead>
<tr>
<th>TIME</th>
<th>6 hours</th>
<th>12 hours</th>
<th>24 hours</th>
<th>Total cumulative dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>8</td>
<td>15</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>12</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>15</td>
<td>31</td>
<td>65</td>
</tr>
</tbody>
</table>

Discussion

- Data did not show a statistical difference in 12 hour BZD requirements, but there may be a trend in decreased total BZD requirements

Discussion

- Clonidine continuation rate was higher than expected
- No differences in rates of hypotension
- Indicative that clonidine was well tolerated
- ED management has downstream effects
Limitations

- Small sample size
- Lack of statistical power
- Retrospective study
- Possible selection bias
- Limitations of REMS
- Included all patients who received clonidine regardless of how many doses he/she received

Conclusions

- Adjunctive clonidine was not associated with a reduction in 12 hour BZD requirements, total BZD requirements, ICU admission rates, or ICU/hospital days
- Clonidine was safe and well-tolerated
  - Clonidine did not result in higher rates of hypotension and was continued after admission in 90% of patients

Future Direction

- Submit manuscript for publication
- Further investigation in a prospective, randomized controlled trial
- Follow up evaluation to determine symptom mitigation and continuation rate of clonidine on discharge

Acknowledgments

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Sean DeFrates, PharmD, BCOP
Noelle Chapman, PharmD, BCPS, FASHP

Role of proton pump inhibitor and recurrent *Clostridium difficile* infection

Jiajun Liu, PharmD
Infectious Diseases Pharmacotherapy Fellow
Midwestern University
Chicago College of Pharmacy

Learning Objectives

3. Identify risk factors associated with recurrent *Clostridium difficile* infection.
4. Recognize the role of proton pump inhibitor exposure in recurrent *Clostridium difficile* infection.
Edwards Hines, Jr. VA Hospital
- Located 12 miles west of downtown Chicago
- Offers primary, extended, and specialty care services
- Has 471 beds and 6 community based outpatient clinics
- Serves 59,000 Veterans

Urgent threat

Risk factors
- Risk factors for the development of Clostridium difficile infection (CDI)
  - Non-CDI-directed antibiotic exposure
  - Advanced age
  - Previous hospitalization
  - Proton pump inhibitor (PPI)
    - Increased risk of CDI
    - Nosocomial and community setting
- Recurrence
  - ~18% to 32% (first)
  - Subsequent recurrence rate ~40% to 60%

Mechanism
- Jump and colleagues
  - Vegetative form of C. difficile may shed into environment and remain viable on moist surfaces
  - Higher pH and survival of the vegetative form
- Hypothesis
  - Ingestion of the viable vegetative form
  - Possible contribution to CDI development due to elevated gastric pH

Which of the following may be risk factor(s) for recurrent CDI?
A. Concomitant PPI use
B. Age <30
C. Receipt of antibiotics (non-CDI treatment)
D. A and C

What is one proposed mechanism between PPI and CDI recurrence?
A. Acid suppression by PPI leads to survival of vegetative form of C. difficile, which increases risk of CDI
B. PPI use may disrupt normal flora in the upper and lower GI tract
C. PPI use may increase inflammation, which increases risk of recurrent CDI
D. There is currently no hypothesized mechanism
Why is this important?

- Limited evidence exists as to how PPIs play a role in recurrent CDI
- Gastric acid suppression and outcomes in Clostridium difficile infection: a population-based study (Khanna et al. 2012)
- Proton pump inhibitors and risk for recurrent Clostridium difficile infection among inpatients (Freedberg et al. 2013)
- Epidemiology of Clostridium difficile infection and risk factors for unfavorable clinical outcomes: results of a hospital-based study in Barcelona, Spain (Rodríguez-Pardo et al. 2013)

Literature review

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Population</th>
<th>Relevant Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khanna et al. 2012</td>
<td>Population‐based</td>
<td>n=485 hospital and community patients, median age 67.5</td>
<td>CDI outcomes, recurrent CDI</td>
<td>Univariate: OR 0.75 (95% CI 0.47-1.20; p=0.22) Multivariate: OR 0.65 (95% CI 0.36-1.16; p=0.08)</td>
</tr>
<tr>
<td>Rodríguez‐Pardo et al. 2013</td>
<td>Prospective surveillance</td>
<td>n=137 patient from 15 hospitals, median age 72</td>
<td>Predictor of recurrent CDAD</td>
<td>Univariate: OR 1.99 (95% CI 1.043-3.81; p=0.035) Multivariate: OR 2.168 (95% CI 1.081-4.347; p=0.029)</td>
</tr>
<tr>
<td>Freedberg et al. 2013</td>
<td>Retrospective</td>
<td>n=994 inpatient adult, mean age 64</td>
<td>Risk factor for recurrence within 15-90 days of initial positive test</td>
<td>Multivariate: HR 0.82 (95% CI 0.58-1.16)</td>
</tr>
</tbody>
</table>

Study focus

- Role of proton pump inhibitor and recurrent Clostridium difficile infection
- Aim
  - To evaluate the association between PPI therapy and first recurrence of CDI

Study methods

- Retrospective, observational, single-center study
- All C. difficile PCR results electronically retrieved
- PCR results were screened via electronic medical record
- Included only the index CDI episode
- Each patient was included only once
- Patients were stratified into PPI-exposure group and non-PPI-exposure group
  - Further categorized based on CDI recurrence status

Study methods – key definitions

- Recurrent CDI
  - CDI diagnosis within 8 weeks after clinical cure of previous initial CDI episode
- Clinical cure
  - Resolution of signs and symptoms of initial CDI and maintenance of resolution for the duration of therapy
  - No further treatment for CDI as of the second day after the end of course of therapy
- PPI exposure
  - Receipt of PPI therapy for at least 48 hours after initial CDI diagnosis and prior to first recurrent episode

Study methods

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Secondary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact of PPI therapy on proportion of recurrent CDI</td>
<td>Impact of age, PPI exposure, and antibiotic use on proportion of recurrent CDI</td>
</tr>
</tbody>
</table>

Inclusion

- Adult patients ≥18 years of age
- In-hospital mortality prior to clinical cure of initial CDI episode
- C. difficile PCR results treated at outside institution and/or insufficient documentation through available electronic record
- CDI not treated
Study methods

Population with (+) PCR assay

- Initial CDI
  - Included
  - Excluded

- Recurrent CDI
  - Included if associated with initial CDI
  - Excluded

Study analyses

- A minimum of 206 unique patients are required to detect a difference of 25% with 80% power
- Two-sided alpha level of 0.05 for statistical significance
- Descriptive statistical analyses conducted using Epi Info™ (version 7.2.1)
- Univariate analyses
  - Continuous variables: Students t-test or Wilcoxon rank sum test
  - Dichotomous variables: Chi-square, Fisher’s exact test, or McNemar’s test


Patient level data

- Age
- Gender
- Race
- Height
- Weight
- Serum creatinine
- Admission date
- Admission from location
- Admission to location
- Discharge date
- Discharge to location
- Location at positive PCR
- CDI onset location
- Hospital length of stay (LOS)
- Prior antibiotics exposure
- Modified Charlson Comorbidity Index (M‐CCI)
- Date of CDI clinical resolution
- Initial CDI treatment
- Duration of CDI therapy (DOT)
- Hepatic dysfunction
- PPI therapy (dose, indication, route)
- Concurrent anti‐inflammatory therapy
- Time from first PPI dose to recurrent CDI
- Immunosuppression status
- Surgical history related to GI
- In‐hospital mortality
- Time to mortality
- Time to recurrence

Results

- Together, 578 valid, positive PCR results were available during the study period
- July 1, 2012 to June 30, 2016
- 442 unique patients were eligible for screening
- 80 patients included thus far
- Pending further data collection
- 13 patients excluded
  - In‐hospital all cause mortality prior to clinical cure (n=6)
  - CDI treated at outside institution and/or insufficient documentation through available electronic record (n=5)
  - Other reasons (n=2)

Baseline characteristics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Patients (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean ± SD (range)</td>
<td>68.4 ± 12.0 (35, 98)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>78 (97.5)</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td>White 62 (77.5) Black 16 (20.0) Unknown 2 (2.5)</td>
</tr>
<tr>
<td>M‐CCI, mean (SD)</td>
<td>3.0 (2.2)</td>
</tr>
<tr>
<td>PPI exposure, n (%)</td>
<td>48 (60.0)</td>
</tr>
<tr>
<td>Previous antibiotics exposure, n (%)</td>
<td>63 (79.8)</td>
</tr>
<tr>
<td>CDI onset location, n (%)</td>
<td>Community 38 (47.5) Residential 42 (52.5)</td>
</tr>
</tbody>
</table>
Results

<table>
<thead>
<tr>
<th>Demographics</th>
<th>No PPI exposure (n=32)</th>
<th>PPI exposure (n=48)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ±SD</td>
<td>67.6 ±13.2</td>
<td>67.0 ±11.2</td>
<td>0.6619</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>31 (96.9)</td>
<td>47 (97.9)</td>
<td>-</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>White</td>
<td>26 (81.3)</td>
<td>36 (75.0)</td>
<td>-</td>
</tr>
<tr>
<td>m-CCI, mean ±SD</td>
<td>2.4 ±1.9</td>
<td>3.5 ±2.4</td>
<td>0.0506</td>
</tr>
<tr>
<td>Prior antibiotics exposure, n (%)</td>
<td>24 (77.4)</td>
<td>39 (81.3)</td>
<td>0.7767</td>
</tr>
<tr>
<td>Recurrence CDI, n (%)</td>
<td>4 (12.5)</td>
<td>9 (18.8)</td>
<td>0.5471</td>
</tr>
<tr>
<td>Community onset, n (%)</td>
<td>17 (53.1)</td>
<td>21 (43.8)</td>
<td>0.4951</td>
</tr>
<tr>
<td>Admit to hospital</td>
<td>11 (34.4)</td>
<td>16 (33.3)</td>
<td>0.4910</td>
</tr>
</tbody>
</table>

Subgroup analyses

- Stratification by the following dichotomous variables and test for association between PPI use and CDI recurrence
  - PPI dose exposure (high dose vs. low dose)
  - Surgical history
  - Immunosuppression
  - DOT for CDI (<14 days vs. >14 days)
  - CDI-directed treatment
  - Admission from location
  - Age
  - Prior antibiotic exposure
  - Race/ethnicity
- Considered statistical significance if p values <0.10

Discussion

- Preliminary data revealed no association between PPI use and recurrent CDI

- Limitation
  - Mostly white, elderly male patients
  - Hospital length of stay is highly variable across groups
  - Likely due to extended rehabilitation stay

Moving forward...

- Pending data
- Evaluate the relationship between PPI exposure and first recurrent CDI
- Assess the duration of PPI therapy and its relationship with recurrent CDI
- Evaluate other potential risk factors for recurrent CDI

Acknowledgements

- Primary investigator
  - Jeffrey Wieczorkiewicz, PharmD, BCPS

- Co-investigator
  - Katie Suda, PharmD, MS

References

References


Hospital Readmission Rates for Patients Treated with Ceftriaxone and Azithromycin Versus Levofloxacin for Community Acquired Pneumonia

Luke Piarowski, PharmD
Clinical Staff Pharmacist
OSF Saint Mary Medical Center

Learning Objectives

5. Identify adverse effects of fluoroquinolones which are less prevalent in ceftriaxone and azithromycin.
6. Discuss resistance considerations when comparing empiric treatment of CAP for inpatients.

Community Acquired Pneumonia (CAP)

• Pneumonia is the primary reason for severe sepsis and infectious death in US.
• Streptococcus pneumoniae
• 75% acute presentations of CAP
• Inpatient non-ICU treatment
• Respiratory fluoroquinolone
• Beta-lactam plus a macrolide
• Both options show efficacy
• Limited data of preferred regimen

Levofloxacin and Azithromycin Plus Ceftriaxone in Moderate to Severe CAP

• Open-label, randomized
• Levofloxacin 500 mg PO/IV
• Azithromycin 500 mg PO and ceftriaxone 1 g IV
• At least 10 days of therapy
• 110 patients in FQ group vs 114 patients in combination
• 94.1% FQ vs 92.3% combo clinical success rate
• 89.5% FQ vs 92.3% combo microbiologic eradication
• 5.3% FQ vs 9.3% combo ADE
• Levofloxacin is at least as effective as combination for CAP

Fluoroquinolones (FQ)

• Black Box Warning
• Tendonitis
• Tendon rupture
• Peripheral neuropathy
• CNS
• Hallucinations
• Dizziness
• Confusion
• FDA Strengthens Warning
• July 2016
• Fluoroquinolones reserved for patients with no other treatment choices
• Acute bacterial sinusitis
• Acute exacerbation of chronic bronchitis
• Uncomplicated urinary tract infection
• Risks may outweigh benefits
Fluoroquinolones (FQ)

- \textit{Clostridium difficile}
  - Cephalosporins, FQ, and clindamycin
  - FQ resistant strain outbreaks\textsuperscript{8}
    - 12 hospitals in Quebec
    - Patients with CDI were more likely to have received a FQ or cephalosporin
    - \textit{C. difficile} strain resistant to FQ determined responsible for outbreak

- \textit{Streptococcus pneumoniae}\textsuperscript{9}
  - 1988 to 1997
    - FQ prescriptions on the rise
    - Pneumococci reduced susceptibility to FQ
      - 0% in 1993
      - 1.7% in 1997 and 1998.
      - Strains associated with penicillin resistance

Purpose

- To determine if the combination ceftriaxone and azithromycin is superior to levofloxacin in treatment of CAP in non-ICU patients based on readmission rates

Endpoints

- Primary
  - All cause 30 day readmission rates
  - Planned admissions or emergency department
- Secondary
  - Length of stay
  - 30 day mortality
  - Total inpatient treatment length
  - \textit{C. difficile} infection development
  - Outpatient treatment length
  - Outpatient treatment choice
  - Adverse effects

Study Setting

- OSF Saint Francis Medical Center, Peoria, IL
  - 629 beds
- OSF Saint Anthony Medical Center, Rockford, IL
  - 254 beds

Methods

- Retrospective chart review
- Hospital quality metric program
- Multi-center
- IRB approval
  - University Illinois College of Medicine Peoria
  - OSF St. Francis and St. Anthony Medical Centers
- Intention to Treat
- Superiority
- Historical data

Inclusion Criteria

- Admitted to:
  - OSF Saint Anthony Medical Center
  - OSF Saint Francis Medical Center
- Community acquired pneumonia DRG
  - 193, 194, 195
- 18 years and older
- Received at least 48 hours of therapy
  - Ceftriaxone and azithromycin
  - Levofloxacin
Exclusion Criteria

- ICU admissions
- Less than 18 years or greater than 88 years
- Pregnant women
- Prisoners
- Received non-study antibiotics within first 48 hours
- Received both study arms within first 48 hours

Exclusion Criteria

- Immunocompromised patients
- Transplant patients on immunosuppressive therapy
- Chemotherapy administration within 90 days
- Greater than 30 days of high dose steroids
- HIV with a CD4 count of less than 350.
- COPD and related DRGs
- Potential misdiagnosed code
- IV antibiotics or 5 days of antibiotics in past 90 days

Data Collection

- Retrospective Chart Review
- Hospital quality metrics program
- Develop patient population
- Facility inclusion
- Simple pneumonia DRG
  - 193, 194, 195
  - Exclude non-CAP isolations
  - Pseudomonas, Staphylococcus aureus, viral, TB etc.
- Exclude DRGs indicating COPD
- June 2014 – September 2016
- Azithromycin and levofloxacin products
  - Separate patient lists

Statistical Analysis

- Chi-square test for categorical values and binary outcomes
- T-test for age comparison within each group
- Wilcoxon rank-sum test for continuous outcomes

Excluded Patients

642 charts reviewed
COPD
IV antibiotics
Multiple antibiotics
203 patients

Treatment Groups

Patients Included

- N = 101, 50%
- Levofloxacin
- N = 102, 50%
- Ceftriaxone and azithromycin
Patient Demographics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total N = 203 (%)</th>
<th>Ceftriaxone + Azithromycin N = 102 (%)</th>
<th>Levofloxacin N = 101 (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ±SD)</td>
<td>67 ± 18.2</td>
<td>67.5 ± 19.0</td>
<td>66.5 ± 17.5</td>
<td>0.687^</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>96 (47.3)</td>
<td>44 (43.1)</td>
<td>52 (51.5)</td>
<td>0.214^</td>
</tr>
<tr>
<td>Male</td>
<td>107 (52.7)</td>
<td>58 (56.9)</td>
<td>49 (48.5)</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>157 (77.3)</td>
<td>72 (70.6)</td>
<td>85 (84.2)</td>
<td>0.033^</td>
</tr>
<tr>
<td>No</td>
<td>46 (22.7)</td>
<td>34 (32.4)</td>
<td>16 (15.8)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>132 (65.0)</td>
<td>65 (64.4)</td>
<td>67 (67.6)</td>
<td>0.431^</td>
</tr>
<tr>
<td>No</td>
<td>71 (35.0)</td>
<td>39 (35.6)</td>
<td>34 (32.4)</td>
<td></td>
</tr>
</tbody>
</table>

^t-test
^Chi-square test

Primary Outcome

• P value
  • 0.241

![Chart showing All-cause 30 Day Readmissions]

Secondary Outcomes

<table>
<thead>
<tr>
<th>Secondary Outcome</th>
<th>Ceftriaxone + Azithromycin N = 102 (%)</th>
<th>Levofloxacin N = 101 (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of Stay</td>
<td>3 (1 – 10) days</td>
<td>3 (1 – 10) days</td>
<td>0.255^</td>
</tr>
<tr>
<td>Outpatient Treatment Length Mean</td>
<td>5 (0 – 14) days</td>
<td>4 (0 – 23) days</td>
<td>0.316^</td>
</tr>
<tr>
<td>Total Inpatient Treatment Length Mean</td>
<td>4 (1 – 9) days</td>
<td>3 (1 – 12) days</td>
<td>0.873^</td>
</tr>
<tr>
<td>C. Difficile Infection</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1.000^</td>
</tr>
<tr>
<td>30 Day Mortality</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>0.432^</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>2 (2)</td>
<td>3 (3)</td>
<td>0.883^</td>
</tr>
</tbody>
</table>

^Wilcoxon rank-sum
^Chi-square test

Discussion

- Statistical power was not met
- 203 of ~650 estimated patients
- Based on estimated readmission rates
- No difference observed
- CHF patients
- Follow-up
- Azithromycin
- Cannot support one therapy as preference
- Clinical factors of patient
- Adverse effects
- Spectrum of activity

Limitations

- Study did not meet power
- Determined during chart review process
- Overestimated readmission rates
- Retrospective chart review
- Narrow population
- Many exclusion factors
- Intention to increase external validity
- Limited patients included
Future Directions

• Future study including patients with COPD
• Additional data points of medication allergies, sputum cultures, Streptococcus pneumoniae urine antigen, and blood cultures
• Increased patient population beyond June 2014
• Further studies to determine preference of levofloxacin or ceftriaxone with azithromycin for initial CAP treatment

Which of the following organisms is the most common cause of CAP and has been associated with increased rates of fluoroquinolone resistance?

A. Streptococcus pneumoniae
B. Haemophilus influenzae
C. Legionella species
D. Mycoplasma pneumoniae

Which of the following is a concerning side effect for fluoroquinolones which is not a black box warning?

A. Tendonitis
B. Clostridium difficile infection
C. Peripheral neuropathy
D. Hallucinations

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Questions for Speakers?