Residency Project Pearls

Adherence to and Outcomes Associated with a Clostridium difficile Infection Guideline at a Large Teaching Institution

RaeAnna C. Zatarski, Pharm.D.
September 15, 2012

Objectives

• Select a treatment plan for a patient with Clostridium difficile infection based on the severity of illness.

• Identify potential barriers to adherence to the Clostridium difficile infection treatment guidelines.

 Advocate Lutheran General Hospital (ALGH)

• Academic research institution
• Level 1 trauma center
• 645 bed capacity
• Located in Park Ridge, Illinois

Clostridium difficile Infection (CDI)

• Causes 20 – 30% of antibiotic associated diarrhea
• Risk factors for CDI
  – Prior antimicrobial or proton pump inhibitor use
  – Recent immunosuppressive therapy
• Epidemiology
  – Incidence: 85,700 in 1993 → 301,200 in 2005
  – Mortality: 5.7 / million in 1999 → 23.7 / million in 2004
  – Incidence at ALGH: 400 patient cases annually


Treatment

• Early treatment of CDI
  – Metronidazole designated as first line agent
  – Vancomycin limited to failures or intolerance
• Increased incidence of metronidazole failures caused shift in clinical practice
• Zar trial (2007)
  – Mild-moderate: metronidazole noninferior to vancomycin
  – Severe: vancomycin superior to metronidazole


Treatment

• ALGH approved physician-managed CDI treatment guidelines in July 2009
  – Stratified patients into severity categories according to clinical signs and symptoms
  – Recommended specific treatment regimens based on severity category
• SHEA / IDSA published their revised CDI treatment guidelines in May 2010

ALGH Recommendations for Initial Treatment

<table>
<thead>
<tr>
<th>Clinical Severity</th>
<th>Supportive Clinical Data</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-moderate</td>
<td>WBC &lt; 15,000 cell/mcL and a serum creatinine level &lt; 1.5 times premorbid level</td>
<td>Metronidazole 500mg PO q8h for 10 - 14 days</td>
</tr>
<tr>
<td>Severe</td>
<td>WBC ≥ 15,000 cell/mcL or serum creatinine level ≥ 1.5 times premorbid level</td>
<td>Vancomycin 125 mg PO q6h for 10 - 14 days</td>
</tr>
<tr>
<td>Severe - complicated</td>
<td>Hypotension, shock, ileus, megacolon</td>
<td>Vancomycin 500 mg PO q6h + metronidazole 500 mg IV q8h</td>
</tr>
</tbody>
</table>

Current Study

- **Rationale**
  - Anecdotal evidence suggested physician non-adherence
  - Concern regarding undertreatment of patients

- **Purpose**
  - To determine if physicians were adherent to the ALGH CDI guidelines
  - To determine if adherence to the guidelines improved patient outcomes

Methods

- Descriptive, retrospective chart review
- **Subject population**
  - Age ≥ 18 years diagnosed July 1, 2009 – June 30, 2011
  - CDI treatment initiated at LGH
- **Assessment**
  - Severity categorized based on clinical signs and symptoms
  - Initial treatment compared to recommended therapy
    - Evaluated for adherence
    - Classified as under, appropriate, or overtreatment

Endpoints

- **Primary endpoint:** percentage of subjects who were treated in accordance with CDI guidelines
- **Secondary endpoints**
  - Incidence of under, appropriate, and overtreatment
  - Incidence of clinical outcomes in treatment groups
  - Impact of proton pump inhibitor or prior antimicrobial use on CDI severity

Definitions

- **Clinical cure:** no need for therapy escalation; resolution of diarrhea by day 6; and subject survival
- **Recurrence:** positive stool toxin assay within 90 days of initial positive stool toxin assay
- **Mortality:** subject expired from any cause within 90 days of positive stool toxin assay
- **Antimicrobial use:** use of at least one dose of an antimicrobial in the eight weeks prior to the positive stool toxin assay

Statistics

- Descriptive study required 130 subjects for 80% power for the primary endpoint
- **Pearson Chi-Square / Fisher’s exact tests used to analyze group differences**
  - Two-tailed p value < 0.05 considered statistically significant for single comparisons
  - Two-tailed p value < 0.02 considered statistically significant for multiple comparisons (Bonferroni’s method)
Results

Baseline Characteristics: Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>[n = 250]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female [no (%)]</td>
<td>141 (56.4)</td>
</tr>
<tr>
<td>Age [mean (SD), range]</td>
<td>67.83 ± 17.36 (18 – 100)</td>
</tr>
<tr>
<td>Ethnicity [no (%)]</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>210 (84)</td>
</tr>
<tr>
<td>African-American</td>
<td>13 (5.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>12 (4.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7 (2.8)</td>
</tr>
<tr>
<td>History of CDI [no (%)]</td>
<td>18 (7.2)</td>
</tr>
</tbody>
</table>

Baseline Characteristics: Encounters

<table>
<thead>
<tr>
<th>Encounters [n = 324]</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Episode</td>
<td>220 (67.7)</td>
</tr>
<tr>
<td>1st recurrence</td>
<td>56 (17.3)</td>
</tr>
<tr>
<td>2nd recurrence</td>
<td>10 (3.1)</td>
</tr>
<tr>
<td>3rd recurrence</td>
<td>5 (1.5)</td>
</tr>
<tr>
<td>Reinfection</td>
<td>33 (10.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity [n = 324]</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-moderate</td>
<td>163 (50.3)</td>
</tr>
<tr>
<td>Severe</td>
<td>105 (32.4)</td>
</tr>
<tr>
<td>Severe-complicated</td>
<td>56 (17.3)</td>
</tr>
</tbody>
</table>

Adherence Rates

<table>
<thead>
<tr>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall [n = 324]</td>
</tr>
<tr>
<td>Mild-moderate [n = 163]</td>
</tr>
<tr>
<td>Severe [n = 105]</td>
</tr>
<tr>
<td>Severe-complicated [n = 56]</td>
</tr>
</tbody>
</table>

p < 0.001

Mild-moderate Treatment Regimens

<table>
<thead>
<tr>
<th>Regimen [n = 163]</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole 500 mg PO q8h</td>
<td>66 (40.5)</td>
</tr>
<tr>
<td>Metronidazole 500 mg IV q8h</td>
<td>22 (13.5)</td>
</tr>
<tr>
<td>Vancomycin 125 mg PO q6h *</td>
<td>51 (31.3)</td>
</tr>
<tr>
<td>Metronidazole 500 mg IV q8h + vancomycin 125 mg PO q6h</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (6.7)</td>
</tr>
</tbody>
</table>

* Appropriate depending on subject's history of illness.

Mild-moderate Treatment Regimens

- Appropriate treatment 97 (59.5%)
- Overtreatment 64 (38.3%)
- Undertreatment 2 (1.2%)
Severe Treatment Regimens

<table>
<thead>
<tr>
<th>Regimen (n = 105)</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole 500 mg PO q8h</td>
<td>19 (18.1)</td>
</tr>
<tr>
<td>Metronidazole 500 mg IV q8h</td>
<td>17 (16.2)</td>
</tr>
<tr>
<td>Vancomycin 125 mg PO q6h</td>
<td>41 (39)</td>
</tr>
<tr>
<td>Metronidazole 500 mg IV q8h + vancomycin 125 mg PO q6h</td>
<td>15 (14.3)</td>
</tr>
<tr>
<td>Metronidazole 500 mg IV q8h + vancomycin 250 mg PO q6h</td>
<td>7 (6.7)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (5.7)</td>
</tr>
</tbody>
</table>

Severe-complicated Treatment Regimens

<table>
<thead>
<tr>
<th>Regimen (n = 56)</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole 500 mg IV q8h</td>
<td>8 (14.3)</td>
</tr>
<tr>
<td>Vancomycin 125 mg PO q6h</td>
<td>12 (21.4)</td>
</tr>
<tr>
<td>Metronidazole 500 mg IV q8h + vancomycin 125 mg PO q6h</td>
<td>16 (28.6)</td>
</tr>
<tr>
<td>Metronidazole 500 mg IV q8h + vancomycin 250 mg PO q6h</td>
<td>5 (8.9)</td>
</tr>
<tr>
<td>Metronidazole 500 mg IV q8h + vancomycin 500 mg PO q6h</td>
<td>10 (17.9)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (8.9)</td>
</tr>
</tbody>
</table>

Overall Treatment Regimens

<table>
<thead>
<tr>
<th>Overall (n = 324)</th>
<th>No (%)</th>
<th>Percent difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate treatment</td>
<td>149 (46%)</td>
<td></td>
</tr>
<tr>
<td>Escalation required</td>
<td>83 (25.6)</td>
<td>29 (34.1)</td>
</tr>
<tr>
<td>Clinical cure</td>
<td>178 (54.9)</td>
<td>35 (41.2)</td>
</tr>
<tr>
<td>Mortality</td>
<td>43 (13.3)</td>
<td>23 (24.7)</td>
</tr>
<tr>
<td>Recurrence free</td>
<td>224 (69.1)</td>
<td>47 (55.3)</td>
</tr>
</tbody>
</table>

p < 0.002  * p = 0.033
Overtreatment versus Appropriate Treatment

<table>
<thead>
<tr>
<th></th>
<th>Overall [n = 324] No (%)</th>
<th>Appropriate treatment [n = 149] No (%)</th>
<th>Overtreatment [n = 90] No (%)</th>
<th>Percent difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escalation required</td>
<td>83 (25.6)</td>
<td>43 (27.5)</td>
<td>13 (14.4)</td>
<td>-11.1</td>
</tr>
<tr>
<td>Clinical cure</td>
<td>178 (54.9)</td>
<td>83 (55.7)</td>
<td>60 (66.7)</td>
<td>+11.0</td>
</tr>
<tr>
<td>Mortality</td>
<td>43 (13.3)</td>
<td>15 (10.1)</td>
<td>7 (7.8)</td>
<td>-2.3</td>
</tr>
<tr>
<td>Recurrence free</td>
<td>224 (69.1)</td>
<td>112 (75.2)</td>
<td>65 (72.2)</td>
<td>-3.0</td>
</tr>
</tbody>
</table>

\( p < 0.02 \)

Proton Pump Inhibitor Use

<table>
<thead>
<tr>
<th>Severity</th>
<th>Used proton pump inhibitor No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall [n = 324]</td>
<td>235 (72.5)</td>
</tr>
<tr>
<td>Mild-moderate [n = 162]</td>
<td>116 (71.6)</td>
</tr>
<tr>
<td>Severe [n = 105]</td>
<td>73 (69.5)</td>
</tr>
<tr>
<td>Severe-complicated [n = 56]</td>
<td>46 (82.1)</td>
</tr>
</tbody>
</table>

Prior Antimicrobial Use

<table>
<thead>
<tr>
<th>Severity</th>
<th>Antimicrobial use in previous 8 weeks No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall [n = 324]</td>
<td>239 (73.8)</td>
</tr>
<tr>
<td>Mild-moderate [n = 162]</td>
<td>121 (74.7)</td>
</tr>
<tr>
<td>Severe [n = 105]</td>
<td>79 (75.2)</td>
</tr>
<tr>
<td>Severe-complicated [n = 56]</td>
<td>39 (69.6)</td>
</tr>
</tbody>
</table>

Limitations

- Retrospective study
- Researcher bias
- Strict adherence to guideline definitions
- Study not powered to analyze secondary endpoints

Conclusions: Primary Endpoint

- 42% overall adherence to CDI guideline
- Adherence lower in severe and severe-complicated CDI
- Barriers to adherence
  - Lack of awareness among hospital staff
  - Subjects unable to take medications by mouth
  - Barriers to using rectal vancomycin
  - Clinically severe subjects with low WBC count

Conclusions: Secondary Endpoints

- Undertreatment versus appropriate treatment
  - Significantly increased incidence of mortality and recurrence
  - Lower incidence of clinical cure
- Overtreatment versus appropriate treatment
  - Failed to show significant improvement in clinical outcomes
  - Potentially leads to increased medication costs and adverse effects
- Proton pumps inhibitor and prior antimicrobial use was not significantly different between severity groups
Patient Case

RW is a 37-year old female with no significant past medical history who is admitted to the hospital for three days of diarrhea after a seven day treatment course of moxifloxacin for community-acquired pneumonia. RW’s symptoms include a white blood cell count of 13.0 cells/mm³, serum creatinine (Scr) of 0.7 g/dL, and a positive stool toxin assay for CDI.

Based on RW’s symptoms, what is her severity of illness?

A. Mild-moderate
B. Mild-moderate, complicated
C. Severe
D. Severe, complicated

Based on RW’s severity of illness, please select the most appropriate treatment option from the list below.

A. Oral vancomycin 125 mg every 6 hours for 14 days
B. Oral metronidazole 500 mg every 8 hours for 14 days
C. Oral vancomycin 250mg every 6 hours for 14 days
D. Intravenous metronidazole 500 mg every 8 hours PLUS oral vancomycin 500 mg every 6 hours for 14 days

Residency Project Pearls

Adherence to and Outcomes Associated with a *Clostridium difficile* Infection Guideline at a Large Teaching Institution

RaeAnna C. Zatarski, Pharm.D.
September 15, 2012
Adherence to and Outcomes Associated with a *Clostridium difficile* Infection Guideline at a Large Teaching Institution

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**Background:** The incidence and severity of *Clostridium difficile* infection (CDI) is on the rise with reports of devastating health outcomes. National CDI treatment guidelines stratify patients based on clinical symptoms and recommend specific treatment based on severity of illness. In 2009, Advocate Lutheran General Hospital adopted guidelines with identical treatment algorithms. The purpose of this project was to determine if patients were being treated in accordance with the CDI guidelines and whether adherence affected patient outcomes.

**Methods:** This was a retrospective, descriptive study. Subjects were identified by CDI-associated ICD-9 codes from July 1, 2009 to June 30, 2011. Subjects were stratified by disease severity based on laboratory values and symptoms. Guideline adherence was assessed based on initial treatment selection and subjects were categorized as undertreated (UT), overtreated (OT), or appropriately treated (AT) accordingly. Secondary endpoints included need for therapeutic escalation, clinical cure, recurrence rates, 90-day all-cause mortality, proton pump inhibitor (PPI) and antimicrobial use.

**Results:** Two hundred fifty subjects with 324 encounters were analyzed. Overall guideline adherence rate was 42.3%. Adherence rates by severity: mild-moderate, 52.8%; severe, 39.0%; and severe-complicated, 17.9% (p < 0.001). 46% of subjects were AT, 27.8% were OT, and 26.2% were UT. Clinical outcomes between UT versus AT subjects: therapeutic escalation required, 34.1% vs. 27.5%; clinical cure, 41.2% vs. 55.7%; mortality, 24.1% vs. 10.1%; and recurrence, 44.7% vs. 24.8%. Clinical outcomes between OT versus AT subjects: therapeutic escalation required 14.4% vs. 27.5%; clinical cure, 66.7% vs. 55.7%; mortality, 7.8% vs. 10.1%; recurrence, 27.8% vs. 24.8%. PPI or antimicrobial use did not affect severity of illness.

**Conclusions:** The majority of subjects were not treated in accordance with the CDI guidelines, particularly those with severe and severe-complicated illness. UT subjects had worse clinical outcomes compared to their AT counterparts whereas, OT subjects failed to show significant improvements in clinical outcomes compared to AT subjects. Emphasis should be placed on CDI guideline adherence as this results in improved outcomes.
Residency Project Pearls

A pilot multidisciplinary team to monitor controlled substance documentation in a community hospital

Tim Humlicek, PharmD
PGY2 Solid Organ Transplant Pharmacy Resident
Rush University Medical Center
Chicago, IL

Disclosure

The author of this presentation has no actual or potential conflicts of interest.

Learning Objectives

• Outline the process of interpreting controlled substance reports generated from automated dispensing machines that can identify high risk users.

• Recognize potential controlled substance diversion episodes using electronic medication administration documentation

NorthShore University HealthSystem

• Four acute care hospitals
  – Evanston Hospital: 354 beds
  – Glenbrook Hospital: 169 beds
  – Highland Park Hospital: 149 beds
  – Skokie Hospital: 195 beds

• NorthShore Medical Group
• NorthShore Research Institute
• NorthShore Foundation

Regulations

• Drug Enforcement Administration (DEA)
  – Enforces the Controlled Substance Act
  – Employee pilferage and units lost in transit:
    • 22.7% of all unaccounted oxycodone in 2000-2003

• Joint Commission Standard MM.4.80
  – Requires processes to address diversion prevention and account for all unused, expired, or returned medications.

Health System Diversion

• Diversion: unlawful channeling of regulated pharmaceuticals from legal sources to illicit market

  • Opportunities
    – Destruction/Waste
    – Intrahospital transfer
    – Large-volume removals
    – Multi-dose vials
    – Patient specific items
    – Point of purchase
    – Unauthorized removals


Background

• Lack of comprehensive published guidelines
  – Available recommendations:
    • Multidisciplinary teams
    • Monitoring in operating rooms
    • Investigative process
    • Drug diversion software
    • Intervention process

University Health System Consortium Survey
  – Operating Room Practices: 44-63% reconciled against dispensing records
  – Use of diversion software: 79%
    • “Sometimes” or “Always” investigate flagged individuals identified by software: 88-99%
    – Discrepancies “always” investigated: 92-98%

Project Objectives

• Primary:
  – Develop and implement a standardized process to identify users with risk of controlled substance diversion

Project Objectives

• Secondary:
  – Quantify potential controlled substance diversion opportunities in users with identified risk of controlled substance diversion
  – Assess the type of controlled substance discrepancies occurring based on controlled substance documentation

Methods

• Pharmacist to upload monthly ADM data to vendor
• Pharmacist organizes vendor report to identify high risk users
• Pharmacist prints controlled substance removals from previous 30 days for identified users
• Nurse Manager audits transactions for appropriate documentation
• Users with potential diversion episodes are assessed by pharmacist and nurse manager for further diversion risks

Methods: Identifying Users

Report 1: Compares removals of all controlled substances by one user to all users
Report 2: Compares all removals of given controlled substance by one user to all users of same ADM
Report 3: Compares removals of given controlled substance by one user to all users of that class/medication
Report 4: Compares daily average removals for one user for given controlled substance to all users of same ADM
Methods: Identifying Users

- Report 1: Users with >3 SDs (SD) above the mean removal of any controlled substance

AND

- Report 2: Users with >2 SD above mean compared to station level peers for given class of controlled medications

AND

- Report 3: Users with >2 SD above mean compared to all hospital users for given class of controlled medications

AND

- Report 4: Users with >2 SD above mean compared to station level peers on a daily basis for given class of controlled medications

Methods: User Audit

- Users had all removals of controlled substances in previous 30 days audited for documentation and potential diversion episodes:
  - Removal without order
  - Removal without documented administration
  - Removal in excess of order that does not require waste
  - Removal in excess of order that requires waste without appropriate waste documentation

Methods: User Audit

<table>
<thead>
<tr>
<th>Behavioral Indicators</th>
<th>Patient Care Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolates self</td>
<td>Incorrect charting</td>
</tr>
<tr>
<td>Frequent disappearances</td>
<td>Inconsistent work quality</td>
</tr>
<tr>
<td>Unscheduled visits</td>
<td>Offers to help other nurses' patients</td>
</tr>
<tr>
<td>Volunteers for additional shifts</td>
<td>Removes excessive amounts of narcotics</td>
</tr>
<tr>
<td>Chaotic home life</td>
<td>Requests specific patients</td>
</tr>
<tr>
<td>Refused compliance with investigations</td>
<td>Inadequate patient pain control with patients</td>
</tr>
</tbody>
</table>

Methods: User Audit

<table>
<thead>
<tr>
<th>Number marked “Yes”</th>
<th>Level of Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 Points</td>
<td>Low</td>
</tr>
<tr>
<td>3-4 Points</td>
<td>Medium</td>
</tr>
<tr>
<td>&gt;5 Points</td>
<td>High</td>
</tr>
</tbody>
</table>

Methods: Discrepancy Audit

- Controlled substance discrepancies were reviewed over the same period assessing for type and severity
  - Level 1: Miscounting
  - Level 2: Mechanical error
  - Level 3: Inappropriate documentation
  - Level 4: Incorrect administration
  - Level 5: Inadequate resolution

Results

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Doses Dispensed ASTEM</td>
<td>62,016</td>
<td>60,049</td>
<td>59,784</td>
<td>54,918</td>
</tr>
<tr>
<td>Average Daily Doses ASTEM</td>
<td>2,067</td>
<td>1,937</td>
<td>1,929</td>
<td>1,894</td>
</tr>
<tr>
<td>% Doses Outside ASTEM</td>
<td>5.11%</td>
<td>4.15%</td>
<td>3.78%</td>
<td>2.69%</td>
</tr>
<tr>
<td>% Doses Outside Station ASTEM</td>
<td>6.40%</td>
<td>7.24%</td>
<td>6.34%</td>
<td>5.64%</td>
</tr>
<tr>
<td>Total Doses</td>
<td>2,958</td>
<td>2,013</td>
<td>2,123</td>
<td>1,991</td>
</tr>
<tr>
<td>% Doses Outside</td>
<td>891</td>
<td>931</td>
<td>917</td>
<td>823</td>
</tr>
<tr>
<td>% Doses Outside Station</td>
<td>1.44%</td>
<td>1.55%</td>
<td>1.50%</td>
<td>1.13%</td>
</tr>
</tbody>
</table>
## Results - User Audits

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Users Audited</td>
<td>5</td>
<td>7</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total Transactions Audited</td>
<td>147</td>
<td>362</td>
<td>174</td>
<td>277</td>
</tr>
<tr>
<td>Transactions Per User</td>
<td>29.6</td>
<td>51.7</td>
<td>34.8</td>
<td>55.4</td>
</tr>
<tr>
<td><strong>Appropriate Documentation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate Record of Administration</td>
<td>147/147 (100%)</td>
<td>357/362 (98.6%)</td>
<td>168/174 (95.9%)</td>
<td>274/277 (98.9%)</td>
</tr>
<tr>
<td>Inappropriate Documentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reminiscent without Order</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reminiscent without Administration</td>
<td>0</td>
<td>5</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Reminiscent Inappropriate Administration</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reminiscent Administration without Documentation</td>
<td>0/18</td>
<td>0/39</td>
<td>0/19</td>
<td>0/43</td>
</tr>
</tbody>
</table>

## Results

- Characteristics of users (n=22)
  - Medical: 13 (59.1%)
  - Surgical: 5 (22.7%)
  - Telemetry: 2 (9.1%)
  - Anesthesia: 1 (4.5%)
  - Intensive Care/Emergency: 1 (4.5%)

## Results - Potential Diversion Episodes

- Six (27.3%) of the users who were audited and 14 (1.1%) of transactions had a potential diversion episode
- Reviews between pharmacist and nurse manager yielded low suspicions of diversion based on behavioral and patient care indicators

## Discussion

- Most transactions of controlled substances had appropriate documentation
- Potential diversion episodes were all due to lack of documented administration
- Variable quantity and severity of discrepancies occurred

## Results - Discrepancies

## Limitations

- Detection of diversion dependent on documentation practices
  - Endpoints rely on mistakes of high volume users
- Inclusion criteria
  - Low threshold for inclusion means more users were audited than necessary
- External Validity
  - Variable workplace practices may limit extrapolation of results to other health systems
Future Directions

• Specify audits for users with highest removals
• Establish protocol for investigating potential diversion episodes in users with medium-high risk:
  – Establish level of suspicion for prioritizing further interventions
• Implement use of refined methods across health-system

Conclusions

• Using objective criteria from usage reports is capable of identifying users with disproportionate removals of controlled substances
• Subjective knowledge of employees is another important aspect of diversion monitoring
• Appropriate documentation occurred most frequently
• Potential diversion episodes lacked an documented administration, but could have been administered by another user
• Discrepancy quantity and severity may be useful as a benchmark to track documentation practices

SELF ASSESSMENT QUESTION #1

Which of the following users meets at least one criteria to be eligible for a controlled substance transaction audit?

a) A user with a monthly average of removals less than 3 SDs of the mean for a particular controlled substance compared to all hospital users
b) A user with a daily average removals less than 2 SDs above the mean for a particular controlled substance compared to all users of a specific automated dispensing machine
c) A user with a monthly average of removals less than 2 SDs above the mean compared to all users of a particular automated dispensing machine
d) A user with a monthly average of removals greater than 3 SDs of the mean for a particular controlled substance compared to all hospital users

SELF ASSESSMENT QUESTION #2

Which of the following could be considered a potential controlled substance diversion episode?

a) Removal of a controlled substance and a documented patient refusal and an appropriate record of return
b) Removal of a controlled substance without an order
c) Removal of a controlled substance with a documented administration to a patient
d) Canceled removal of a controlled substance with subsequent documented administration
Special thanks to:
• Carol Heunisch, PharmD, BCPS
• Nancy Lechowicz, RN, MS
• Monica Sherlock, RN, MSN
• Rita Walter, RN, MS
• Mary Keegan, RN, MS

References

Questions?
Contact Information:
Tim Humlicek, PharmD
Rush University Medical Center
timothy_j_humlicek@rush.edu
Residency Project Pearls

Prolonged Antibiotic Prophylaxis After Cardiovascular Implantable Electronic Device Implantation and Its Effect on Device-Related Infections

Natasha Lopez, PharmD, BCPS
Critical Care Pharmacist
Rush University Medical Center
Chicago, IL

Background

• Cardiac implantable electronic device (CIED) infections have remained a major complication after implantation
• The incidence of infection related to CIED implantation ranges from 0.13% to 19.9%
• Variations in the populations and practices at different sites account for this range of incidence rates
• With the expanded indications for CIED implantation and higher risk patient population receiving therapy, the prevention and management of CIED infections continues to be studied

Microbiology of CIED Infections

Antibiotic Prophylaxis for Pacemakers

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent/Dose/Regimen</th>
<th>No. of Patients</th>
<th>Follow-up in Months (range)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biddison et al</td>
<td>Cefazolin 2g IV before and 1g by mouth for 2 days after</td>
<td>N=100</td>
<td>Alen 50 Control 50</td>
<td>M=1-12</td>
</tr>
<tr>
<td>Franceschi et al</td>
<td>Cefazolin 1g with amoxicillin 1g IV before and 1g by mouth for 2 days after</td>
<td>N=100</td>
<td>Alen 50 Control 50</td>
<td>M=1-12</td>
</tr>
<tr>
<td>Biddison et al</td>
<td>Cefazolin 1g IV before and 1g by mouth for 2 days after</td>
<td>N=100</td>
<td>Alen 52 Control 14</td>
<td>M=1-12</td>
</tr>
<tr>
<td>Giacca et al</td>
<td>Cefazolin 1g IV daily for 5 days</td>
<td>N=100</td>
<td>Alen 50 Control 50</td>
<td>N=1</td>
</tr>
<tr>
<td>Neumanny et al</td>
<td>Cefazolin 1g IV before, 1g by mouth up to 48 hours</td>
<td>N=100</td>
<td>Alen 25 Control 25</td>
<td>12-24</td>
</tr>
</tbody>
</table>

 Disclosure Statement

The speaker has no actual or potential conflict of interest in relation to this presentation.
Antibiotic Prophylaxis

American Heart Association (AHA)

- Preoperative prophylaxis with an antibiotic that has in vitro activity against staphylococci should be administered (Level of Evidence: A)

- Antimicrobial prophylaxis in the postoperative period is not recommended due to lack of evidence and risk of adverse drug events and antimicrobial resistance


Background

- At Rush University Medical Center (RUMC), 72 hours of postoperative prophylactic antibiotics are used after CIED implantation

- Currently no study has specifically examined the efficacy of postoperative antibiotic prophylaxis in this patient population

Study Purpose

- To determine if postoperative antibiotic prophylaxis with cephalaxin administered for 72 hours reduces the incidence of infection in patients undergoing CIED procedure

Research Hypothesis

- There is no difference in the incidence of CIED infection between 72 hour postoperative cephalaxin and no postoperative antibiotic regimens

Methods - Design

- Retrospective chart review
  - January 2007 – October 2011

- Single center, Rush University Medical Center
  - 673 bed, university affiliated medical center

Methods- Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Compare the incidence of CIED related infections between 72 hour postoperative cephalaxin to no postoperative antibiotics</td>
</tr>
<tr>
<td>Secondary</td>
<td>Identify the patient characteristics that correlated with the primary outcome</td>
</tr>
<tr>
<td></td>
<td>Time to infection</td>
</tr>
</tbody>
</table>

Methods- Patient Population

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 18 and ≤ 89 years</td>
<td>Documented penicillin and/or cephalosporin allergy</td>
</tr>
<tr>
<td>Recipients of a new, upgrade, generator replacement revision or lead revision of CIED</td>
<td>Received antibiotics for another indication prior to CIED</td>
</tr>
<tr>
<td>Received preoperative antibiotics with cefazolin prior to CIED procedure</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Patients who underwent thoracotomy with implantation</td>
<td></td>
</tr>
</tbody>
</table>
Methods - Data Collection

- Demographics
  - Age
  - Gender
  - Comorbidities
  - LVEF
- Procedure factors
  - CIED type
  - Leads
  - Length of procedure
- Medication
  - Anticoagulants
  - Immunosuppressants
- Outcomes
  - Device Infection
  - Cultures
    - Culture positive
    - Culture negative
  - Time to infection
  - Organism identified
    - Gram positive
    - Gram negative
  - Susceptibilities

Patient Population

**Inclusion**
- Age ≥18 and ≤70 years
- Recipient of new implanted CIED
- Received, upgrade, generator replaced

**Exclusion**
- History of previous antibiotic failure
- History of previous infection
- History of previous anticoagulant
- History of previous pacemaker

**Enrollment**
- Inclusion criteria
- Exclusion criteria
- Patient characteristics

Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CIED (n=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>63 (54-74)</td>
</tr>
<tr>
<td>Male sex, no. (%)</td>
<td>95 (61.3)</td>
</tr>
<tr>
<td>Weight (kg), median (IQR)</td>
<td>81.6 (68.9-97.3)</td>
</tr>
<tr>
<td>Ethnicity, no. (%)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>80 (51.6)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>51 (32.9)</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>25 (15-35)</td>
</tr>
<tr>
<td>SCR (mg/dl), median (IQR)</td>
<td>1.1 (0-3.4)</td>
</tr>
<tr>
<td>Co-morbidities, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>54 (34.8)</td>
</tr>
<tr>
<td>COPD</td>
<td>32 (20.6)</td>
</tr>
<tr>
<td>CHF</td>
<td>108 (69.7)</td>
</tr>
<tr>
<td>CIED</td>
<td>47 (30.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>49 (31.6)</td>
</tr>
<tr>
<td>HTN</td>
<td>128 (82.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Obstructive Sleep Disorder</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td></td>
</tr>
<tr>
<td>Renal Failure</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Alcohol Abuse</td>
<td></td>
</tr>
<tr>
<td>Tobacco Use</td>
<td></td>
</tr>
<tr>
<td>Other Comorbidities</td>
<td></td>
</tr>
</tbody>
</table>

Results - Infections

<table>
<thead>
<tr>
<th>Infection (n=6)</th>
<th>Time to infection (days)</th>
<th>Organism</th>
<th>Procedure (prior to infection)</th>
<th>Device</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>Culture negative</td>
<td>Upgrade</td>
<td>CRT-D; 2 leads</td>
<td>Levofloxacin &amp; linezolid ≤4 d</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>Culture negative</td>
<td>Generator replacement</td>
<td>IC D; 2 leads</td>
<td>Vancomycin + piperacillin/susco ≤4d</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>Staphylococcus aureus (MSSA)</td>
<td>Atrial lead revision &amp; generator replacement</td>
<td>PFM; 2 leads</td>
<td>Ceftazidime ≤4 d</td>
</tr>
<tr>
<td>4</td>
<td>128</td>
<td>Pseudomonas aeruginosa</td>
<td><em>Global</em></td>
<td>IC D; 2 leads</td>
<td>Vancomycin + Ceftazidime ≤4 d; Levofloxacin ≥7 d Duration ≥ 21 d</td>
</tr>
</tbody>
</table>

Results - Characteristics of Patients with CIED Infection

<table>
<thead>
<tr>
<th>Infection (n=6)</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>DM</th>
<th>CIED</th>
<th>COPD</th>
<th>History of Valve Repair</th>
<th>Oral Anticoagulant</th>
<th>Immunosuppressant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>85</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Study Limitations

- Dependent on consistency and completeness of medical charts
- ICD-9 code dependent identification of patients with new CIED and infection
- Selection and dosing of medications by prescriber bias

Conclusion

- Previous studies utilizing only preoperative antibiotic prophylaxis document a 0.5-1% incidence of infection
- Currently data are insufficient to confidently assess postoperative antibiotic prophylaxis after CIED procedures
- The existing data does not allow definitive recommendations for clinical practice

Future Application

- Vancomycin comparison group
- Review of postoperative antibiotic prophylaxis regimen prior to 2007
- Prospective evaluation of infection rate

Self-Assessment Questions

Which of the following is recommended by the 2010 American Heart Association Guidelines to prevent CIED infections at time of device implantation?

A. Preoperative antibiotic prophylaxis
B. Preoperative and 72 hour postoperative antibiotic prophylaxis
C. 72 hour postoperative antibiotic prophylaxis
D. No antibiotic prophylaxis

Self-Assessment Questions

Common organisms responsible for CIED infections include all of the following, EXCEPT?

A. Coagulase-negative Staphylococcus
B. Methicillin resistant Staphylococcus aureus
C. Methicillin sensitive Staphylococcus aureus
D. Candida species

Residency Project Pearls

Prolonged Antibiotic Prophylaxis After Cardiovascular Implantable Electronic Device Implantation and Its Effect on Device-Related Infections

Researcher:
Natasha Lopez, PharmD, BCPS

Research Committee:
Christopher Crank, PharmD, Ms, AQ-ID
Payal Gurnani, PharmD, BCPS
Residency Project Pearls

From Dabigatran to Warfarin: A Change in Progress

Ashley Jacobs, Pharm.D.
Clinical Staff Pharmacist
Lutheran Health Network
Fort Wayne, IN
September 2012

Disclosure: The speaker has no actual or potential conflict of interest in relation to this presentation.

Common Oral Anticoagulants

• Warfarin: A vitamin-K antagonist whose indications include prevention of thromboembolic events in atrial fibrillation
• Dabigatran: A direct thrombin inhibitor approved to reduce the risk of systemic embolism and stroke in patients with non valvular atrial fibrillation

Dabigatran and Warfarin

Dabigatran
• Pros
  – No routine monitoring required
  – Standard dosages available
• Cons
  – No antidote available
  – Post-marketing reports of bleeding

Warfarin
• Pros
  – Therapy can be tailored to patient specific needs
  – Long history of use
  – Antidote available
• Cons
  – Routine monitoring required
  – Difficulty managing unstable INRs
  – Bleeding

RE-LY: Warfarin vs. Dabigatran

• The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study compared dabigatran 110 mg BID and 150 mg BID to dose-adjusted warfarin
  – Primary outcome event was stroke or systemic embolism
  – Dabigatran 150 mg BID had lower rates of stroke or systemic embolism, but similar rates of major hemorrhage, when compared to warfarin

Adverse Events in the RE-LY Study

• In the RE-LY study, bleeding and gastrointestinal events (ex: dyspepsia and gastrointestinal hemorrhage) were the most frequent causes of dabigatran treatment discontinuation

Dabigatran

• Approved in the Fall of 2010 with the following dosing recommendations:
  • CrCl >30: 150 mg PO BID
  • CrCl 15 to 30: 75 mg PO BID
  • CrCl <15 or patients on dialysis: No recommendation can be provided
• In patients 75 years old and older, there is an increased risk for bleeding
Study Background

- Observation of patients previously treated with dabigatran being switched to warfarin
  - Pharmacist managed Lutheran Hospital Anticoagulation Clinic
  - Inpatients

Objective

- To determine reasons for discontinuation of dabigatran and re-initiation or initiation of warfarin in a real-world setting

Methods

- Patient interviews and retrospective chart reviews at the Lutheran Hospital Anticoagulation Clinic and Lutheran Hospital
- Potential causes of dabigatran treatment discontinuation evaluated include: failure of therapy, adverse drug events, and cost of therapy
- Patients were selected from the time dabigatran was released in Fall 2010 until April 2012

Results

<table>
<thead>
<tr>
<th>Patient Demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>22</td>
</tr>
<tr>
<td>Inpatients</td>
<td>9</td>
</tr>
<tr>
<td>Outpatients</td>
<td>13</td>
</tr>
</tbody>
</table>
| Gender               | Men: 55%  
                       | Women: 45% |
| Age                  | Average: 76  
                       | Max: 93  
                       | Min: 34 |

Summary of Reasons for Discontinuation

- Some patients had more than one reason for discontinuation of therapy

Duration of Dabigatran Therapy

- Average treatment duration: 4 months

Duration of dabigatran therapy (N=8)
Reasons for Discontinuation

- Gastrointestinal Side Effects
  - Diarrhea
  - Heartburn
  - Upset stomach
- Off-label Indications
  - DVT prophylaxis and aortic stenosis
- Clot Formation
  - Patient admitted with a PE

Cost Comparison

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cash price for 150 mg BID 30 day supply at certain pharmacies</td>
<td>Anticoagulation Clinic visit</td>
</tr>
<tr>
<td>$326.32</td>
<td>Visit: $68.48</td>
</tr>
</tbody>
</table>

Comparison of Results

- RE-LY Study
  - Overall rate of discontinuation: 15.5%
    - Discontinuation due to gastrointestinal symptoms: 130 patients (2.1%)%
- Current Study
  - Total number of Lutheran Medical Group patients prescribed dabigatran: 66
    - Rate of discontinuation for the current study: 25%
    - Discontinuation due to gastrointestinal symptoms: 3 patients (14%)%

Evaluation

- Benefits
  - Results provided an opportunity for pharmacists to educate prescribers about dabigatran and what to consider prior to initiating therapy
    - Ex: Evaluate the patient’s age and past medical history before prescribing dabigatran
  - Adverse events were identified that can be reported

Evaluation

- Limitations
  - Small sample size
  - We do not have a baseline value to compare our data to because we do not know the percentage of patients currently on warfarin, who were initially on dabigatran

Conclusion

- Considerations for dabigatran initiation
  - Cost, age, renal function, and a patient’s willingness to handle gastrointestinal side effects need to be taken into account
A patient has a CrCl of 25 mL/min. Which dose of dabigatran should be prescribed for this patient?

- A: 150 mg PO daily
- B: 75 mg PO BID
- C: 150 mg PO BID
- D: Dabigatran is contraindicated in this patient

Which organ system is commonly associated with dabigatran side effects?

- A: Respiratory system
- B: Endocrine system
- C: Excretory system
- D: Digestive system

References


Residency Project Pearls

From Dabigatran to Warfarin: A Change in Progress

Ashley Jacobs, Pharm.D.
Clinical Staff Pharmacist
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Fort Wayne, IN
September 2012

Disclosure: The speaker has no actual or potential conflict of interest in relation to this presentation.
Residency Project Pearls

Extended Stability of Intravenous Acetaminophen in Syringes and Opened Glass Bottles

Jennifer L. Kwiatkowski, Pharm.D.
Pediatric Specialist at St. John’s Hospital, Springfield, IL
September 2012

Great Lakes Presentation from PGY2 Pediatric Pharmacy Residency at the University of Michigan

The speaker has no actual or potential conflict of interest in relation to this presentation.

Therapeutic Uses

- Unable to tolerate oral or rectal drug administration
- Potential reduction in opioid or NSAID related adverse effects
- Insufficient response to IV opioids or NSAIDs
- Contraindication to IV NSAIDs

Drug Development

- Intravenous acetaminophen approved for use in Europe in 2001
- Marketed in over 80 countries
- Food and Drug Administration (FDA) approved in November 2010

Product Formulation

- Limited water solubility
  - Higher at room temperature compared to refrigeration
- Stability in aqueous solution

Aqueous Decomposition

- Acetaminophen → Hydrolysis
- $p$-aminophenol and acetic acid → Oxidation
- $p$-benzoquinoneime → Hydrolysis
- $p$-benzoquinone

Influence of pH

- Target pH 5-6
  - Reported half life 19-22 years
- Acidic environment
  - Reported half life <1 year at pH 2
- Basic environment
  - Reported half life 2 years at pH 9
- Product formulation
  - Sodium hydroxide or hydrochloric acid with buffer dibasic sodium phosphate

The speaker has no actual or potential conflict of interest in relation to this presentation.
Excipients

- Cysteine hydrochloride: antioxidant
- Nitrogen gas in vial to reduce oxidation
- Mannitol: isotonicity
- No preservatives

Usage Guideline

- Intravenous acetaminophen supplied as 1 gram, 100 mL bottle with 6-hour usage guideline

Audience Question

Which of the following is a limitation of the current 6-hour usage guideline for intravenous acetaminophen?

A. Potential for infusion related reactions due to administration guidelines
B. Potential for dosing errors when dispensing the 1000 mg bottle of intravenous acetaminophen
C. Potential for increased cost in adult patients receiving a 1000 mg dose of intravenous acetaminophen
D. Potential for product waste for pediatric patients who require only a portion of the 1000 mg bottle

Pediatric Limitations

- Weight-based dosing
- Use of a fraction of the bottle
- Product waste
- Increased costs
- Disruption in pharmacy workflow

Beyond Use Dating

- USP 797 guidelines for sterile compounding
- Low-risk level
  - Sterile for 48 hours at room temperature
  - Aseptic manipulations within ISO Class 5 air quality or better
  - Institutional specifications for final dating

Extended Stability of Intravenous Acetaminophen in Syringes and Opened Glass Bottles

Jennifer Kwiatkowski, PharmD
Cary Johnson, Pharm.D., FASHP
Deb Wagner, Pharm.D., FASHP
University of Michigan Hospitals and Health Centers
Specific Aim

- Specific aim
  - Determine if intravenous acetaminophen is stable over an 84 hour time period over a range of doses stored in syringes and a range of volumes remaining in the original opened bottle
- Hypothesis
  - Intravenous acetaminophen will maintain at least 90% of the original concentration over an 84 hour time period at room temperature

HPLC Components

- Stationary phase
  - C-18 reverse phase column
  - 5-µm particle size (250 mm x 4.6 mm)
- Mobile phase
  - Mixture of acetonitrile and deionized-distilled water (20:80 v/v) containing 0.15% formic acid

Sample Detection

- UV light detector
  - λ set at 243 nm
- Flow rate
  - 1 mL/min
- Samples
  - Diluted to 50 µg/mL expected concentration with mobile phase
  - Prepared in triplicate, each sample assayed in duplicate

Acetaminophen Standard Curve

- Analytical grade acetaminophen powder
- 5-point standard curve
  - 40, 45, 50, 55, 60 µg/mL
- Standard was run after every 10th assay sample as an external control

Audience Question

According to ASHP guidelines for conducting a drug stability experiment, drug samples must be assayed how many times?
A. Once
B. Twice
C. Three times
D. Four times
Sample Preparation

- Intravenous acetaminophen supplied as 10 mg/mL, 100 mL bottle
- Doses in syringes (triplicate)
  - 100 mg (10 mL in 10 mL syringe)
  - 250 mg (25 mL in 30 mL syringe)
  - 500 mg (50 mL in 60 mL syringe)
- Volumes in original opened bottle (triplicate)
  - 250 mg (25 mL in bottle)
  - 900 mg (90 mL in bottle)

Sample Analysis

- Visually inspected for color change and precipitate formation
- pH measured
- Microbiological testing not performed

Stability-Indicating Assays

- Forced decomposition of intravenous acetaminophen
  - 3% hydrogen peroxide
  - 1 N sodium hydroxide (pH 12)
  - 1 N hydrochloric acid (pH 2)
- Procedure
  - Heat to 90°C for 2 hours
  - Neutralized to pH 7

Results

Sample Acetaminophen Chromatogram

- Acetaminophen peak at 4.05 minutes
- HPLC Peak Height

Results

Stability-Indicating Capability of HPLC Assay

<table>
<thead>
<tr>
<th>Degradation Solution</th>
<th>Degradation Peaks (minutes)</th>
<th>Acetaminophen Degradation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3% hydrogen peroxide</td>
<td>2.46</td>
<td>5</td>
</tr>
<tr>
<td>1 N hydrochloric acid (pH 2)</td>
<td>2.70, 6.08, 7.35</td>
<td>8</td>
</tr>
<tr>
<td>1 N sodium hydroxide (pH 12)</td>
<td>2.64, 5.23, 7.35</td>
<td>25</td>
</tr>
</tbody>
</table>

Acetaminophen peak: 4 minutes
p-aminophenol peak: 7.35 minutes
### Stability of Intravenous Acetaminophen (10 mg/mL) at Room Temperature in Varying Storage Containers

<table>
<thead>
<tr>
<th>Sample</th>
<th>Actual Initial Drug Concentration* (mg/mL)</th>
<th>% Initial Concentration Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>24 hours</td>
</tr>
<tr>
<td>100 mg (syringe)</td>
<td>9.94 ± 0.05</td>
<td>99.11 ± 0.52</td>
</tr>
<tr>
<td>250 mg (syringe)</td>
<td>9.96 ± 0.02</td>
<td>99.66 ± 1.11</td>
</tr>
<tr>
<td>500 mg (syringe)</td>
<td>9.96 ± 0.03</td>
<td>100.13 ± 0.37</td>
</tr>
<tr>
<td>250 mg (bottle)</td>
<td>9.98 ± 0.03</td>
<td>99.67 ± 0.36</td>
</tr>
<tr>
<td>500 mg (bottle)</td>
<td>9.93 ± 0.04</td>
<td>99.76 ± 0.33</td>
</tr>
</tbody>
</table>

*Mean ± S.D. of duplicate determinants for three samples (n = 3).

### Results

- No detectable change in sample color
- No visible drug precipitation
- No appreciable change in the initial pH (5.77 ± 0.02)
- Interday coefficient of variation: 1.8%
- Intraday coefficient of variation: 1%

### Conclusion

- Intravenous acetaminophen (10 mg/mL) was physically and chemically stable in a range of volumes for up to 84 hours in the opened bottles and in polypropylene syringes

### Significance

- Benefits of extending the stability of intravenous acetaminophen
  - Decreased product waste
  - Cost savings to patients and the healthcare system
  - Pharmacy workflow optimized by minimizing need for urgent dose preparation

### References

Questions?

Residency Project Pearls

Extended Stability of Intravenous Acetaminophen in Syringes and Opened Glass Bottles

Jennifer L. Kwiatkowski, Pharm.D.
Pediatric Specialist at St. John’s Hospital, Springfield, IL
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