Residency Project Pearls
Safety of extended infusion piperacillin-tazobactam plus vancomycin versus standard infusion piperacillin-tazobactam plus vancomycin in general medicine patients with a diagnosis of healthcare associated pneumonia
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Rolla T. Sweis, Pharm.D., M.A., BCPS

Learning Objectives
1. Define acute kidney injury (AKI).
2. Recognize common medications that may contribute to developing AKI.

Epidemiology
- According to United States data, the reported prevalence of hospital-acquired Acute Kidney Injury (AKI) is estimated to be up to 7.1%
- AKI has a poor prognosis with mortality ranging from 10%-80%

Definition
- Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines define AKI as:
  - An absolute increase in serum creatinine (SCr) of ≥0.3mg/dL within 48 hours, or
  - ≥25% increase in SCr within seven days, or
  - A reduction in urine output
    - Documented oliguria of < 0.5 ml/kg/hr for > 6 hours

Conflict of Interest
- The speaker has no actual or potential conflict of interest in relation to this presentation

Advocate Christ Medical Center (ACMC)
- Private, non-profit, 694-bed community teaching institution
- Nearly 1,000 affiliated physicians
- Level 1 trauma center, providing emergency care for more than 95,000 patient visits annually
- Recognized by the American Nurses Credentialing Center as a Magnet Medical Center
Drug-Induced Acute Kidney Injury

- Complications lead to:
  - Increased hospital stay
  - Increased cost
  - Increased mortality
- Several medications have the potential to cause AKI such as:
  - Vasopressors
  - Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
  - Diuretics
  - Antibiotics

Vancomycin

- Class: Glycopeptide
- Elimination: Renal
- Spectrum of activity:
  - Gram positive organisms including methicillin-resistant Staphylococcus aureus (MRSA)

Piperacillin-Tazobactam

- Class: Beta-lactam/beta-lactamase inhibitor
- Elimination: Renal
- Spectrum of activity:
  - Gram-positive organisms
  - Gram-negative organisms including Pseudomonas aeruginosa
  - Anaerobes

Piperacillin-Tazobactam Administration

- Standard Infusion Piperacillin-Tazobactam (SIPT)
  - Administered over 30 minutes
  - Dosing interval of every 6-8 hours
- Extended Infusion Piperacillin-Tazobactam (EIPT)
  - Administered over 4 hours
  - Dosing interval of every 8-12 hours

Extended Infusion

- Extending the administration time of beta-lactam antibiotics maximizes the time free drug is available at concentrations above the minimum inhibitory concentration (MIC)
- Pharmacodynamic dosing of beta-lactam antibiotics by extended infusion has been well referenced in the literature for years
AKI Secondary to Vancomycin and Piperacillin-Tazobactam

- Penicillins have the potential to cause AKI such as acute interstitial nephritis
- Vancomycin’s nephrotoxic potential is not fully understood
- Combination use may increase the risk of AKI compared to administration of either agent alone
- Safety data regarding extended infusion combination therapy have been limited to mortality outcomes
  - Morbidity outcomes have not been fully evaluated

Observational Data

- Hellwig et al.
  - Retrospective evaluation of 735 adult patients
  - Compared patients on combination therapy of vancomycin + pip-tazo vs. monotherapy of either agent alone
  - AKI defined as an increase in SCR of ≥0.5 mg/dL or a 50% increase from baseline
  - Results

<table>
<thead>
<tr>
<th>Group</th>
<th>General Medicine % AKI</th>
<th>Intensive Care Unit % AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin monotherapy</td>
<td>4.9</td>
<td>6.0</td>
</tr>
<tr>
<td>Pip-tazo monotherapy</td>
<td>11.1</td>
<td>12.2</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>18.6</td>
<td>21.2</td>
</tr>
</tbody>
</table>

Change in Protocol

- In October 2012, ACMC transitioned from SIPT to an EIPT protocol
- Based on observational data and anecdotal experience from Infectious Disease physicians, concern arose about the possible increase incidence of AKI in patients on combination therapy

Primary Objective

- To assess the incidence of AKI in patients on EIPT and vancomycin therapy versus SIPT and vancomycin in general medicine patients with a diagnosis of HCAP

Safety of extended infusion piperacillin-tazobactam plus vancomycin versus standard infusion piperacillin-tazobactam plus vancomycin in general medicine patients with a diagnosis of healthcare associated pneumonia
Methods

- Single-center retrospective chart review
- Institutional Review Board (IRB) approved
- Analyzed subjects who were admitted to the hospital with a diagnosis of HCAP from January 2012 to March 2012 and compared them to similar subjects admitted with the same diagnosis from January 2013 to March 2013
- The baseline SCr was defined as the lowest SCr prior to initiating antibiotics

Primary Endpoint

- Incidence of AKI
  - AKI defined as an increase in serum creatinine of at least 0.5 mg/dL or a 50% increase in SCr from baseline

Statistical Methods

- Pearson Chi-square
- Fisher’s exact test
- Mann-Whitney U test
- Computed utilizing SPSS® (Version 21)

Criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of HCAP</td>
<td>Age less than 18 years</td>
</tr>
<tr>
<td>Age greater than or equal to 18 years</td>
<td>Patients on hemodialysis</td>
</tr>
<tr>
<td>Received at least one dose of piperacillin-tazobactam and vancomycin concomitantly</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>General medicine patients (non-intensive care unit)</td>
<td></td>
</tr>
<tr>
<td>A baseline serum creatinine level and a serum creatinine level post antibiotic initiation</td>
<td></td>
</tr>
</tbody>
</table>

Patient Enrollment

N=1035 subjects were assessed

SIPT N=597

467 subjects excluded

N=130

EPT N=438

327 subjects excluded

N=110

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SIPT N=130</th>
<th>EPT N=110</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Age (years)</td>
<td>70.87 (20-104)</td>
<td>70.56 (22-95)</td>
<td>0.88</td>
</tr>
<tr>
<td>Male (%)</td>
<td>76 (58.0)</td>
<td>61 (55.0)</td>
<td>0.58</td>
</tr>
<tr>
<td>Average Weight (Kg)</td>
<td>78.4 (40-140)</td>
<td>76.5 (45-170)</td>
<td>0.68</td>
</tr>
<tr>
<td>Average Height (cm)</td>
<td>169.6 (140-190.5)</td>
<td>169.5 (144-190.5)</td>
<td>0.97</td>
</tr>
<tr>
<td>Average SCr mg/dL (Range)</td>
<td>1.1 (0.34-3.2)</td>
<td>1.2 (0.5-3.5)</td>
<td>0.25</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>46 (35.4)</td>
<td>43 (39.1)</td>
<td>0.55</td>
</tr>
<tr>
<td>Caucasian</td>
<td>82 (63.1)</td>
<td>58 (52.7)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (1.5)</td>
<td>7 (6.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>0 (0)</td>
<td>2 (1.8)</td>
<td>0.20</td>
</tr>
</tbody>
</table>
Baseline Characteristics

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>SIPT N=130</th>
<th>EIPT N=110</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (%)</td>
<td>87 (66.9)</td>
<td>87 (78.4)</td>
<td>0.048</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>43 (33.1)</td>
<td>44 (39.6)</td>
<td>0.29</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>37 (28.5)</td>
<td>30 (27.0)</td>
<td>0.80</td>
</tr>
<tr>
<td>CKD (%)</td>
<td>16 (12.3)</td>
<td>21 (18.9)</td>
<td>0.15</td>
</tr>
<tr>
<td>Cancer (%)</td>
<td>9 (6.9)</td>
<td>10 (9.0)</td>
<td>0.54</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>26 (20.0)</td>
<td>28 (25.2)</td>
<td>0.33</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>14 (10.8)</td>
<td>15 (13.5)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Baseline Characteristics

<table>
<thead>
<tr>
<th>Nephrotoxic Agents</th>
<th>SIPT n=130</th>
<th>EIPT n=110</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Contrast (%)</td>
<td>17 (13.1)</td>
<td>23 (20.7)</td>
<td>0.11</td>
</tr>
<tr>
<td>NSAIDs (%)</td>
<td>7 (5.4)</td>
<td>4 (3.6)</td>
<td>0.51</td>
</tr>
<tr>
<td>ACEI/ARB (%)</td>
<td>33 (23.8)</td>
<td>28 (25.2)</td>
<td>0.80</td>
</tr>
<tr>
<td>Loop Diuretic (%)</td>
<td>36 (27.7)</td>
<td>34 (30.6)</td>
<td>0.62</td>
</tr>
<tr>
<td>Hydrochlorothiazide (%)</td>
<td>0</td>
<td>1 (0.9)</td>
<td>0.46</td>
</tr>
<tr>
<td>Spironolactone (%)</td>
<td>5 (3.8)</td>
<td>6 (5.4)</td>
<td>0.31</td>
</tr>
<tr>
<td>Aminoglycoside (%)</td>
<td>4 (3.1)</td>
<td>1 (0.9)</td>
<td>0.38</td>
</tr>
<tr>
<td>Antiviral (%)</td>
<td>1 (0.8)</td>
<td>5 (4.5)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Primary Outcome Results

<table>
<thead>
<tr>
<th>SCR Increase of ≥ 0.5mg/dL or by 50%</th>
<th>SIPT N=130</th>
<th>EIPT N=110</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 (20%)</td>
<td>11 (10%)</td>
<td></td>
<td>0.033</td>
</tr>
</tbody>
</table>

Patients with AKI

<table>
<thead>
<tr>
<th>Average Increase in SCR</th>
<th>SIPT N=26</th>
<th>EIPT N=11</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.33 ± 1.02</td>
<td>1.02 ± 0.61</td>
<td></td>
<td>0.52</td>
</tr>
</tbody>
</table>

Average Vancomycin Dose and Levels

<table>
<thead>
<tr>
<th>SIPT n=130</th>
<th>EIPT n=110</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Total Daily Vancomycin Dose (Range)</td>
<td>1610 mg (375-6000)</td>
<td>1590 mg (500-3750)</td>
</tr>
<tr>
<td>Average Vancomycin Trough (Range)</td>
<td>11.8 mcg/mL (2.9-57.3)</td>
<td>12.6 mcg/mL (3.2-36.9)</td>
</tr>
</tbody>
</table>

Magnitude of SCr Change

<table>
<thead>
<tr>
<th>Increase in SCr (mg/dL)</th>
<th>SIPT N=26 (%</th>
<th>EIPT N=11 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50 – 1.5</td>
<td>29 (75.9)</td>
<td>10 (90.9)</td>
</tr>
<tr>
<td>1.51 – 2.5</td>
<td>4 (15.4)</td>
<td>0</td>
</tr>
<tr>
<td>2.51 – 3.5</td>
<td>2 (7.7)</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>3.51 – 5.0</td>
<td>1 (3.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

Vancomycin Dose Ranges

<table>
<thead>
<tr>
<th>Total Daily Vancomycin Dose (mg)</th>
<th>SIPT N=26 (%)</th>
<th>EIPT N=11 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500-750</td>
<td>8 (30.7)</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>1000-1500</td>
<td>7 (26.9)</td>
<td>3 (45.4)</td>
</tr>
<tr>
<td>1750-2000</td>
<td>8 (30.7)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>3000-4000</td>
<td>1 (3.8)</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>4500-6000</td>
<td>2 (7.7)</td>
<td>0</td>
</tr>
</tbody>
</table>
Discussion

• In contrast to physician concerns prior to this study, there was a lower incidence of AKI in general medicine floor patients receiving vancomycin plus EIPT compared to vancomycin plus SIPT for the treatment of HCAP
• Average vancomycin doses and troughs were comparable between the groups
• Nephrotoxic agents were not confounding variables
• No difference in baseline characteristics except for hypertension

Limitations

• Single center study
• External validity
• Retrospective
• Excluded ICU patients
• Small patient sample size
• Not evaluated
  – Time to onset and resolution of AKI
  – Duration of therapy
  – Overlapping administration of both antibiotics
  – Different drug products used for the two groups

Conclusion

• There was a significantly lower incidence of AKI in general medicine patients diagnosed with HCAP on EIPT compared to the SIPT

Future Direction

• Larger, multicenter, prospective studies comparing EIPT + Vancomycin vs. SIPT + Vancomycin
• More prospective studies comparing other beta-lactam antibiotics in combination with vancomycin should be conducted to further confirm these findings

Assessment Question #1

Which of the following statements is true?

a. AKI is defined as an increase in serum creatinine of at least 0.5mg/dL or a 50% increase in serum creatinine from baseline
b. AKI is defined as an increase in serum creatinine of at least 0.5mg/dL or a 30% increase in serum creatinine from baseline
c. AKI is defined as an increase in serum creatinine of at least 1mg/dL
d. AKI is defined as a 75% increase in serum creatinine from baseline

Assessment Question #2

According to recent observational data, which of the following medications may contribute to the development of AKI when administered with Vancomycin?

a. Dabigatran
b. Piperacillin-Tazobactam
c. Atenolol
d. Metronidazole
Acknowledgements

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• Christopher Blair, Director of Research Services
• Brian Maynard, Pharm.D.
• Sarah Sienko, Pharm.D.

References


Questions
Clinical Impact of Dual Antimicrobial Therapy in Critically Ill Patients with Gram Negative Sepsis or Septic Shock

Mary Lenefsky, PharmD
PGY-2 Critical Care Resident Midwestern Chicago College of Pharmacy/Northwestern Memorial Hospital
Chicago, IL

The speaker has no actual or potential Conflict of Interest in relation to this presentation

Objectives

• Describe the rational behind using two active antimicrobial agents in patients with sepsis or septic shock
• List reasons antibiotics with overlapping coverage may be problematic

Sepsis: systemic host response to infection

- Severe sepsis (organ dysfunction)
- Septic shock (severe sepsis + hypotension not responsive to fluids)
- Severe sepsis and septic shock kill 1 in 4 people
- Speed and appropriateness of therapy ultimately influence patient outcome

Gram negative bacteremia

• Mortality ranges 20-60%1
• Initial coverage usually directed at P. aeruginosa
  – Associated with higher mortality rates
• Initial regimens often include two agents active against P. aeruginosa
  – 1989: lower mortality rates with combo vs. monotherapy2
  – Not pertinent to current practice

What are the potential mechanisms?

- Potential mechanisms1,2
  – Synergistic activity
  – Broad coverage with agents with differing spectra of activity/resistance patterns
  • Prevention of resistance development during antimicrobial therapy

Potential issues

- Unnecessary use of antibiotics leads to
  – Resistance
  – Increased adverse effects
  – Increased costs
  – Increased risk of superinfection
  – Increased risk of C. difficile infection

Past research

- 2004- Baddour, et al. 1
- 2007- Rodriguez, et al. 2
- 2010- Martinez, et al. 3

- Post hoc analysis-possible benefit 4
  - Neutropenic patients
  - Patients presenting with shock

Surviving sepsis 2012

<table>
<thead>
<tr>
<th>TABLE 1. Recommendations: Initial Resuscitation and Infection Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>(review)</td>
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<td></td>
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</tbody>
</table>

Cochrane review

Beta lactam antibiotic monotherapy versus beta lactam-
monotherapy with aminoglycoside: randomized controlled trial for sepsis

<table>
<thead>
<tr>
<th>Authors’ conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>The addition of an aminoglycoside to beta-lactam for sepsis should be discouraged. All-cause mortality rates were similar. Combination treatment carries a significant risk of nephrotoxicity.</td>
</tr>
</tbody>
</table>

Self-assessment: Question 1

Double coverage of Pseudomonas has shown a mortality benefit in patients presenting with which of the following characteristics?

A. Liver transplant and neutropenia
B. Neutropenia and shock
C. Kidney failure and neutropenia
D. Shock and kidney transplant

Self-assessment: Question 2

Potential outcomes of overusing antibiotics include which of the following?

A. Increased risk of infection
B. Decreased risk of superinfection
C. Decreased risk of resistance
D. Decreased cost to the patient and the hospital

Northwestern Memorial Hospital

- 894-bed Academic Medical Center Hospital in downtown Chicago
- Primary teaching affiliate of Northwestern University Feinberg School of Medicine
- 6 adult ICUs
  - NSICU, CCU, CTICU, SICU, MICU
Our research project: study design

• Retrospective chart review

• January 1, 2013-December 31, 2013
  – Patients with ICD-9 Code for “Sepsis” or “Septic shock”
  – Patients with positive blood culture for Gram Negative bacillus

• Cross referenced both reports

Study participants

• Double coverage
  – Beta-lactam and at least 1 dose of an aminoglycoside or ciprofloxacin within 48 hours
  – Active therapy determined by previously defined 2013 CLSI breakpoints

• Single coverage
  – Beta-lactam only

Methods

• Inclusion criteria
  – Admitted to an ICU within 24 hours of diagnosis of sepsis/septic shock
  – Total hospital stay at least 48 hours
  – Positive GNR blood culture

• Exclusion Criteria
  – Patients with multi-drug resistant (MDR) organisms
  – Those receiving triple active coverage
  – No MIC/incomplete susceptibility data
  – Palliative/not actively seeking care

Study participants

• Double coverage
  – Beta-lactam and at least 1 dose of an aminoglycoside or ciprofloxacin within 48 hours
  – Active therapy determined by previously defined 2013 CLSI breakpoints

• Single coverage
  – Beta-lactam only

Outcomes

• Primary outcome
  – In hospital mortality

• Secondary outcomes
  – Length of ICU stay
  – Length of positive blood cultures
  – Days of vasopressor use
  – Days of steroid use
  – Days of ventilator use

Results

<table>
<thead>
<tr>
<th>Table 1. Baseline Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Systolic HF*</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
<tr>
<td>Asthmatics/Disease</td>
</tr>
<tr>
<td>Circumference/crop</td>
</tr>
</tbody>
</table>

* = Fisher’s exact test performed

Statistical analysis

149 patients screened
68 patients excluded
80 patients included
34 encounters received single coverage
47 encounters received double coverage

8/14/2014
Table 1. Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Single coverage (n=34)</th>
<th>Double coverage (n=47)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known liver disease</td>
<td>9 (27)</td>
<td>5 (11)</td>
<td>0.063</td>
</tr>
<tr>
<td>History of liver transplant*</td>
<td>8 (12)</td>
<td>0 (0)</td>
<td>0.026</td>
</tr>
<tr>
<td>Current cancer</td>
<td>8 (23)</td>
<td>11 (23)</td>
<td>0.971</td>
</tr>
<tr>
<td>Central line on admission*</td>
<td>8 (24)</td>
<td>11 (23)</td>
<td>0.971</td>
</tr>
<tr>
<td>Prior hospitalization within 30 days</td>
<td>15 (44)</td>
<td>19 (40)</td>
<td>0.776</td>
</tr>
<tr>
<td>Surgery within 30 days</td>
<td>12 (35)</td>
<td>8 (17)</td>
<td>0.310</td>
</tr>
<tr>
<td>Antibiotic use within 30 days</td>
<td>14 (41)</td>
<td>15 (41)</td>
<td>0.613</td>
</tr>
</tbody>
</table>

* = Fisher’s exact test performed

Table 2. Characteristics When Diagnosed with Sepsis or Septic Shock

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Single coverage (n=34)</th>
<th>Double coverage (n=47)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRS criteria average</td>
<td>3.3 +/- 0.655</td>
<td>3.5 +/- 0.684</td>
<td>0.217</td>
</tr>
<tr>
<td>APACHE IV</td>
<td>56.4 +/- 26</td>
<td>62.8 +/- 33.1</td>
<td>0.351</td>
</tr>
<tr>
<td>ANC &lt;500 cells/μL*</td>
<td>0</td>
<td>4</td>
<td>0.143</td>
</tr>
<tr>
<td>Serum creatinine baseline (mg/dL)</td>
<td>2.4 +/-1.4</td>
<td>1.4 +/-1.4</td>
<td>0.400</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>123.4 +/- 226.1</td>
<td>61.5 +/- 75.4</td>
<td>0.090</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>122.1 +/- 175.7</td>
<td>67.7 +/- 122.8</td>
<td>0.120</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>6.7 +/- 10.6</td>
<td>4.8 +/- 16.4</td>
<td>0.585</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dL)</td>
<td>11.5 +/- 37.1</td>
<td>1.3 +/- 2.3</td>
<td>0.110</td>
</tr>
<tr>
<td>Lactate (mg/dL)</td>
<td>3.7 +/- 2.6</td>
<td>2.9 +/- 1.7</td>
<td>0.147</td>
</tr>
</tbody>
</table>

* = Fisher’s exact test performed

59% of patients received double coverage

Double Coverage Antibiotic (n=47)
- Aminoglycoside 19%
- Ciprofloxacin 15%
- G Double Coverage Antibiotic 46%

GNRs in single coverage
- Escherichia sp. (14) 19% 0% 17%
- Klebsiella sp. (7) 19%
- Pseudomonas sp. (1) 14%
- Enterobacter sp. (1) 14%
- Proteus sp. (1) 14%
- Acinetobacter sp. (1) 14%
- Citrobacter sp. (1) 14%
- Serratia sp. (1) 14%
- Other (1) 14%

73% of patients received double coverage

Double Coverage Antibiotic (n=47)
- Aminoglycoside 14%
- Ciprofloxacin 19%
- G Double Coverage Antibiotic 46%

GNRs in double coverage
- Escherichia sp. (22) 46% 0% 17%
- Klebsiella sp. (7) 14%
- Pseudomonas sp. (1) 14%
- Enterobacter sp. (1) 14%
- Proteus sp. (1) 14%
- Serratia sp. (1) 14%
- Other (1) 14%

20% of patients with PSA infections compared to mortality

38% in-hospital mortality
Results

Source of GNR Infection

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Urinary Tract</th>
<th>Intra-abdominal</th>
<th>Other</th>
<th>Unknown</th>
<th>Lung</th>
<th>IV Catheter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Cases</td>
<td>20</td>
<td>25</td>
<td>30</td>
<td>15</td>
<td>20</td>
<td>5</td>
</tr>
</tbody>
</table>

Results: primary outcome

In Hospital Mortality

- Single coverage: 21%
- Double coverage: 15%

P-value = 0.504

Results: secondary outcomes

Secondary Outcomes

- Days of ICU stay (IQR)
- Days of positive blood cultures
- Days of vasopressor therapy
- Days of steroid therapy
- Days of mechanical ventilation

<table>
<thead>
<tr>
<th>Single Coverage</th>
<th>Double Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of ICU stay</td>
<td>2.00</td>
</tr>
<tr>
<td>Days of positive blood cultures</td>
<td>1.00</td>
</tr>
<tr>
<td>Days of vasopressor therapy</td>
<td>1.40</td>
</tr>
<tr>
<td>Days of steroid therapy</td>
<td>1.11</td>
</tr>
<tr>
<td>Days of mechanical ventilation</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Limitations

- Retrospective
- Small sample size
- Single institution
- Institution bias
- PK/PD parameters not analyzed
- ICU's may have different practices

Conclusions

- Double coverage with a beta-lactam and an aminoglycoside or ciprofloxacin was not associated with an improvement in hospital mortality (p=0.504)
- There was no difference in time to clearance of blood cultures (p=0.160)
- There was no difference in length of ICU stay (p=0.872)
- There was no difference between days of vasopressor therapy or days of mechanical ventilation (p=0.974, p=0.241)

Going forward

- Data from this study suggest there may not be a mortality benefit in sepsis/septic shock
- Things to consider
  - Patient specific factors
  - Your institution’s antibiogram
  - PK/PD parameters
Acknowledgements

• John Esterly, PharmD, BCPS, AQ-ID
• Bryan Lizza, PharmD, BCPS
• Erik J. Rachwalski, PharmD, BCPS

Clinical Impact of Dual Antimicrobial Therapy in Critically Ill Patients with Gram Negative Sepsis or Septic Shock

Mary Lenefsky, PharmD
PGY-2 Critical Care Resident Midwestern Chicago College of Pharmacy/Northwestern Memorial Hospital Chicago, IL

The speaker has revealed no potential conflict of interest in relation to this presentation.
Implementation of a Clinical Decision Support Tool to Facilitate Formulary Medication Utilization

Kristopher Lozanovski, PharmD
PGY2 Pharmacy Informatics Resident
NorthShore University HealthSystem
Evanston, Illinois

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

NorthShore University HealthSystem

- Four community hospitals:
  - Evanston: 354 beds
  - Glenbrook: 173 beds
  - Skokie: 156 beds
  - Highland Park: 149 beds
  - Total: 832 beds
- NorthShore Medical Group
- NorthShore Research Institute
- NorthShore Foundation

Background:
Computerized Provider Order Entry and Clinical Decision Support

Computerized Provider Order Entry (CPOE)

- Direct entry of clinical orders within an electronic health record (EHR) by licensed clinicians with ordering privileges
- Allows for direct transmission of orders from providers to pharmacists for verification via a computer system
- Advantages:
  - Standardization of orders
  - Legible, complete orders
  - Integration of clinical decision support systems (CDSS)

Clinical Decision Support System (CDSS)

- The use of health information technology to provide providers with intelligently filtered information to aid in the clinical decision making process
- Alerts healthcare providers during order placement and review via CPOE
- Common alerts
  - Drug-drug interactions
  - Drug-allergy interactions
  - Drug-disease interactions
  - Best practice alerts
  - Dose discrepancies
### Potential Advantages and Disadvantages of CDSS

<table>
<thead>
<tr>
<th>Disadvantages</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alert Desensitization</td>
<td>Provides automatic up to date and evidence based practices</td>
</tr>
<tr>
<td>Can be perceived as a threat to clinical judgment</td>
<td>Reduced clinical practice variation</td>
</tr>
<tr>
<td>Promote over-reliance on software</td>
<td>Improved patient safety and quality of care</td>
</tr>
<tr>
<td>Time-consuming</td>
<td>Facilitate workflow</td>
</tr>
<tr>
<td>Maintenance, support, training</td>
<td>Decrease costs</td>
</tr>
</tbody>
</table>

**Background:**

Formulary Medications and Formulary Decision Support

- **Formulary Decision Support**
  - The use of CDSS functionality to improve formulary compliance
    - Guides clinicians toward prescribing formulary medications over non-formulary options
  - **Potential options:**
    - Include only formulary options in the CPOE order catalog
    - Indicate the medication as “non-formulary” when ordering the medication
    - Display a pop-up alert when the clinician attempts to order a non-formulary medication while providing a selectable list of alternative formulary options

- **Efficacy of Formulary Decision Support**
  - Fischer MA, et al. (2008)
    - Study the effect of e-prescribing with formulary decision support over a 18 month period
    - **Results:**
      - Formulary medications: +6.6% (95% CI: +5.9% to +7.3%)
      - Non-formulary medications: -5.2% (95% CI: -5.9% to -4.5%)
  - Teich JM, et al. (2000)
    - Study the effect of a pop-up formulary decision support alert on histamine H2 antagonist prescribing over a 24 month period
    - **Results:**
      - Preferred agent use: Increased from 15.6% to 81.3% (P<0.001)

- **Project Objective**
  - Implement a dynamic formulary decision support tool within the electronic health record to facilitate formulary compliance at the point of order entry
Methods

- Proof of concept
- Form taskforce
- Preliminary review and testing
- Communication and implementation
- Analysis

Current Prior to Admission (PTA) Medication Prescribing Workflow

- Nurse obtains and inputs medication history into EHR
- Patient admitted to hospital
- Providers place prior to admission orders

Current Pharmacy Workflow

- Non-formulary medication ordered:
  - Pharmacist may contact physician suggesting formulary alternatives
  - Patient may supply own medication for use
  - Pharmacy may borrow medication from another facility
  - Pharmacy may purchase the medication
- Notify nursing and prescriber reason for the delay in dispensing the medication

Potential Impact

<table>
<thead>
<tr>
<th>Pharmaceutical Subclass</th>
<th>Average # of non-formulary orders per month</th>
<th>Estimated # of non-formulary annual orders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylates</td>
<td>393</td>
<td>3531</td>
</tr>
<tr>
<td>Oil Soluble Vitamins</td>
<td>285</td>
<td>2562</td>
</tr>
<tr>
<td>Multivitamins</td>
<td>186</td>
<td>1659</td>
</tr>
<tr>
<td>Iron</td>
<td>170</td>
<td>1524</td>
</tr>
<tr>
<td>Calcium</td>
<td>169</td>
<td>1515</td>
</tr>
<tr>
<td>Angiotensin II Receptor Antagonists</td>
<td>144</td>
<td>1296</td>
</tr>
<tr>
<td>Prostatic Hypertrophy Agents</td>
<td>100</td>
<td>894</td>
</tr>
<tr>
<td>Urinary Antispasitics</td>
<td>90</td>
<td>807</td>
</tr>
<tr>
<td>Prostaglandins – Ophthalmic</td>
<td>69</td>
<td>618</td>
</tr>
<tr>
<td>Cobalamins</td>
<td>66</td>
<td>591</td>
</tr>
</tbody>
</table>

Average total orders (Ordered: 10/1/2013 – 01/31/2014)

- 181,437 orders

Average non-formulary PTA orders (Ordered: 10/1/2013 – 01/31/2014)

- 4,195 orders

Average % non-formulary PTA orders

- 2.3%

Potential Impact

- Iron 170 1524
- Calcium 169 1515
- Angiotensin II Receptor Antagonists 144 1296
- Prostatic Hypertrophy Agents 100 894
- Urinary Antispasitics 90 807
- Prostaglandins – Ophthalmic 69 618
- Cobalamins 66 591

Proof of Concept

- Formulary decision support
  - Pop-up alert that appears when a clinician orders a non-formulary prior to admission medication
  - Only affects orders placed through the admission medication reconciliation process
- Goals:
  - Reduce prior to admission non-formulary ordering
  - Reduce call volume between pharmacists and providers
Proof of Concept

• Dynamic functionality:
  – If the non-formulary medication has the same generic medication available on formulary:
    • Generic equivalents are suggested

Example

Input by nurse (prior to admission):

Prior to admission medication list:

The ordering provider can select one of the suggested formulary alternatives or continue with the original order
  – If the original order is continued, a reason for using the non-formulary medication is required

Proof of Concept

• Dynamic functionality:
  – If the non-formulary medication has no generic formulation available on formulary:
    • Alternate formulary medications are suggested based on pharmaceutical subclass of the ordered non-formulary medication
    • This functionality can be suppressed by specific pharmaceutical subclasses

Example

Input by nurse (prior to admission):

Prior to admission medication list:

The ordering provider can select one of the suggested formulary alternatives or continue with the original order
  – If the original order is continued, a reason for using the non-formulary medication is required
**Taskforce**

- Health Information Technology (HIT)
- Pharmacy Super Users (HIT Liaisons)
- Pharmacy Clinical Specialists
- Inpatient Physicians and Medical Residents

**Preliminary Review**

- Pharmaceutical subclass
  - Supplied by data vendor
- Determination of pharmaceutical subclasses to suppress
  - Assessed each subclass using annual ordering reports
  - Suppression considerations:
    - Relevant to prior to admission medications
    - Safety
    - Multiple mechanisms of action
    - User friendly
  - Overall: 346 / 439 subclasses suppressed (79%)

- Testing and Troubleshooting

**Preliminary Review**

- Determination of the verbiage displayed in the alert
  - Displayed alternatives may not be therapeutically equivalent
  - Clinical judgment should be used when selecting a formulary alternative
  - Addressing potential issues:
    - “Continue with Original Order” disabled
    - Matching dose and frequency to original order

- Pharmacy and Therapeutics for approval

**Example**

Displayed formulary decision support alert:

**Communication and Implementation**

- Communicate with on-site trainers
  - Nurses
  - Inpatient physicians (hospitalists, residents)
  - Pharmacists

- Implementation: March 11, 2014

**Results**

- Analysis periods:
  - Pre-implementation: 82 days (12/18/2013 - 03/10/2014)
  - Post-implementation: 82 days (03/11/2014 - 05/31/2014)
- A chi-squared test was used to determine statistical significance (p < 0.05)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total number of medication orders (formulary + non-formulary)</th>
<th>Number of non-formulary medication orders</th>
<th>Percentage</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-implementation</td>
<td>470,351</td>
<td>10,227</td>
<td>2.2 %</td>
<td></td>
</tr>
<tr>
<td>Post-implementation</td>
<td>531,476</td>
<td>8,328</td>
<td>1.6 %</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Percent reduction in non-formulary orders: -27.9 % < 0.0001
Results

<table>
<thead>
<tr>
<th>Pharmaceutical Subclass</th>
<th># of non-formulary orders (Pre-implementation)</th>
<th># of non-formulary orders (Post-implementation)</th>
<th>Percent change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivitamins</td>
<td>313</td>
<td>77</td>
<td>-78.2%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Angiotensin II Receptor Antagonists</td>
<td>255</td>
<td>165</td>
<td>-42.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prostatic Hypertrophy Agents</td>
<td>155</td>
<td>126</td>
<td>-28.1%</td>
<td>0.0008</td>
</tr>
<tr>
<td>Lithium Antagonists</td>
<td>150</td>
<td>142</td>
<td>-10.2%</td>
<td>0.3801</td>
</tr>
<tr>
<td>Prostaglandins – Ophthalmic</td>
<td>118</td>
<td>126</td>
<td>+1.34%</td>
<td>0.9215</td>
</tr>
<tr>
<td>Colchicines</td>
<td>130</td>
<td>43</td>
<td>-69.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Folic Acid/ Folicates</td>
<td>60</td>
<td>43</td>
<td>-36.6%</td>
<td>0.0015</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>66</td>
<td>29</td>
<td>-61.1%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Artificial Tears and Lubricants</td>
<td>91</td>
<td>88</td>
<td>-12.9%</td>
<td>0.0094</td>
</tr>
<tr>
<td>Antidepressants – Non-Sedating</td>
<td>43</td>
<td>17</td>
<td>-60.0%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Limitations

- Impact on non-formulary medication ordering also affected by a second project
  - Prior to admission preference list
  - Implemented on the same day with this project
- Small subset of non-formulary orders placed outside of admission processes not affected
- Subjective criteria for selecting pharmaceutical subclasses to suppress

Conclusion

- The use of formulary decision support has the potential to reduce non-formulary prior to admission medication ordering

Future Directions

- Further assess impact on non-formulary ordering
- Evaluate additional pharmaceutical subclasses for intervention

Assessment Question #1

- Which of the following is a potential disadvantage of clinical decision support?
  A. Improved patient safety
  B. Alert desensitization
  C. Enhanced quality of care
  D. Medication cost reduction

Assessment Question #2

- Which of the following criteria is necessary to support dynamic formulary clinical decision support alert functionality when suggesting formulary alternatives?
  A. Pharmaceutical subclass
  B. Route of administration
  C. Ordering provider type
  D. Name of the medication
Acknowledgements

- Muriel Forbes, PharmD  
  Clinical specialist – Pharmacy Informatics, Project Preceptor
- Lynn Boecler, PharmD, MS  
  Senior Director, Pharmacy Services
- Hina Patel, PharmD, BCPS  
  Clinical Manager
- Jenny Szparkowski, PharmD, BCPS  
  Clinical Specialist – Pharmacy Informatics
- Jillian Lesniewski  
  Senior Applications Analyst

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References


Implementation of a Clinical Decision Support Tool to Facilitate Formulary Medication Utilization

Kristopher Lozanovski, PharmD  
PGY2 Pharmacy Informatics Resident  
NorthShore University HealthSystem  
Evanston, Illinois
A Retrospective Review of a Renal Sparing Protocol (RSP) in Orthotopic Liver Transplantation (OLT)

ICHP Annual Meeting 2014
Presented by: Brett J Pierce PharmD
PGY2 Solid Organ Transplant Resident

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

Objectives
Identify adverse effects associated with immunosuppressive agents.
Recognize the need for renal sparing protocols and strategies that they employ.

Renal Dysfunction in OLT
Renal dysfunction is commonly seen with liver disease
Among cirrhotics:
44% have acute tubular necrosis (ATN)
17% have hepatorenal syndrome (HRS)
Acute renal failure complicates up to 60% of OLTs
Increases morbidity and mortality
Increases length of hospital stay
End stage renal disease (ESRD) increases mortality 40%

Tacrolimus (TAC)
Classification
Calcineurin inhibitor (CNI)
Mechanism of Action
Forms drug-protein complex FKBP12
Inhibits calcineurin phosphatase
Prevents T-Cell activation

Adverse Effects
Neurotoxicity
Hyperglycemia
Hyperkalemia
Hypertension
Nephrotoxicity

Tacrolimus Induced Nephrotoxicity
Tacrolimus induced nephrotoxicity occurs in 17-44% of OLTs
Tacrolimus binding proteins are concentrated in renal tissues
Toxicity occurs by multiple methods:
Direct renal toxicity via:
Epithelial vacuolization
Antiproliferative effects
Interstitial fibrosis
Renal vasospasm

Mycophenolate (MMF)
Mechanism of Action
Inhibits inosine monophosphate dehydrogenase
Prevents de novo purine synthesis
Inhibits T and B cell proliferation

Adverse Effects
GI Intolerance
Myelosuppression
Opportunistic Infections

S Phase
Question #1
Which of these is a side effect that may be caused by mycophenolate?
A. Tremor  
B. Hyperglycemia  
C. Neutropenia  
D. Constipation

Protocol Comparison

<table>
<thead>
<tr>
<th></th>
<th>Non-Renal Sparing (NRS)</th>
<th>Renal Sparing Protocol (RSP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>Methylprednisolone Day 0</td>
<td>Methylprednisolone Day 0</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Tacrolimus</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td></td>
<td>Prednisone Taper</td>
<td>Prednisone Taper</td>
</tr>
<tr>
<td>Tacrolimus Start</td>
<td>Post-Op Day 0</td>
<td>Post-Op Day 1</td>
</tr>
<tr>
<td>Initial TAC</td>
<td>8-10ng/ml</td>
<td>5-8ng/ml</td>
</tr>
<tr>
<td>Target Trough</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RSP Inclusion Criteria

SCR > 1.5mg/dL?  
CrCl < 60mL/min?  
On Renal Replacement Therapy?  
Use Renal Sparing Protocol  
SCR increase > 50% from baseline

Existing Literature

What Is Known?
Renal Sparing effect of decreased CNI exposure is well documented
MMF has been used extensively in patients receiving OLT

What Is Published?
Eight trials compare low-dose CNI + MMF with standard dose CNI
Of these 2 looked at de novo MMF
Neither evaluated delayed initiation of TAC

Rao et al.

Population
84 OLT Patients at Northwestern Memorial Hospital  
42 Renal Sparing Protocol (RSP)  
42 Simultaneous Liver Kidney (SLK)

Treatment
NMH Renal Sparing Protocol  
LD-Delayed TAC + HD-MMF + Prednisone

Results
SCR improved at 1 year in both groups  
Similar death, rejection, and infection rates


Question #2
What method do renal sparing protocols employ?
A. Using increased doses of steroids  
B. Decreasing renal exposure to tacrolimus  
C. Decreasing renal exposure to mycophenolate mofetil  
D. Using alternative methods for opportunistic infection prophylaxis.
**Study Question**

**Primary Question**
Does the use of a renal sparing protocol put OLT patients at a higher risk of acute rejection within the first year after transplant?

**Secondary Question**
Does the addition of high-dose mycophenolate, increase the occurrence of neutropenia, thrombocytopenia, and gastrointestinal side effects?

**Outcome Measures**

**Primary Outcome**
Occurrence of acute rejection within one year of transplant

**Secondary Outcomes**
Occurrence of:
- Neutropenia — ANC<1000
- Thrombocytopenia — PLTs<150,000
- GI Side Effects — Leading to discontinuation of MMF
- Opportunistic Infections:
  - Cytomegalovirus (CMV)
  - Herpes Simplex Virus (HSV)
  - Pneumocystis Pneumonia (PCP)
  - Aspergillosis
  - Candidiasis

**Study Population – Inclusion/Exclusion**

**Inclusion Criteria**
Adult, deceased donor, OLT patients at NMH
Transplanted between 2010-2012

**Exclusion Criteria**
Non-DeNovo RSP start
Deviated from protocol
Prior transplant recipients
Previously received immunosuppression
End Stage Liver Disease (ESLD) due to autoimmune hepatitis

**Study Site**

**Northwestern Memorial Hospital**
894 Bed academic medical center
Level 1 trauma center
46,000 inpatient admissions per year

**Kovler Organ Transplantation Center**
Established 1964
>1300 OLTs to date
110-130 per year
90% Deceased Donors

**Statistics**
This study was approved by the Northwestern University Investigational Review Board

Continuous variables were analyzed with Student’s t-test and Wilcoxon Rank-Sum test

Categorical variables were analyzed with Chi-square and Fisher’s Exact

All data were analyzed with Epi-Info 7.1.3; Atlanta, GA

**233 Total Patients**

- 16 Autoimmune Hepatitis
- 14 Multiple Transplants
- 16 Non-DeNovo RSP Start
- 40 Deviated from protocol

**147 Patients Included**

- 79 RSP
- 68 NRS
Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>RSP N=79</th>
<th>NRS N=68</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (yrs)</td>
<td>55.9 STD(11.0)</td>
<td>58.0 STD(8.1)</td>
<td>0.20</td>
</tr>
<tr>
<td>Male (%)</td>
<td>51 (64.6%)</td>
<td>50 (71.4%)</td>
<td>0.24</td>
</tr>
<tr>
<td>White (%)</td>
<td>56 (70.9%)</td>
<td>46 (67.7%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Black (%)</td>
<td>9 (11.4%)</td>
<td>6 (8.8%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>12 (15.2%)</td>
<td>13 (19.1%)</td>
<td>0.40</td>
</tr>
<tr>
<td>MELD Score at Transplant</td>
<td>Median: 29</td>
<td>Median: 20.5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>IQR: (25.0-36.0)</td>
<td>IQR: (17.0-26.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min:15, Max:47</td>
<td>Min:11, Max:47</td>
<td></td>
</tr>
<tr>
<td>Serum Creatinine at Transplant</td>
<td>Median: 1.95</td>
<td>Median: 1.05</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>IQR: (1.46-2.62)</td>
<td>IQR: (0.8-1.21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min:0.61, Max:2.62</td>
<td>Min:0.49, Max:1.9</td>
<td></td>
</tr>
</tbody>
</table>

Baseline Demographics

<table>
<thead>
<tr>
<th>CMV Serology At Transplant</th>
<th>RSP N=79</th>
<th>NRS N=68</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>D+/R- (High Risk)</td>
<td>14 (17.7%)</td>
<td>12 (17.6%)</td>
<td>0.80</td>
</tr>
<tr>
<td>D+/R+ (Intermediate Risk)</td>
<td>17 (46.6%)</td>
<td>34 (50.0%)</td>
<td>0.79</td>
</tr>
<tr>
<td>D-/R+ (Intermediate Risk)</td>
<td>20 (53.5%)</td>
<td>16 (21.5%)</td>
<td>0.99</td>
</tr>
<tr>
<td>D-/R- (Low Risk)</td>
<td>8 (10.1%)</td>
<td>6 (8.8%)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Baseline Demographics

<table>
<thead>
<tr>
<th>ESLD Etiology</th>
<th>RSP N=79</th>
<th>NRS N=68</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis C</td>
<td>27 (34.2%)</td>
<td>33 (48.5%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Alcoholic Liver Disease</td>
<td>21 (26.6%)</td>
<td>16 (23.5%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Cryptogenic Cirrhosis</td>
<td>10 (12.2%)</td>
<td>1 (1.47%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Rejection

<table>
<thead>
<tr>
<th>Rejection Within 1 Year</th>
<th>RSP N=79</th>
<th>NRS N=68</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>19 (24.1%)</td>
<td>15 (22.1%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Biopsy Proven Acute Rejection (BPAR)</td>
<td>10 (12.7%)</td>
<td>4 (5.9%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Empirically Treated</td>
<td>9 (11.4%)</td>
<td>11 (16.2%)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Neutropenia

<table>
<thead>
<tr>
<th>Neutropenia Within 1 Year</th>
<th>RSP N=79</th>
<th>NRS N=68</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>39 (49.4%)</td>
<td>15 (22.1%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Moderate (500&lt;ANC&lt;1000)</td>
<td>18 (23.8%)</td>
<td>10 (14.7%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Severe (0&lt;ANC&lt;500)</td>
<td>21 (26.6%)</td>
<td>5 (7.4%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Opportunistic Infections

<table>
<thead>
<tr>
<th>Opportunistic Infections Within 1 Year</th>
<th>RSP N=79</th>
<th>NRS N=68</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>21 (26.6%)</td>
<td>8 (11.8%)</td>
<td>0.02</td>
</tr>
<tr>
<td>CMV</td>
<td>13 (16.5%)</td>
<td>5 (7.4%)</td>
<td>0.09</td>
</tr>
<tr>
<td>HSV</td>
<td>4 (5.1%)</td>
<td>1 (1.5%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Aspergilosis</td>
<td>3 (3.8%)</td>
<td>2 (2.9%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Candidias</td>
<td>1 (1.2%)</td>
<td>0 (0%)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

MMF Discontinuation

RSP patients who stopped MMF due to adverse affects:

- Total Patients: N=7 (8.9%)
- GI Issues: N=2 (2.5%)
- Neutropenia: N=5 (6.3%)
Renal Function/Thrombocytopenia

<table>
<thead>
<tr>
<th></th>
<th>Serum Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RSP N=79  NRS N=68 P</td>
</tr>
<tr>
<td>SCr at Transplant</td>
<td>Median 1.95 IQR (1.46-2.62)</td>
</tr>
<tr>
<td>SCr at 3 months</td>
<td>Median 1.36 STD (0.54) IQR (0.80-2.00)</td>
</tr>
<tr>
<td>SCr at 6 months</td>
<td>Median 1.44 STD (0.61) IQR (0.80-2.10)</td>
</tr>
<tr>
<td>SCr at 12 months</td>
<td>Median 1.40 STD (0.80) IQR (0.80-2.00)</td>
</tr>
<tr>
<td>∆ From Baseline</td>
<td>Median Decrease 0.65 IQR (0.17-1.52)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thrombocytopenia</th>
<th>RSP N=79  NRS N=68 P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>7 (8.9%) 8 (11.8%) 0.56</td>
</tr>
</tbody>
</table>

Limitations

- Retrospective study design
- Tacrolimus levels were not recorded
- Limited to patients during the protocol period
- Unable to analyze biopsy proven rejection only

Summary

Renal impairment is commonly associated with ESLD
Tacrolimus is an effective immunosuppressant, but can cause significant nephrotoxicity
A renal sparing protocol utilizing high dose mycophenolate, and low dose, delayed initiation tacrolimus does not appear to put patients at a higher risk of rejection within 1 year following transplant
A renal sparing protocol does appear to cause higher rates of opportunistic infections and neutropenia

Acknowledgements

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Chad L. Richardson, PharmD
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John Esterly, PharmD, BCPS-AQ-ID
Noelle RM Chapman, PharmD, BCPS-AQ-ID
Josh Levitsky, MD.
References


Immunosuppression

<table>
<thead>
<tr>
<th></th>
<th>MMF Dose Post Tx</th>
<th>Total Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months (N=72)</td>
<td></td>
<td>1458.3 STD (508.73)</td>
</tr>
<tr>
<td>6 months (N=67)</td>
<td></td>
<td>1311.43 STD (498.75)</td>
</tr>
<tr>
<td>12 months (N=65)</td>
<td></td>
<td>1153.8 STD (529.76)</td>
</tr>
<tr>
<td>Prednisone Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months post Tx</td>
<td>RSP (N=74)</td>
<td>NRS (N=65)</td>
</tr>
<tr>
<td></td>
<td>5.87 STD 3.14</td>
<td>15.29 STD 3.91</td>
</tr>
</tbody>
</table>

Death and Time to Rejection

<table>
<thead>
<tr>
<th></th>
<th>RSP Group (N=79)</th>
<th>NRS Group (N=68)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death Within 1 Year</td>
<td>6 (7.6%)</td>
<td>6 (8.8%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Transplant (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to Rejection</td>
<td>Median 3</td>
<td>Median 1</td>
<td>0.06</td>
</tr>
<tr>
<td>(Weeks)</td>
<td>IQR1-24</td>
<td>IQR1-4</td>
<td></td>
</tr>
</tbody>
</table>

Neuberger et al.

<table>
<thead>
<tr>
<th>525 OLT Patients</th>
<th>Patient Population</th>
<th>195 OLT patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: TAC (≥10ng/ml)</td>
<td>Treatment</td>
<td>A: TAC (≥12ng/ml) + MMF</td>
</tr>
<tr>
<td>B: TAC (&lt;8ng/ml) + MMF</td>
<td></td>
<td>B: TAC (&lt;10ng/ml) + MMF</td>
</tr>
<tr>
<td>C: Daclizumab + MMF/TAC (&lt;8ng/ml, POD5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Boudjema et al.

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Primary Outcome(s)</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute rejection</td>
<td>LI-TAC and MMF reduces the occurrence of renal dysfunction and the risk of graft rejection.</td>
</tr>
<tr>
<td></td>
<td>Renal dysfunction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arterial hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td></td>
</tr>
</tbody>
</table>

Daclizumab induction with delayed, LI-TAC and MMF improved renal outcomes with no change in safety or efficacy.