ADJUNCTIVE USE OF TOPICAL VANCOMYCIN FOLLOWING CRANIOTOMIES FOR SURGICAL SITE INFECTION PROPHYLAXIS

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PharmD Candidate Class of 2018
OBJECTIVES

- Discuss surgical site infections (SSIs) as well as the standard of care for SSIs
- Review of vancomycin drug information
- Discuss literature involving the topical use of vancomycin
- Provide recommendations for pharmacy practice
TOPIC INTEREST
SURGICAL SITE INFECTIONS (SSIs)

- Infection that occurs at incision site within appropriate surveillance period
  - 90-day surveillance period recommended for craniotomy
- Often affects subgaleal space, subdural space, cranial bone, or brain
- Incidence rate:
  - About 5%
    - 2.2% among low-risk patients
    - 4.7% among high-risk patients
  - 1 in 20 people
- Costly $$$

CDC.gov
Journal of Neurosurgery. Feb 2014; 120(2); 509-521
RISK FACTORS

- Surgical technique
- Duration of surgery (over a 4 hour period)
- Hospital and operating room environments
- Instrument sterilization
- Preoperative preparation
- Perioperative management
- Underlying medical condition(s)
- Patient specific factors
  - Age
  - Cigarette Smoking
  - Immunosuppression
  - Recent surgery
TYPES OF INFECTION FOLLOWING CRANIOTOMY

- Osteomyelitis
- Deep Incisional Primary (DIP)
- Intracranial infection
- Meningitis or ventriculitis
- Sinusitis
- Superficial Incisional Primary (SIP)

Culprits:
- *S. aureus*, coagulase-negative staphylococci, MRSA, *P. acnes*
- Some gram-negative bacteria has been isolated in polymicrobial infections

SCIP/ASHP guidelines
STANDARD OF CARE FOR SSI – CRANIOTOMIES
**General Spectrum of Antibiotics**

**GRAM POSITIVE BACTERIA**

- VRE
- MRSA
- MSSA
- Enterococcus
- Strep

- Linezolid
- Vancomycin
- Daptomycin
- Penicillin
- Ampicillin/Amoxicillin
- Amoxicillin/Clavulanate/Amp-Sulbactam
- Nafcillin/Dicloxacillin
- Piperacillin/Tazobactam
- Carbapenems

**GRAM NEGATIVE BACTERIA**

- Gut Anaerobes
- Enterobacteriaceae
- Pseudomonas
- ESBL
- KPC
- Atypical

- Fluoroquinolones
- 1st (Cephalaxin/Cefazolin)
- 2nd (Cefuroxime)
- 3rd (Ceftriaxone/Cefotaxime)
- 4th (Cefepime)
- 5th (Ceftaroline)
- TMP-SMX
- Tigecycline

- Doxycycline
- Clindamycin
- Macrolides
- (Campylobacter, H. flu, M. cat)
- Aminoglycosides
- Aztreonam
- Metronidazole
- Colistin/Polymixin

**Notes:**
- Daptomycin does not have activity in the lung.
- Ertapenem does not cover Pseudomonas.
- Only moxi has anaerobic coverage.
- Tmp-smx also covers PJP, Nocardia, Toxo, and Steno.

This document is for educational purposes only. It is not intended as a guideline for clinical practice. It is a graphic representation of the general spectrum of antibiotics. Please refer to culture susceptibilities, institutional antibiogram, or published antibiotic guides for additional guidance. Also consider Infectious Disease consultation for further assistance.
BACKGROUND

- Mechanism of action

https://en.wikipedia.org/wiki/Vancomycin
SYSTEMIC ADVERSE EVENTS AND TOXICITY - FYI

- **Red Man Syndrome**
  - Hypotension, flushing, rash
- **Nephrotoxicity**
  - Goal trough 15-20 mcg/mL
- **Ototoxicity** – serum peaks > 80 mcg/mL
- **Pain and spasm syndrome**
  - Due to high infusion rates
- **Thrombophlebitis**
- **Neutropenia and thrombocytopenia with prolonged therapy**

https://www-uptodate-com.ezproxy.lib.utah.edu/contents/vancomycin-drug-information?source=search_result&search=vancomycin%20toxicity&selectedTitle=1~150
ABSORPTION OF VANCOMYCIN

- Sites of systemic absorption:
  - Blood
  - Brain
  - Heart
  - Lung
  - Bone

- Topical bone absorption:
  - No real data
  - One (1) study in rat femurs showing minimal systemic absorption

Am J Health-Syst Pharm. 2009; 66:82-98
FORMULATIONS

- **IV**
  - 15-20 mg/kg with re-dosing given at 12-hour intervals with trough levels taken before every fourth dose (Goal ranged between 10-20 mcg/mL)

- **Oral**
  - Used for *C. difficile* due to its lack of absorption in the gastrointestinal tract
  - 125-500 mg QID depending on severity x 10-14 days

- **Topical powder for craniotomies ???**

https://cdn.thinglink.me/api/image/639925606242320384/1240/10/scaletowidth
Where the data though?
QUESTIONS?

https://i.pinimg.com/736x/6b/af/90/6baf902ecb61e0adcf94245b6dcf5866--pharmacy-humour-pharmacy-funny.jpg
STUDY I: ABDULLAH 2015

APDULLAH 2015

Objective

- Appears to be safe and effective
- Not studied systematically

Hypothesis

- Application of topical vancomycin would reduce cranial wound infection rates

Journal of Neurosurgery. 2015. 123(6), 1600-1604.

ABDULLAH 2015

Design

Retrospective cohort study

150 patients underwent craniotomy conducted at the Hospital of the University of Pennsylvania

75 control patients

75 treated patients

Mean follow-up time:

| Control group: 9.5 months ±187 days | Treatment group: 7 months ±143 days |

Journal of Neurosurgery. 2015. 123(6), 1600-1604.
**ABDULLAH 2015: OUTCOMES**

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of SSI within three (3) months</td>
<td>Tissue pH from subgaleal drain</td>
</tr>
<tr>
<td></td>
<td>Vancomycin levels from subgaleal space and circulating serum</td>
</tr>
</tbody>
</table>

Journal of Neurosurgery. 2015. 123(6), 1600-1604.
ABDULLAH 2015

Inclusion

- Over the age of 18 years
- Underwent open craniotomy
- Had a wound designation of “clean” for their index surgery

Exclusion

- Not clearly addressed
Each patient received standard of care for cranial procedures
75 control patients and the 75 treated patients (with vancomycin)

Standard treatment:
Pre- and post-operative antibiotic prophylaxis with IV cefazolin (1-2 g within 30 min of incision and 2 repeat post-op doses spaced 8 hours apart)

Study treatment:
1 g vancomycin powder sprinkled evenly over the bone flap

Penicillin allergy: treated with 1 g IV vancomycin pre and post surgery
Statistics

- Descriptive statistics (means and SDs)
  - Used for all parameters

- Fisher exact tests, 2-sample proportion z-tests, and unpaired t-tests
  - Used to assess categorical and continuous variables and their interrelationships

An independent rater (blinded to grouping and patient identification) performed all data collection and analysis in collaboration with a biostatistician.
### TABLE 1. Demographics of patients in this study*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Patients (n = 75)</th>
<th>Treated Patients (n = 75)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>52.1 ± 16.6</td>
<td>49.4 ± 15.6</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.8 ± 5.7</td>
<td>28.1 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex</td>
<td>38</td>
<td>37</td>
<td>NS</td>
</tr>
<tr>
<td>Previous op</td>
<td>17</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>CAD</td>
<td>7</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Current tobacco use</td>
<td>7</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Previous tobacco use</td>
<td>18</td>
<td>21</td>
<td>NS</td>
</tr>
<tr>
<td>Steroid use</td>
<td>69</td>
<td>63</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Length of op (mins)</strong></td>
<td><strong>191 ± 89</strong></td>
<td><strong>231 ± 107</strong></td>
<td>0.01†</td>
</tr>
<tr>
<td>SSI</td>
<td>5</td>
<td>1</td>
<td>0.048†</td>
</tr>
</tbody>
</table>

*Statistic significant at the .05 level.
Primary Outcome

SSI within 3 months

- Six (6) patients experienced infection
  - Overall incidence = 4% [6 out of 150]
- Five (5) controls and one (1) study patient experienced infection (P < 0.05)
  - Incidence in control group: 6.7%
  - Incidence in study group: 1.3%

- NNT = 19
- RRR = 81%
- OR = 0.189
Secondary Outcomes

- Tissue pH
  - Mean post-op pH levels within 2 hours of closure: 7.45 and 7.7 from drains and sera (blood serum), respectively
  - Post-op levels at 6 and 12 hours: WNR (7.4±0.1)

- Vancomycin concentrations
  - Mean local concentration from wound drains = 499 mcg/mL
  - Mean serum concentration: undetectable – lower limit of detectability of 3.5 mcg/mL

- Time to infection
  - All infections occurred between days 10 and 34
ABDULLAH 2015: STRENGTHS/LIMITATIONS

**Strengths**

- Consistency (being done with 1 surgeon at 1 institution – pros and cons to this)
- Similar demographics in patient population examined
- Serum levels examined

**Limitations**

- Single-center institution
- Single surgeon (not generalizable)
- “Hawthorne effect” due to potential increase in attention to reducing infection rates
- Far more functional craniotomies in treated group
- Size of exposed bone?
- Was an irrigation used?
- Does not state how many patients received prophylactic dose of vancomycin vs cefazolin
## ABDULLAH 2015: CONCLUSIONS

<table>
<thead>
<tr>
<th>Author’s</th>
<th>Seminarian’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safe and effective for reducing surgical site</td>
<td>Study provides some evidence for the use of topical vanco in preventing SSIs</td>
</tr>
<tr>
<td>infections</td>
<td>at Pennsylvania</td>
</tr>
<tr>
<td></td>
<td>Need equal/consistent craniotomy types</td>
</tr>
<tr>
<td></td>
<td>More data needed at more institutions as an RCT to provide more reliable</td>
</tr>
<tr>
<td></td>
<td>results as well as strengthening the study</td>
</tr>
</tbody>
</table>
QUESTIONS?

I DON'T ALWAYS DOSE VANCOMYCIN

BUT WHEN I DO, THE TROUGH IS ALWAYS 15

http://s2.quickmeme.com/img/5b/5b8f142043dee6ee9099d771e2b3912747f9e04ce20a14bfb88237bff33b7b51.jpg
STUDY II: RAVIKUMAR 2017

Objective

Evaluate the efficacy of topical vancomycin for the prevention/reduction of SSIs rates following craniotomies

Hypothesis

Application of topical vancomycin during closure of craniotomy would reduce the incidence of SSIs postoperatively
Design

Retrospective study

Observed open craniotomy patients at Stanford Hospital from 2011 to 2015

Pre-intervention cohort included 225 initial patients who underwent surgery from July 2011 to June 2014

Post-intervention cohort of 125 patients received intra-operative vancomycin powder

Minimum of three (3) month follow-up period with all patients
RAVIKUMAR 2017: OUTCOMES

**Primary**

- Determine whether topical vanco reduced incidence of cranial infections

**Secondary**

- Examine cost effectiveness of topical vanco in determining whether it is an “economical solution to replace the current standard of care”
All pts received standard of care antibiotics prophylaxis. 225 control patients and 125 treated patients.

Standard treatment:
1 g IV ceftriaxone or cefazolin 30 min before incision.

Post-intervention cohort treated with 1 gm of vancomycin powder after bone flap replacement or bone flap substitute.

Penicillin allergy: given 1 gm vanco IV.
Descriptive statistics
- Two (2) sample proportion z-tests and unpaired t-tests employed for analysis of relationships between the variables

Ad hoc cost analysis used to contrast expenses associated with standard of care and vancomycin in craniotomy patients
### TABLE 1. Patient Demographics Organized by Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 225)</th>
<th>Treated patients (n = 125)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative steroids</td>
<td>121</td>
<td>81</td>
<td>.03*</td>
</tr>
<tr>
<td>Perioperative steroids</td>
<td>105</td>
<td>64</td>
<td>.15</td>
</tr>
<tr>
<td>Age</td>
<td>55.5 ± 18.4</td>
<td>51.69 ± 18.69</td>
<td>.065</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.9 ± 6.5</td>
<td>27.46 ± 5.75</td>
<td>.79</td>
</tr>
<tr>
<td>Male sex</td>
<td>133</td>
<td>63</td>
<td>.09</td>
</tr>
<tr>
<td>Previous craniotomy</td>
<td>48</td>
<td>37</td>
<td>.15</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>7</td>
<td>5</td>
<td>.79</td>
</tr>
<tr>
<td>Previous tobacco use</td>
<td>65</td>
<td>46</td>
<td>.13</td>
</tr>
<tr>
<td>Current tobacco use</td>
<td>28</td>
<td>13</td>
<td>.53</td>
</tr>
<tr>
<td>Diabetes</td>
<td>24</td>
<td>21</td>
<td>.11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78</td>
<td>51</td>
<td>.2</td>
</tr>
<tr>
<td>Operation duration</td>
<td>177.22 ± 154.73</td>
<td>168.02 ± 124.89</td>
<td>.52</td>
</tr>
<tr>
<td>SSI</td>
<td>5</td>
<td>0</td>
<td>.046*</td>
</tr>
</tbody>
</table>

*P < .05
Primary Outcome

- Topical vanco use and reduced incidence of cranial infection
  - 2.2% vs 0%
  - Risk difference 5%
  - OR of 0
  - RRR of 100%
  - P < 0.046
  - NNT 45 to prevent 1 infection
Secondary Outcome

- Cost effectiveness of topical vancomycin
  - $14,216 per patient with craniotomy infection per O’Keeffe et al (Oxford craniotomies infection database: cost analysis of craniotomy infection)
    - Total cost for 5 pts = $71,080
  - $49.40 per patient receiving 1 gm vancomycin powder following craniotomy
    - Total cost per pts = $11,115
    - Total cost for topical vancomycin for 125 pts = $6,175
  - Total cost savings for hospital = $59,965 with topical vancomycin
RAVIKUMAR 2017: OUTCOMES

- Safety
  - No documented adverse events or side effects in treatment group

Neurosurgery. 2017; 80(5), 754-758.
### RAVIKUMAR 2017: STRENGTHS/LIMITATIONS

<table>
<thead>
<tr>
<th><strong>Strengths</strong></th>
<th><strong>Limitations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Good clinical question</td>
<td>Single surgeon – generalizability and aseptic technique not representative across U.S.</td>
</tr>
<tr>
<td>Appropriate follow-up time</td>
<td>Single-center institution</td>
</tr>
<tr>
<td>Presents some evidence for efficacy of topical vancomycin in SSI prophylaxis following craniotomy</td>
<td>Sample size fairly large but not large enough to definitively imply a true outcome</td>
</tr>
<tr>
<td></td>
<td>Size of exposed bone?</td>
</tr>
<tr>
<td></td>
<td>Irrigation?</td>
</tr>
<tr>
<td></td>
<td>Again, which patients got prophylactic vancomycin vs cefazolin or ceftriaxone?</td>
</tr>
</tbody>
</table>
## RAVIKUMAR 2017: CONCLUSIONS

<table>
<thead>
<tr>
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<th>Seminarian’s</th>
</tr>
</thead>
</table>
| • May be considered given the decrease in SSI rate, safety profile, and associated cost savings found | • Provides some evidence on the use of topical vacomycin for SSI prophylaxis at Stanford  
| | • HOWEVER, more data is needed at more institutions  
| | • RCT would provide more reliable results and strengthen study |
QUESTIONS?

YOU GET VANCOMYCIN
AND YOU GET VANCOMYCIN
EVERYONE GETS VANCOMYCIN

**OVERALL CONCLUSIONS**

- Shows some promise in preventing SSI following craniotomy
- There is not sufficient evidence to implement this practice routinely
- It may be beneficial for patients who are considered to be at higher risk for infection
- More trials, specifically RCTs with:
  - Inclusion/exclusion criteria clearly stated
  - More than a single-center institution
RECOMMENDATIONS FOR PRACTICE

- Appropriate antibiotic dosing
  - Kidney function, allergies, weight, etc.
- Appropriate use of antibiotics
- Monitor trough levels
- Don’t be afraid to ask questions
Questions?

https://memegenerator.net/img/instances/66537805/one-does-not-simply-order-vancomycin.jpg
SPECIAL THANKS

- Dr. LeeAnn Miles
- Dr. Heather Nyman
- Dr. Holly Gurgle

- And all of you for listening
REFERENCES

- https://www.cdc.gov/nhsn/pdfs/psc/faqs-SSI.pdf
- UpToDate.com. Surgical Site Infections in Adults
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