ANTIBIOTICS/CELLULITIS

...AN EVIDENCE-BASED RANT

John Kennedy

Early-2017
THANKS

"IF SOME OF A DRUG IS GOOD,
THEN MORE MUST BE BETTER..."
PLAN

• **SLOWLY – GENTLY**
• **ONE SIMPLE TAKE HOME MESSAGE**
• **ONE RELEVANT ASIDE**
WARNINGS

(1) Language

(2) Motives
Monday 10 April

0630-0800 REBOA for bleeding hemorrhoids – stick that up your cloaca
Breakfast symposium – sponsored by REBOA

0800-0810 14 thoughts I had about trauma while on the toilet this morning
Edward James Talkheimer Jnr, Traumatologist, Somewhere in Ohio

0810-0815 ECMO during ED thoracotomy for blunt trauma arrest in Antarctica
Associate Assistant Deputy Emeritus Professor, Quadruple Boarded in Stuff

0815-0830 Five uses for billiard balls in exsanguinating hemorrhage
Major General Captain, US Marine Corps

0830-0835 Everything you need to know about pediatric US in 5 minutes
Susanne Rapides, Pediatric Attending, UCLCSTCX, Somewhere in California
5 YEARS AGO

CELLULITIS ON HOLIDAY

FEBRILE ++, LETHARGIC, VOMITING

5 DAYS OF ORAL CEPHALEXIN

FIXED
THE RISE & RISE

...OF THE USE OF STAT/SINGLE DOSE IV ANTIBIOTICS

...ESPECIALLY BETA LACTAMS IN UNCOMPPLICATED CELLULITIS

...BUT FIRST, A BRIEF FORAY INTO CELLULITIS WITH ABSCESS
CAPUT TUUM IN ANO EST
Abscess Treatment: Controversies

Huge practice variation

- Irrigation?
- Packing?
- Antibiotics?

48%

Schmitz et al. West J Emerg Med 2013

Treatment of cutaneous abscesses: Comparison of emergency medicine providers’ practice patterns
IRRIGATION?

Almost universally recommended in texts/guidelines

...but not often done in practice

Irrigation of cutaneous abscesses does not improve treatment success


• 209 patients, convenience sample randomized to irrigation or not
• 15% treatment failure – same in both groups
PACKING?

Almost universally recommended in texts/guidelines

- Widely practiced (at least in the USA)…but there are only 2 studies that look at this sacred cow…

1) Routine packing of simple cutaneous abscesses is painful and probably unnecessary

   O’Malley G, Acad Emerg Med 2009

- 48 patients, randomized to pack/no pack after I&D
- All given Bactrim
- No difference in need for further procedure
- Increased pain score & analgesic use in packed group

2) Randomized trial comparing wound packing to no wound packing following incision and drainage of superficial skin abscesses in the pediatric emergency department.

   Kessler, Pediatr Emerg Care 2012

- 57 patients – no difference
ANTIBIOTICS?

UNIVERSALLY DISCOURAGED – "I & D IS CURATIVE"

TALAN ET AL. TRIMETHOPRIM-SULFAMETHOXAZOLE VERSUS PLACEBO FOR UNCOMPPLICATED SKIN ABSCESS. NEJM 2016

• 1200 patients, absolute difference in cure 7%; NNT 14
• But 86% of I&D only group → cured
• Controversy - is 7% benefit worth it? Bactrim is cheap...
ABSCESSES – OMG!

• So…what’s the answer??

• Irrigation – maybe not (most don’t do it anyway)
• Packing – maybe not
• Antibiotics – maybe – WTF ?!

…and there’s more: ultrasound? Loop drainage? Partial primary closure?

The truth is not clear…
• Simple cellulitis
• The role of single dose IV antibiotics
• Is it just where I work ??
Cefazolin 2g IV
Cephalexin 1g BD

Flucloxacillin IV 2g
PO 500mg QID

Flucloxacillin IV 2g
PO 500mg QID

Lincomycin IV
Clindamycin PO

Cephazolin 2g IV
Cephalexin 500mg QID

Flucloxacillin IV
Flucloxacillin PO 500mg QID
Evidence??

- No direct studies

But there are principles of pharmacology & related studies of antibiotics

...that scream out "bull shit"
RATIONALE FOR SINGLE-DOSE ANTIBIOTICS?

• To “load” the patient & get good drug levels to kick start the killing process

  If some of a drug is good, then more must be better!!

  Pharmacologically this is rubbish…

• Aided & abetted by the prevalence of the cannula at triage
  …and by the increased use of EMU/EDSSU
TO GIVE A “LOADING DOSE”??

- We use loading doses for some drugs
- β-lactams/penicillins/cephalosporins & clindamycin – all have relatively small $V_D$
BIOAVAILABILITY?

- Many of the antibiotics we use for skin infections have good oral bioavailability
  - Cephalexin 90% (and hits peak serum levels in about 1 hour)
  - Clindamycin 90%
  - Bactrim 90-100%
  - Doxycycline 90-100%
Figure 1: Observed plasma clindamycin concentrations (closed circles) and population pharmacokinetic based model-predicted clindamycin concentrations (curve) as a function of time for i.v. infusion (black) and oral dosing (blue)
### Predictors of Bacterial Eradication: Pharmacokinetic/Pharmacodynamic Profiles

<table>
<thead>
<tr>
<th>Pattern of Activity</th>
<th>Antibiotics</th>
<th>Goal of Therapy</th>
<th>PK/PD Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentration-dependent killing and Prolonged persistent effects</td>
<td>Aminoglycosides, Daptomycin, Fluoroquinolones, Ketolides</td>
<td>Maximize concentrations</td>
<td>24h-AUC/MIC, Peak/MIC</td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>Type II</strong></td>
<td></td>
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</tr>
<tr>
<td>Time-dependent killing and Minimal persistent effects</td>
<td>Carbapenems, Cephalosporins, Erythromycin, Linezolid, Penicillins</td>
<td>Maximize duration of exposure</td>
<td>T&gt;MIC</td>
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<td></td>
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<tr>
<td><strong>Type III</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Time-dependent killing and Moderate to prolonged persistent effects</td>
<td>Azithromycin, Clindamycin, Oxazolidinones, Tetracyclines, Vancomycin</td>
<td>Maximize amount of drug</td>
<td>24h-AUC/MIC</td>
</tr>
</tbody>
</table>

- **Peak/MIC**
  - Aminoglycosides
  - Beta-lactams
  - Clindamycin
  - Erythromycin
  - Linezolid
- **T > MIC**
  - Azithromycin
  - Quinolones
  - Vancomycin
- **24h-AUC/MIC**

**Higher Levels to Kill More Germs??**
...but surely IV is “better, stronger”?! 

...otherwise, we wouldn’t HITH or admit the sick ones.

‘though there are other admit reasons can’t tolerate orals elevation/rest/analgisia IV fluids – pressors etc
ORAL VERSUS IV IN CELLULITIS

• Nobody has looked at the benefit (or otherwise) of single-dose IV
• 3 relevant studies – IV versus oral
• 2 of them pretty useless

• BMJ 2002, 204 patients, oral pristinamycin (WTF?) versus IV penicillin
  • Oral stuff better – 81% vs 67% cure
• Infection 1984, 60 patients, oral versus IV penicillin
  • Found no difference
Oral versus parenteral antimicrobials for the treatment of cellulitis: A randomized non-inferiority trial
Aboltins et al, J Antimicrob Chemother 2015

- Australian, non-inferiority, 24 & 23 patients
- Included those with fever, HR > 90, raised markers – and those sent by LMO
- Oral cephalixin 1g QID
  vs IV cephalolin 2g BD
  • Clindamycin if immediate hypersensitivity
- Outcome – days until no advancement of area of cellulitis

Oral 1.29 – IV 1.78 days. Mean difference -0.49 (-1.02 to +0.04)
= non-inferior

...Canadian trial in progress (cephalexin versus cephalolin/probencid)
<table>
<thead>
<tr>
<th>Oral Antibiotics</th>
<th>Consult 'Antimicrobial Home Treatment - Acute/Post Acute Care (APAC)' Guideline</th>
<th>To treat infection with either streptococci or staphylococci, use initially:</th>
</tr>
</thead>
<tbody>
<tr>
<td>To cover:</td>
<td></td>
<td>□ Flucloxacillin 1 g PO, 6 hourly for 5 to 10 days.</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td></td>
<td>□ Cephalosporin 2 g IV, daily plus Probenecid 1 g orally daily</td>
</tr>
<tr>
<td>and Streptococcus</td>
<td></td>
<td>□ If probenecid is contraindicated use: Cephalosporin 2 g IV, BD</td>
</tr>
<tr>
<td>Pyogenes, use:</td>
<td></td>
<td>□ Cephalexin 1 g PO, 6 hourly for 5 to 10 days.</td>
</tr>
<tr>
<td>Phenoxymethylpenicillin 500 mg PO, 6 hourly for to 10 days.</td>
<td></td>
<td>□ Clindamycin 450 mg PO, 8 hourly;</td>
</tr>
<tr>
<td>For patients with penicillin hypersensitivity excluding immediate hypersensitivity, use:</td>
<td></td>
<td>□ Vancomycin 25 - 30 mg/kg IV loading dose, using actual body weight (ABW), with second dose and interval to be determined according to creatinine clearance. (See N/Vancomycin Dosing and Administration Guideline - NSLHD).</td>
</tr>
</tbody>
</table>

As per Sepsis Pathway or contact ID for advice.
SO WHAT?

• There may be no proven benefit but Surely there’s no disadvantage..?
  • Intellectually offensive
  • Time & resources in ED
  • The tendency to do blood tests if a cannula is placed
  • The evils of the unnecessary cannula
Half of All Peripheral Intravenous Lines in an Australian Tertiary Emergency Department Are Unused: Pain With No Gain?

Eva L. Limb, MBBS; Xin Fang, MBBS; Claire Dendle, MBBS, FRACP, GCHPE; Rhonda L. Stuart, MBBS, FRACP, PhD; Diana Egerton Warrington, MBBS, FACEM, MCliniEpi

Study objective: Our study aims to determine the incidence of unused peripheral intravenous cannulas inserted in the emergency department (ED).

Methods: A retrospective cohort study using a structured electronic medical record review was performed in a 640-bed tertiary care hospital in Melbourne, Australia. During a 30-day period, all patients who had a peripheral intravenous cannula recorded as a procedure on their electronic medical record in the ED were included in this study.

Results: Fifty percent of peripheral intravenous cannulas inserted in the ED were unused. Patients presenting with obstetric and gynecologic and neurologic symptoms were significantly more likely to have an unused cannula. Forty-three percent of patients admitted to the hospital with unused peripheral intravenous cannulas in the ED continued to have them unused 72 hours later.

Conclusion: There is a high incidence of unused peripheral intravenous cannulas inserted in the ED. The risk of having an unused peripheral intravenous cannula is associated with the patient’s presenting complaint. Efforts should be directed to reduce this rate of unused peripheral intravenous cannula insertion, especially in patients being admitted, to minimize the risk of complications. [Ann Emerg Med. 2013;62:521-525.]

- Pain
- Sharps risk
- ¼ Healthcare assoc S. aureus bacteraemia
- Costing $29,000 each
“NOT DOING STUFF…”

- Analogous to the cricoid story
  - No evidence of benefit
  - Some evidence of harm

...Don’t do it
BALANCE...

(1) The PK/PD of some antibiotics favour a stat dose
   • Gentamicin – concentration-dependent & prolonged killing
   • Ceftriaxone – long $t_{1/2}$
     …so this probably doesn’t wash for, say, UTI/pyelonephritis

(2) Adding probenecid introduces a nice little PK sleight of hand

(3) You have to use an adequate dose/Regime of β-lactam
SUMMARY

• **Abscesses → incise & drain...and whatever!**

• **Trend to giving a single IV dose of IV antibiotic in cellulitis. This makes little sense.**

• **Cannulation is not harmless**

• **Think twice before giving a single stat dose of IV antibiotics**
SUMMARY

SOMETIMES, IF SOME OF A DRUG IS GOOD, MORE IS NOT BETTER

(This doesn’t apply to red wine)
CHEERS!

QUESTIONS ?