**Maine Medical Center**

**Department of Emergency Medicine**

**Journal Club Summary Template**

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| **Date: 8/17/17** | **Presenter Name:** Andrew Fried |

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| **Article Citation:** J Antimicrob Chemother. 2015 Feb;70(2):581-6doi: 10.1093/jac/dku397 Advance Access publication 21 October 2014“Oral versus parenteral antimicrobials of the treatment of cellulitis: a randomized non-inferiority trial”Aboltins et al. |
| **Country(ies):****Australia**  |
| **Funding Source(s):** Northern Health, a Victorian public health service [ ]  None Stated |

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| **Purpose** |
| **Research Question(s):**Are outcomes for patients with cellulitis treated with oral antimicrobials as good as for those who are treated with parenteral antimicrobials?[ ]  None Stated |
| **Hypotheses:**Oral antimicrobials are at least as effective as parenteral antimicrobials.[ ]  None Stated |
| **Study Purpose:**To compare the outcomes for patients with uncomplicated cellulitis who are treated with oral antimicrobials with those who are treated with parenteral antimicrobials.  |

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| **Methods** |
| **Study Design:**Randomized, open-label, non-inferiority trial at a single site. |
| **Outcome(s) *[or Dependent Variable]:***Primary outcome: Time until no advancement of the area of cellulitisSecondary outcomes: Failure of treatment, pain, complications of treatment, satisfaction with care |
| **Intervention *[or Independent Variable]:***Oral arm: 1g cephalexin orally QID for 10 days (or clinda 450 TID x 10d, if they had ß- lactam hypersensitivity)Parenteral arm: 2g cefazolin IV Q12 (or clinda 450mg IV Q8 if they had ß- lactam hypersensitivity). These abx were continued until the area of cellulitis **was no longer progressing and the patient was afebrile.** Then they received oral abx as above for a total duration (IV + PO duration) of 10 days.  |
| **Ethics Review:** [ ]  IRB Review [ ]  IACUC Review [x]  **Other: Northern Healthy Research and Ethics Committee**[ ]  None Stated |
| **Research Setting:**Single, tertiary teaching hospital in metropolitan Melbourne, population ~728,000 |
| **Study Subjects:**Patients referred by emergency department staff for treatment of cellulitis with parenteral abx because of either the severity of cellulitis or because of progression despite prior oral abx. |
| **Inclusion Criteria:**>16 yo with cellulitis that was deemed to be “severe” or with progression despite oral antibiotics**Cellulitis defined as:** presence of acute dermal/epidermal inflammation lasting <5 days and associated with any of the following:-pain-fever (>37.8)-HR > 90-systemic symptoms (reported fever, rigors, nausea, malaise)-elevated inflammatory markers |
| **Exclusion Criteria:**-Inability to give consent-unavailable for follow up-alternative diagnosis to cellulitis-necrotizing fasciitis-complicated cellulitis (presence of severe sepsis, extensive bullous skin changes, abscess formation)-mild cellulitis (limited area and no systemic symptoms)-cellulitis complicated trauma-periorbital cellulitis-immunosuppressed patients-vomiting precluding oral therapy-prior treatment with abx (>48 hours if oral, >12 hours if IV) |
| **Study Interventions:**Oral arm: 1g cephalexin orally QID for 10 days (or clinda 450 TID x 10d, if they had ß- lactam hypersensitivity)Parenteral arm: 2g cefazolin IV Q12 (or clinda 450mg IV Q8 if they had ß- lactam hypersensitivity). These abx were continued until the area of cellulitis **was no longer progressing and the patient was afebrile.** Then they received oral abx as above for a total duration (IV + PO duration) of 10 days.  |
| **Study Groups:**Randomized 1:1 in 4 block schedule to either oral or parenteral treatment arms.There were also some patients that were treated as inpatients, while others were treated with outpatient parenteral antimicrobial therapy (OPAT) via the “hospital in the home” program. Location of treatment determined as per standard hospital protocols (they were admitted if there were other medical problems going on besides the cellulitis, otherwise they went home). |
| **Instruments/Measures Used:**-Measurement of cellulitis area but drawing the outline and measuring the maximum diameter, assessed daily-Pain assessed with visual analogue scale, range 0-10-Patient medication diary for oral antibiotics-Satisfaction survey |
| **Data Collection:**Completed by study nurses who had undergone training and calibration. |
| **Data Analysis:*****A priori* sample size calculation?** [x]  **Yes** [ ]  No [ ]  Not Described [ ]  N/AYes, but don’t incorrectly first. Initial pre-recruitment calculation with sample size of 58 was later found to be “based on incorrect assumptions”. Revised calculation was made prior to interim examination of results for safety and monitoring committee. **This was to find non-inferiority defined as:** The upper limit of the 95% CI in the oral arm being less than +15% of the mean value in the parenteral arm**Statistical analyses used:**-Mann-Whitney test for the primary outcome-X2 and Fisher’s exact test used for contingency tables-all two-tailed with <0.05 used as P value of significance**Adjustment for potential confounders?** [ ]  Yes [ ]  No [x]  Not Described [ ]  N/A **If yes, list:** |

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| **Results** |
| **Study participants:**-47 patients enrolled: 23 in parenteral arm, 24 in oral arm-1 patient from the parenteral group had treatment failure on day 3 and was lost to follow up after day 7-1 patient in oral group had only 50% of the dose given-1 patient (oral arm) ended up needing clindamycin after hypersensitivity reaction (at 5 days) |
| **Brief answers to research questions *[key findings]:***Mean days of advancement of cellulitis:1.29 for oral1.78 parenteralMean difference of -0.49 (95% CI -1.02 to +0.04)+0.04 (the upper limit) was below the specified non-inferiority margin at +15% (+0.27 days)So the upper limit of the CI for the oral arm was not more than 15% greater than the mean for the parenteral arm indicating that the oral treatment was non-inferior to parenteral treatment. |
| **Additional findings:**-Rate of failure was higher in parenteral arm (5/23) vs oral (1/24), significant P=0.10-Pain on day 1 was higher in oral group. Parenteral (2.8) vs oral (4.8), significant with P=0.03 -however baseline pain in oral group was higher and decreased similarly to IV group-complications of treatment: 32% parenteral vs 29% oral, P=0.85-similar satisfaction scores: 3.7 parenteral vs 3.9 oral |
| **Limitations:*** VERY Small, single centered
* not a blinded study
* primary outcome not the most patient-centered outcome (maybe useful as a surrogate for when these patients would be discharged if they were inpatients?)
* not powered to evaluate treatment failure
* no description of the antibiotics patients were on before enrollment
* No separate analysis for outcomes of first presentation of cellulitis vs “failed outpatient treatment” (which made up almost 50% of the enrolled patients) (11/24 in the oral group and 9/23 in the parenteral group)
* the oral arm trending towards less treatment failures, though not statistically significant, doesn’t pass the sniff test, makes me wonder if this study is just too small to draw conclusions from, or that the OPAT is too far from what we do here as to make these results applicable
* exclusion criteria included oral abx for greater than 48 hours, which gives a very narrow window for a “failed treatment” of oral antibiotics, however this does seem to be consistent with other literature on cellulitis

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| **Clinical Implications** |
| **Applicable?** Maybe… It was out of the emergency department, which is great. The author states that they have very low rates of CA-MRSA in Australia. If this is true, it is certainly different than here, or at least the general perception of MRSA prevalence here and therefore common practice patterns. None of these patients were on abx directed against MRSA. One of the first things we seem to do in “treatment failure” here is broaden to abx against MRSA (If they aren’t already on them). However, our patient’s are so often started on something with MRSA coverage to begin with (doxy or bactrim), that this issue might not be that relevant and these data may still be applicable. The biggest difference, however, is that most of these patients were treated as outpatients regardless of the arm, which is very different from here. **Feasible?** It would certainly be feasible to start discharging this subset of patients with continued oral abx if more robust data can support this hypothesis.**Clinically relevant?** Yes**Comments:** The major takeaway I have from this article is that maybe we are just calling “failure” of outpatient oral abx treatment too early. I assume that the patients in the oral arm were essentially continued on the same regimen (because there were no data on the original abx regimen) and eventually got better. IV or not, it appears a subset of patients just take longer for the erythematous area of cellulitis to stop spreading. While it is probably safe to continue these patients with just oral antibiotics, this very small, single-centered study was underpowered to inform us on the outcome we really care about: treatment failure. |
| **Level of evidence generated from this study** |
| [ ] Ia: evidence obtained from meta-analysis of randomized controlled trials[x] Ib: evidence obtained from at least one randomized controlled trial[ ] IIa: evidence obtained from at least one well-designed, controlled study without randomization[ ] IIb: evidence obtained from at least one other type of well-designed quasi-experimental study[ ] III: evidence obtained from a well-designed, non-experimental study[ ] IV: expert committee reports; expert opinion; case study; case report |

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| **Additional Comments/Discussion/Notes** |
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