The management of outpatient cellulitis at the Moncton hospital before and after the initiation of a clinical treatment pathway

Abstract

Introduction: Antimicrobial stewardship is a coordinated effort to improve the appropriate use of antimicrobials. Inappropriate antibiotic use is a major contributor of emerging antibiotic resistance. Broad-spectrum intravenous antibiotics are commonly used for moderate to severe skin and soft tissue infections when narrower-spectrum options would be adequate.

Objective: Objectives included characterizing the antibiotic prescribing for the management of uncomplicated cellulitis in an outpatient setting. In addition, a clinical treatment pathway (CTP) was developed and its use was evaluated.

Methods: The study was a retrospective chart review looking at antibiotic prescribing in The Moncton Hospital Emergency Department and included patients treated before and after the introduction of an outpatient management pathway for cellulitis. The pathway recommended once daily probenecid 1g followed by cefazolin 2g IV. Antibiotic usage, treatment failure rates, and adverse events were compared between the two groups.

Results: In the pre-intervention group; 3 patients received cefazolin, 50 received Ceftriaxone, and 1 received Levofloxacin. After the introduction of the clinical treatment pathway there was an absolute increase of 53.8% (n=35) in the use of cefazolin and absolute decrease of 53.7% (n=23) in the use of Ceftriaxone. Both results were statistically significant (p<0.001). In eligible patients, the treatment pathway was utilized 61.1% of the time.

Conclusion: The introduction of a clinical treatment pathway outlining the preferential use of once daily cefazolin plus probenecid for the treatment of outpatient cellulitis led to a significant increase in the use of cefazolin, and decrease use of Ceftriaxone, thus demonstrating a positive stewardship effect at a local level.

Keywords: cellulitis, antibiotic stewardship, skin & soft tissue infections, beta-hemolytic Streptococci, Staphylococcus aureus, antibiotic therapy

Definitions

Cefazolin: a first-generation cephalosporin antibiotic
Ceftriaxone: a third-generation cephalosporin antibiotic
Cellulitis: recent onset of soft-tissue erythema associated with signs of infection that include ≥1 of the following symptoms: pain, swelling, lymphangitis, and fever
CTP: clinical treatment pathway
IV: intravenous
Probenecid: a uricosuric medication that prevents the excretion of cefazolin in the urine
Broad spectrum therapy: an antibiotic that has a wide range of activity against disease-causing bacteria
Narrow spectrum therapy: an antibiotic that has a narrow range of activity against disease-causing bacteria
Primary outcomes: The type and duration of antibiotics used to treat outpatient cellulitis and adherence to the clinical order set

Secondary outcomes: Treatment failure and rate of C. difficile infection within 30 days of treatment.

Introduction

The Infectious Diseases Society of America defines antimicrobial stewardship as a coordinated effort to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration. One of the recommendations they make is through the use of guidelines and clinical treatment pathways that involve evidence-based approaches to treating common infections. This aims to improve prescribing patterns while trying to avoid the unintended consequences such as antimicrobial resistance, adverse drug events, and cost. Skin and soft tissue infections are a common reason for patients to seek medical care. Cellulitis is generally defined as recent onset of soft-tissue erythema associated with signs of infection that include ≥1 of the following symptoms: pain, swelling, lymphangitis and fever. Many of these patients are systemically well and can be managed in an outpatient setting.

A retrospective chart review in one Canadian city with 5 urban Emergency Departments reported a predominant diagnosis of cellulitis...
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The objectives of this study were:

a. To determine what antibiotics are currently being prescribed in the management of moderate to severe cellulitis that requires outpatient intravenous antibiotic therapy;

b. To evaluate the success of a clinical treatment pathway (CTP) outlining optimal therapy, guided in the principles of antimicrobial stewardship.

Methods

Study design

This is a retrospective before and after intervention study. The goal was to identify at least 50 patients that received intravenous antibiotics both before and after the intervention. The before intervention analysis consisted of a retrospective chart review identifying patients that were discharged from the Emergency Department at The Moncton Hospital with a diagnosis of cellulitis which was considered severe enough to require the patient to return daily for intravenous antibiotics. A clinical treatment pathway for the outpatient management of cellulitis with intravenous antibiotics was produced and made available before the second half of data collection. The treatment pathway had defined usage criteria, exclusion criteria, and outlined management using once daily cefazolin plus probenecid (Appendix 1). The inclusion and exclusion criteria of the chart review aligned with the treatment pathway to assess its applicability. A standard data collection form was used to collect demographics, co-morbidities, antimicrobial treatment, inclusion/exclusion criteria, treatment failure, rates of C. difficile infection, and use of the CTP (Appendix 2). The chart review identified patients from September 2015 to February 2017. The CTP was made available in May 2016, along with hospital promotion and physician education. Prior to release of the CTP, feedback was obtained from the Departments of Family Medicine, Internal Medicine, Emergency Medicine, and Pharmacy.

Outcomes

Primary outcomes included:

i. The choice and duration of intravenous antibiotic prescribed,

ii. Adherence to the clinical treatment pathway in the post intervention group.

Secondary outcomes included:

i. Treatment failure defined as admission to the hospital within 30 days for an infection at the same site or escalation of antibiotic therapy,

ii. Infection with C. difficile within 30 days of treatment.

Data Analysis

All statistical analyses were performed using the R statistical software, version 3.2.5 ©GNU General Public License, 2016. A MANOVA test has been used for comparing demographics. A chi-square test was used to compare the amount of cefazolin and Ceftriaxone being prescribed, before versus after implementation of the CTP. A two-way ANOVA test was used to compare failure rates and C. difficile infection in patients receiving IV Ceftriaxone versus IV cefazolin. Research Ethics Board approval was granted through the Horizon Health Network.

Results

A total of 295 charts were reviewed during the study period. Of

Citation: Dalziel SA, Ghaly A, Smyth D, et al. The management of outpatient cellulitis at the Moncton hospital before and after the initiation of a clinical treatment pathway. Pharm Pharmacol Int J. 2018;6(2):138–147. DOI: 10.15406/ppij.2018.06.00170
these charts, 222 patients were diagnosed with cellulitis and treated with an antibiotic as an outpatient. Intravenous antibiotics were given to 113 (50.9%) of these patients, with 54 in the pre-CTP group and 59 in the post-CTP group, while the rest received oral antibiotics. The remaining patients did not meet diagnostic inclusion criteria or were admitted for treatment. Baseline characteristics of patients receiving IV antibiotics were not statistically different between the pre- and post-CTP groups (Table 1). The median ages were 54.5 versus 57. Co-morbidities were similar with diabetes mellitus present in 12% versus 15%, chronic kidney disease in 2% versus 3%, and immunosuppression in 2% versus 1%. One patient in the pre-group had a documented allergy to cefazolin while none in the post group did.

Table 1 Baseline demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before intervention (N=54)</th>
<th>After intervention (N=59)</th>
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<tbody>
<tr>
<td>Median age-years</td>
<td>54.5</td>
<td>57</td>
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<tr>
<td>Male sex-no. (%)</td>
<td>31 (57.4)</td>
<td>32 (54.2)</td>
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<tr>
<td>Diabetes Mellitus-no. (%)</td>
<td>12 (22.2)</td>
<td>15 (26.3)</td>
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<tr>
<td>Chronic Kidney Disease-no. (%)</td>
<td>2 (3.7)</td>
<td>3 (5.1)</td>
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<tr>
<td>Immunosuppressed-no. (%)</td>
<td>2 (3.7)</td>
<td>1 (1.7)</td>
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<tr>
<td>Allergy to Cefazolin-no. (%)</td>
<td>1 (1.8)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Baseline characteristic of the patients included in the study. There were 54 patients in the before intervention group and 59 patients in the after intervention group. There was no significant difference between the two groups in any characteristic using a MANOVA test with p=0.83.

Primary Outcomes

In the pre-CTP arm, there were 54 patients that received IV antibiotics, consisting of cefazolin (3), ceftriaxone (50), clindamycin (2), and Levofloxacin (1). There were two patients in this arm that received double coverage with clindamycin, and Levofloxacin, respectively, in addition to their cephalosporin. The median duration of IV therapy was 3.5 days (Table 2). There was a statistically significant increase in the use of cefazolin, 3 patients versus 35 patients (p<0.001), corresponding to a 93.8% absolute increase, after the introduction of the CTP. There was also a statistically significant increase in the use of Ceftriaxone, 50 patients versus 23 patients (p<0.001), corresponding to a 56% absolute increase, after the introduction of the CTP (Figure 1).

In the post-CTP arm, there were 53 (out of 59) patients eligible for therapy with cefazolin based on the inclusion/exclusion criteria of the treatment pathway (Appendix 1). Of these 53 patients, 34 (64.1%) were started on the protocol. The protocol was only deviated from once where a patient was prescribed oral clindamycin during day 3 of cefazolin therapy due to “minimal improvement” as documented on the chart. The majority of follow up for patients on the CTP was by the Emergency Room Physician or Nurse Practitioner on duty. Various other services provided follow up for the remaining patients: Infectious Disease (3.4%), other (10.2% consisting of Family Medicine, General Surgery, Dermatology, Gynecology, and Ophthalmology), while 3.4% of patients were not followed up.

Table 2 IV antibiotic usage

<table>
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<th>Characteristic</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>54</td>
<td>59</td>
<td>P=0.719</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>3</td>
<td>35</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>50</td>
<td>23</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>2*</td>
<td>1</td>
<td>P=0.831</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1*</td>
<td>0</td>
<td>P=1.000</td>
</tr>
<tr>
<td>Median duration of therapy (days)</td>
<td>4</td>
<td>3.5</td>
<td>P=0.719</td>
</tr>
</tbody>
</table>

Choice of intravenous antibiotic prescribed before and after the introduction of a clinical treatment pathway outlining preferential use of once daily cefazolin plus probenecid. *There were two patients in the before intervention group that received double coverage; one patient received clindamycin and the other received Levofloxacin in addition to a cephalosporin.

Figure 1 Intravenous antibiotic usage.

Use of Cefazolin and Ceftriaxone before and after the introduction of a clinical treatment pathway outlining preferential use of once daily cefazolin plus probenecid for the treatment of moderate to severe cellulitis. There was a significant increase use of cefazolin and decrease use of Ceftriaxone (*p<0.001) after the introduction of the clinical treatment pathway. Error bars represent standard error within both groups.

Secondary outcomes

There was no statistically significant difference in rates of treatment failure defined as admission to hospital within 30 days with worsening or similar infection in that area or escalation in antibiotic therapy when comparing cefazolin versus Ceftriaxone (Table 3). There were no cases of diagnosis of C. difficile infection in either group within 30 days of antibiotic therapy (Table 3).

Discussion

The microbiology of skin and soft tissue infections remains primarily beta-haemolytic Streptococci and Staphylococcus aureus. Historically patients were admitted to the hospital for frequent infections.
intravenous infusions of antibiotics when treating moderate to severe cellulitis until the use of once daily administration of Ceftriaxone, a broad spectrum third-generation cephalosporin, was favored. 11–13 This therapy allowed outpatient treatment without the need to hospitalize patients but with the growing emergence of antibiotic resistance it is desirable to use more targeted, narrow spectrum therapy. In recent years there has been a push to use once daily cefazolin with probenecid for broad spectrum coverage.22 When given with probenecid, a uricosuric agent that prevents its renal elimination thereby prolonging its half-life, it allows for once daily dosing instead of traditional dosing every eight hours, facilitating convenient outpatient therapy.16–20 The purpose of this study was to characterize current patterns in antibiotic prescribing for the treatment of cellulitis at the Moncton Hospital, and also to assess the effectiveness of a clinical treatment pathway outlining optimal treatment of these infections. We hypothesized that the majority of patients being treated at The Moncton Hospital were receiving unnecessarily broad spectrum antibiotics and that with the introduction of a clinical treatment pathway outlining therapy with once daily cefazolin; we would see a shift in this prescribing pattern.

Table 3 Secondary outcomes

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Cefazolin* (N=38)</th>
<th>Ceftriaxone* (N=73)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Admission-no. (%)</td>
<td>5(13.1)</td>
<td>10(13.6)</td>
<td>0.781</td>
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<tr>
<td>Change of therapy-no. (%)</td>
<td>7(18.4)</td>
<td>11(15.0)</td>
<td>0.831</td>
</tr>
<tr>
<td>C. difficile infection-no. (%)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Secondary outcome measures comparing patients who received cefazolin versus Ceftriaxone. Both groups include patients from before and after the introduction of the treatment pathway. Admission was defined as admission to hospital within 30 days of initial diagnosis, for cellulitis or another infection at that same site. Change of therapy indicated an escalation or change in antibiotic therapy within 30 days of diagnosis. C. difficile infection was defined as occurring within 30 days of receiving antibiotics as evidence from microbiology results in the electronic medical record.

The results demonstrated that the majority of patients (92.6%) received Ceftriaxone while only a small minority (5.6%) of patients received cefazolin before the introduction of the CTP. This confirmed the overwhelming preference for Ceftriaxone in this population of patients treated for cellulitis. We suspect this is primarily due to once daily dosing of Ceftriaxone versus dosing every eight hours with cefazolin. After the introduction of the CTP, cefazolin was used in 59.3% of patients while Ceftriaxone use fell to 39.0%. This represented a significant increase in the use of cefazolin and a significant decrease in the use of Ceftriaxone. We attributed this in part to the use of the clinical treatment pathway. Looking at treatment outcomes, there was no significant difference in rates of treatment failure comparing cefazolin versus Ceftriaxone. This aligns with prior research indicating their similar efficacy in treating cellulitis.20,21 Although Ceftriaxone is associated with an increased risk of secondary C. difficile infection25 we did not see a difference in this outcome compared to cefazolin. This is perhaps due to the overall low numbers included in the study. When comparing costs, the hospital price of Ceftriaxone and cefazolin were similar therefore no cost saving measures were recorded after the CTP. It should be noted that there are extremely low rates of MRSA colonization in Moncton, NB, which is reflected by the low use of MRSA active antimicrobials during the study. A limitation of this study was that it was retrospective in nature. There was no randomization of antibiotic therapy and could therefore introduce selection bias on the part of the treating clinician based on how severe they determined the infection to be. Small study numbers may have been insufficient to detect differences in efficacy and adverse events. Data collection also relied upon review of paper and electronic charting which is prone to error or omission.

Conclusion

There is a growing trend of antimicrobial resistance worldwide due to overuse of broad-spectrum antibiotics. The concept of antimicrobial stewardship was developed to help combat this problem, promoting optimal antimicrobial therapy and monitoring. This study supported the introduction of a clinical treatment pathway outlining the treatment of outpatient cellulitis with the use of once daily cefazolin plus probenecid as a narrower alternative to once daily Ceftriaxone. The study also demonstrated a measurable change in prescribing patterns when the CTP was introduced leading to more use of cefazolin and less use of Ceftriaxone in managing outpatient cellulitis.

Acknowledgement

I would like to thank Dr. Ahmed Ghaly, Dr. Daniel Smyth, and Timothy MacLaggan for their guidance, support, and manuscript revision in this study. I would also like to thank Dr. George Stoica for statistical analysis.

Conflict of interest

The authors report no conflict of interest.

References

The management of outpatient cellulitis at the Moncton hospital before and after the initiation of a clinical treatment pathway


Appendix

Appendix 1

<table>
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<tr>
<th>Outpatient Cellulitis Protocol</th>
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<tbody>
<tr>
<td>Department of Internal Medicine</td>
</tr>
<tr>
<td>Clinical Order Set</td>
</tr>
</tbody>
</table>

**APPROVED FOR USE IN ER/CLINIC C, ZONE-1 MONCTON ONLY**

<table>
<thead>
<tr>
<th>No Known Allergies □</th>
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<tbody>
<tr>
<td>Allergies:</td>
</tr>
<tr>
<td>Describe Reaction:</td>
</tr>
</tbody>
</table>

**INSTRUCTIONS**

1. The following order will be carried out only on the authority of a physician on call.
2. A bold preceding an order indicates the order is standard and should always be implemented.
3. A check box preceding an order indicates the order is optional and must be checked off to be implemented.
4. Applicable boxes to the right of an order must be checked off and initialed by the person implementing the order.
5. All boxes must be written legibly. All times must be on the 24-hour clock.

**General Principles**

This clinical order set can be used for the treatment of outpatients with uncomplicated cellulitis requiring IV antimicrobial therapy. If cellulitis is mild to moderate in nature and unlikely to require parenteral antibiotics then patient should be treated with oral  cefuroxime or cefuroxime by the attending physician.

**Criteria**

- Clinical evidence of cellulitis characterized by recent onset of soft-tissue swelling associated with signs of infection that included greater than 1 of the following symptoms: pain, swelling, erythema, and fever
- Hemodynamically stable and no evidence of sepsis
- Not associated with contiguous osteomyelitis
- No evidence of necrotizing infection or pain out of proportion of clinical findings
- Diabetic foot ulcer less than 2 weeks duration
- No evidence of foreign body or prosthesis material underlying cellulitis (i.e., prosthesis joint, vascular graft)
- No contraindications to probenecid, allergy to probenecid, acute gout, nephrotoxic use, history of renal stones or kidney
- Creatinine Clearance less than 30 mL/min (see page 2)
- AST, ALT, AKP, Prolactin less than 2 times upper limit of normal if known
- No history of allergy to cefazolin (immediate hypersensitivity to penicillin classified as anaphylaxis, bronchospasm, angioedema, hypotension, urticaria or pruritus is NO a contraindication)

**Day 1 – Initial Consultation**

- CBC, serum creatinine (ordered by referring physician)
- Probenecid 1g PO x 1 dose AND cefazolin 2g IV x 1 dose 30 to 60 minutes after receiving probenecid
- Follow-up to be completed by:
  - Primary Care Physician OR Emergency Department OR Infectious Diseases Service (dictated, called)

**Days 2 – 3** (or more if day 4 falls on a weekend or holiday)

- Probenecid 1g PO once daily AND cefazolin 2g IV once daily 30 to 60 minutes after receiving probenecid x ___ days
- In Clinic OR ED

**Fax to Pharmacy Services**

Prescriber's signature: ___________________________  Date: ________________  Time: ________________

Note: This is a controlled document. Any documents in paper form is not controlled and should ALWAYS be checked against the electronic version prior to use.

**Citation:** Dalziel SA, Ghaly A, Smyth D, et al. The management of outpatient cellulitis at the Moncton hospital before and after the initiation of a clinical treatment pathway. *Pharm Pharmacol Int J.* 2018;6(2):138-147. DOI: 10.15406/ppij.2018.06.00170
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### Clinical Information

**Cellulitis Antimicrobial Prescribing Research Project**

<table>
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<tr>
<th>Initials:</th>
<th>Age:</th>
<th>Gender:</th>
<th>Unique #:</th>
<th>Attending Service:</th>
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**Medical Co-morbidities:**
- Diabetes: Yes/No
- HgbA1c:
- Chronic Renal Failure: Yes/No
- Immunosuppression: Yes/No
- Others: __________

**Medication(s)**

<table>
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<tr>
<th>Allergies</th>
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**Diagnosis of Cellulitis:** Yes/No

**Documented Clinical Symptoms:**
- Pain
- Swelling
- Lymphangitis
- Fever

**Exclusion Criteria:**
- Diabetic foot infection greater than 2 weeks duration
- Hemodynamically unstable or sepsis
- Associated with contiguous osteomyelitis
- Immune deficiency
- Evidence of necrotizing infection
- Evidence of foreign body or prostatic material underlying cellulitis (is prostatic joint vascular graft)
- Estimated creatinine clearance <30mL/min
- AST, ALT, All Phos > 2 times upper limit of normal (if known)
- Allergy to cefazolin (or immediate hypersensitivity to penicillin)
- Allergy to probenecid

**Study ID:** __________

**Appendix 2**

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**Citation:** Dalziel SA, Ghaly A, Smyth D, et al. The management of outpatient cellulitis at the Moncton hospital before and after the initiation of a clinical treatment pathway. *Pharm Pharmacol Int J.* 2018;6(2):138–147. DOI: 10.15406/ppij.2018.06.00170
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### Antibiotic Therapy

<table>
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<th>Day</th>
<th>Type</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
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<th>Dose</th>
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### Outcomes

- Admission to hospital within 30 days for cellulitis or other infection in similar area: □ Yes □ No
- Escalation or change of IV therapy within 30 days: □ Yes □ No
- Use of clinical order set: □ Yes □ No □ N/A (met exclusion criteria) □ No (but used cefazolin plus probenecid as treatment)
  - If yes, was there deviation from the order set? □ Yes □ No □ Other Explained:
- Follow up by: □ FP □ ED □ ID □ None □ Other
- Diagnosis of C. difficile within 30 days: □ Yes □ No