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Intramuscular Ceftriaxone with Oral Antibiotic Therapy in the Treatment of Outpatient Cellulitis

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Abstract

Purpose: Oral antibiotics are the treatment of choice for outpatient cellulitis; however, intramuscular (IM) antibiotics are frequently used in addition to oral antibiotics in the clinic setting. This study compared outcomes among patients with cellulitis who were administered IM ceftriaxone in addition to oral antibiotics versus those who received oral antibiotics alone.

Methods: This study was a retrospective chart review of 982 adult primary care patients designed to evaluate rates of treatment failure of outpatient cellulitis among patients who received IM ceftriaxone and oral antibiotics versus oral antibiotics alone. Treatment failure was defined as: 1) hospital admission for intravenous (IV) antibiotics within 30 days of diagnosis, 2) prolonged antibiotic course, or 3) requiring a different antibiotic after initial antibiotic course.

Results: Of the 982 patients in the study cohort, 104 (10.6%) received IM ceftriaxone in addition to oral antibiotics while 878 (89.4%) did not. In the IM ceftriaxone group, hospitalization within 30 days was seen in 10.6% vs. 4.2% of the oral treatment only group (p=0.004). Initial outpatient use of IM ceftriaxone was associated with a 3.031 (95% CI 1.928-4.765, p<0.001) increased adjusted odds ratio for treatment failure. Age, gender, race, the use of tobacco, and diagnosis of diabetes mellitus were not associated with adverse outcomes when controlling for all other variables.

Conclusions: The patients who received an initial dose of IM ceftriaxone in addition to oral antibiotics were more likely to experience treatment failure than the non-ceftriaxone cohort. With increasing emergence of antibiotic resistant organisms, antibiotic prescribing practices must be reviewed to ensure efficacy and minimize risks associated with unnecessary antibiotic exposure.

Keywords: Antimicrobial stewardship; Antibiotic choice; Obesity; Primary care; Cephalosporin

Introduction

Skin and soft tissue infections (SSTIs) are among the most frequent infections seen in the ambulatory setting, with an incidence that has increased from approximately 8 to 14 million annual visits between 1997 and 2005 [1]. Cellulitis is a clinical diagnosis often made at the point of care when a patient presents with erythema of the skin, swelling, pain and tenderness. These infections are among the most common indications for antibiotics; however, antimicrobial choice is often left to the experience and discretion of the prescribing provider. Primary care providers may choose to treat common skin infections with a single dose of intramuscular (IM) ceftriaxone in addition to a course of oral antibiotics, as it is frequently available in the ambulatory clinic setting for other indications: gonococcal infections, pelvic inflammatory disease, pyelonephritis, etc. [2-4].

Oral beta-lactam antibiotics are recommended for mild infections most commonly seen in the outpatient setting [5]. The Infectious Diseases Society of America (IDSA) guidelines for treatment of SSTIs recommend intravenous (IV) ceftriaxone as an option for treatment of moderate nonpurulent SSTIs, including cellulitis, with systemic signs of infection (temperature >38°C, heart rate >90 beats per minute, respiratory rate >24 breaths per minute, or white count >12,000 or <400 cells/μL) [5]. However, these patients are frequently managed in the hospital setting. Data is lacking in support of combining IM ceftriaxone with a course of oral antibiotics for the management of outpatient cellulitis.

Cephalexin is a first-generation cephalosporin and one of the most common antibiotics used in the treatment of cellulitis due to low cost and rapid absorption, with peak serum concentration achieved within 1 hour of administration. Ceftriaxone is a third-generation cephalosporin allowing for additional gram-negative coverage; however, time to peak serum concentration is 2-3 hours [6]. Ceftriaxone does not provide an advantage in speed of absorption nor does it provide Methicillin-resistant Staphylococcus aureus (MRSA)

coverage in cases where cellulitis is associated with abscess formation. Since most cases of cellulitis are caused by beta-hemolytic *streptococci* and *staphylococci* [4], it is arguable that IM ceftriaxone in the setting of outpatient cellulitis would qualify as an avoidable antimicrobial exposure.

Antimicrobial choice is of particular concern to primary care providers, as the association between antibiotic prescribing practices and antimicrobial resistance is well-documented [7-10]. In a recent study conducted within the Denver Health system, it was found that half of all uncomplicated skin infections involved avoidable antibiotic exposure [11]. Therefore, given the need for antimicrobial stewardship, cost, resistance and adverse effects, it is still relevant to consider the potential etiology of the cellulitis and our choice of antibiotics in the outpatient setting.

The objectives of this study were to compare rates of outpatient treatment failure in cellulitic skin infections among those who received IM ceftriaxone in addition to oral antibiotics versus oral antibiotics alone. Because ceftriaxone's broadened spectrum of antimicrobial activity does not specifically target the most common causes of cellulitis, nor does it have an advantage in rate of absorption or distribution as it pertains to skin infections, we hypothesized that there will be no improvement in rates of treatment failure in patients receiving both IM ceftriaxone and oral antibiotics versus oral antibiotics alone.

Methods

This was a retrospective study involving Mayo Clinic primary care patients from the Rochester, Minnesota area who had a principal ICD-9 (International Classification of Diseases, revision 9) diagnosis of cellulitis from June 2008 through June 2013. This study was approved by the organization's institutional review board (IRB) and included adult patients, age 18 years and older, who had given prior research authorization. The majority of the data was collected using automatic processes. Demographic data included age, gender, and race. Clinical data abstracted included height, weight, body mass index (BMI), and co-morbid diagnosis of diabetes. Manual review of patient charts were performed by two of the authors (JM and MT) to obtain information regarding tobacco use within the past 12 months, antibiotic choice, dose, duration, as well as utilization of IM ceftriaxone as an initial outpatient treatment (yes/no). The dependent variables were hospital admission (regardless of therapeutic intervention) with a primary diagnosis of cellulitis within 30 days of the index diagnosis date, length of hospital stay, and treatment failure as defined by: a prolonged antibiotic course (equal to or greater than 14 days) or different antibiotic prescribed after initial course was completed. As the focus of the study was outpatient management of cellulitis, any patient with a direct admission to the hospital for cellulitis was excluded from the analysis. Patients who did not receive oral antibiotics were excluded. Medical records with an obvious error in documentation were removed from the study cohort.

Continuous variables were analyzed utilizing a Student t- test. Chi-Square testing was utilized for the statistical evaluation of categorical data. Regression modeling for the dependent outcomes was performed while retaining all independent variables studied. A prior study on a similar cohort had demonstrated the impact of marked obesity (BMI>50) and weight of >120 kg, thus these were also included in the univariate analysis and regression modelling [12]. Statistical significance was set at $p<0.05$. Calculations were performed on MedCalc software (www.medcalc.org, version 14.10.2).

Results

Of the 982 patients in the study cohort, 104 (10.6%) received IM ceftriaxone as an initial outpatient treatment for their cellulitis while 878 (89.4%) did not. The oral antibiotic most commonly used was cephalexin alone, and less commonly cefadroxil, dicloxacillin, amoxicillin-clavulanate, sulfamethoxazole-trimethoprim, doxycycline, levofloxacin, and numerous combinations or the above antibiotics. Between the two groups of patients, there was no statistical difference between the two in regard to age, gender (% female), race (% white), BMI>50, baseline weight of >120 kg, diagnosis of diabetes mellitus or tobacco use (Table 1). In the IM ceftriaxone group, hospitalization within 30 days was seen in 10.6% vs. 4.2% of the oral treatment only group (p=0.004). Of the hospitalized patients, the length of hospital stay for the 11 patients given IM ceftriaxone ranged from 2 to 11 days, with a median time of 4 days. The length of the hospital stay for the 37 patients who were initially treated with oral antibiotics ranged from 1 to 14 days; also with a median of 4 days, with no statistical significance between the two groups (p=0.951) (Table 1).

N= 982	Use of IM ceftriaxone (N=104)	Oral treatment only (N=878)	P
Age: mean (range)	50.5 (21.0-91.0)	51.7 (19.0-98.0)	0.462
Sex: % female (N)	62.5% (65)	66.3% (582)	0.441
Race: % white (N)	95.2% (99)	95.6% (813)	0.331
BMI >50	6.7% (7)	6.9% (61)	0.934
Weight >120 kg	31.7% (33)	24.0% (211)	0.086
Diagnosis of diabetes	18.3% (19)	21.5% (189)	0.442
Smoker: % yes (N)	22.1% (23)	16.2% (142)	0.126
Hospitalized within 30 days with cellulitis diagnosis	10.6% (11)	4.2% (37)	0.004
Prolonged course of treatment	34.6 % (36)	15.5% (136)	<0.001
Adverse Outcome	34.6% (36)	15.8% (139)	<0.001
BMI- Body mass index			

Table 1: Comparison of primary care patients diagnosed with cellulitis who were given IM ceftriaxone in addition to oral antibiotics at diagnosis versus those treated with oral antibiotics alone.

Logistic regression modeling of outpatient cellulitis in the study cohort while retaining all the demographic variables demonstrated that initial outpatient use of IM ceftriaxone was associated with a 3.031 (95% CI 1.928-4.765, $p<0.001$) increased adjusted odds ratio of adverse outcome (prolonged antibiotic course, change in antibiotic, or hospitalization). Age, gender, race, use of tobacco, and diagnosis of diabetes mellitus were not associated with increased odds of an adverse outcome, when controlling for all other variables (Table 2). Consistent with prior analysis on a similar cohort, those with BMI>50 had a 2.923 (95% CI 1.690-5.056, $p<0.001$) increased odds ratio of adverse outcomes, independent of treatment with IM ceftriaxone or oral antibiotics.

Adverse Outcome was defined as either a prolonged antibiotic course, change of antibiotic, or hospitalization with a cellulitis diagnosis within 30 days.

N= 982	Adjusted Odds Ratio for Adverse Outcome	95% CI	P
Index BMI >50	2.923	1.690 to 5.056	<0.001
IM Ceftriaxone use	3.031	1.928 to 4.765	<0.001
Age	1.01	0.999 to 1.022	0.077
Sex (female)	0.984	0.691 to 1.403	0.931
Race (white)	0.753	0.403 to 1.407	0.374
Tobacco use (Yes)	1.097	0.702 to 1.714	0.684
Diabetes diagnosis (Yes)	1.11	0.735 to 1.678	0.619
BMI- Body mass index			

Table 2: Regression modeling by variable for adverse outcome for primary care patients diagnosed with cellulitis.

Discussion

Lower extremity cellulitis is a common condition, with an incidence rate of about 199 per 100,000 person-years in Olmsted County, the location of our patient population, with twenty-two percent of cellulitis cases ultimately requiring hospitalization [13]. Though our study looked at all cases of outpatient cellulitis, the increasing incidence and proportion of patients requiring hospitalization obviates the need for better practices towards prevention of outpatient treatment failure. This study specifically addressed the use of IM ceftriaxone at the first presentation of cellulitis in the outpatient setting.

In this study, only 10% of patients received an initial dose of IM ceftriaxone for management of cellulitis. However, we were able to show a significant difference between rates of treatment failure in patients treated with an initial dose of IM ceftriaxone compared to oral antibiotic therapy alone. There are multiple possible explanations for the difference in these outcomes. First, while the two groups were largely similar in terms of age, gender, BMI and underlying comorbidities commonly associated with cellulitis, there may have been differences in the severity of their disease presentations. In order to explore this question further and ultimately account for differences in severity of disease presentation, we looked at only hospitalized cases of cellulitis and compared length of hospital stay between those who received IM ceftriaxone in the outpatient setting and those who did not. Though the sample size was small, there was still no statistically significant difference in length of stay despite ceftriaxone administration.

This question could be explored further in future studies accounting for findings such as presence of fever, location of cellulitis, and presence of tinea pedis or other chronic dermopathies. Previous studies have shown that (with the exception of fever), these clinical findings are significantly associated with recurrent lower extremity cellulitis [14]. Additionally, patients in Emergency Room observation units for cellulitis demonstrated a greater likelihood of hospital admission if they have fever, elevated lactate or hand cellulitis [15]. Extrapolating from these factors as potential severity surrogates, it is possible that these or other factors may also contribute to the response to initial antimicrobial regimen. A prospective study would help to answer this question more fully and determine if the IM ceftriaxone itself acts as an independent risk factor for poor outcome.

This distinction is important. If IM ceftriaxone proves not to be clinically advantageous, there could be improvement in prevention of avoidable antibiotic exposure. Additionally, ceftriaxone is more closely linked to C. difficile infection than other beta-lactam antibiotics [9], so it is reasonable to be reserved for cases where patients are unable to tolerate oral medications or when medication adherence is a concern. Our study clearly showed poorer outcomes with IM ceftriaxone use in cellulitis, as measured by prolonged antibiotic use or subsequent hospitalization. Nevertheless, ceftriaxone could still be considered in certain clinical situations. Advantages to IM ceftriaxone administration include once daily dosing, avoidance of intravenous line placement, and ease of administration in the outpatient setting.

There were several limitations to this study which include reliance on clinical diagnoses of cellulitis which is often misdiagnosed [16]. There are certain clinical variables that may impact treatment outcomes including chronic medical conditions beyond those accounted for in this study: diabetes, obesity, and those associated with tobacco use. Pre-existing stasis dermatitis, vascular disease, traumatic mechanism of injury, and immunocompromised state all would theoretically impact treatment outcomes. This study looked at all cases of cellulitis; however, cellulitis can be more severe depending on the location of the infection, so our results may not completely generalize to less common locations, for example, the hand and face. Future studies evaluating other variables such as comorbidity indexes and standardized diagnoses of cellulitis would be intriguing.

Conclusion

The majority of our primary care patients presenting to the outpatient setting with cellulitis received oral antibiotic therapy. The patients who received an initial dose of IM ceftriaxone were more likely to experience treatment failure, defined by either prolonged course of antibiotics or hospitalization, than the non-ceftriaxone cohort. More studies are needed to guide recommendations on the use of IM ceftriaxone for cellulitis in the outpatient setting.

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