Research Article

Ceftriaxone Usage and Resistance Rates in Internal Medicine Departments

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Background: Ceftriaxone has been recommended for empiric treatment for urinary tract and respiratory tract infections, but continued widespread use might increase resistance rates.

Objectives: To determine if ceftriaxone usage has increased resistance rates over a three-year period.

Methods: We included all patients hospitalized in internal medicine departments from 2019-2021 and extracted administered antibiotics, urine, and blood cultures with resistance reports from the computerized data base. We compared the yearly proportion of patients treated with specific antibiotics and the resistance rates of urine and blood pathogens.

Results: Overall, 44.1% of patients received antibiotics during 63.3% of the hospital days. The proportion of patients treated with ceftriaxone increased from 22% in 2019 to around 30% in 2020 and 2021. Resistance rates to ceftriaxone were approximately 30% for *Escherichia coli*, and 40-50% for *Klebsiella pneumonia* and *Proteus mirabulis* without significant changes over the three-year period. The overall usage rates of carbapenems and amikacin were 3.4% and 1.4% respectively, with low resistance rates that did not change over the follow-up period. The resistance rates for blood cultures were the same observed for urine bacteria.

Conclusions: We conclude that despite increased usage, resistance rates to ceftriaxone have remained stable over the past three years, and rates of resistance to broader-spectrum antibiotics have remained low. Longer follow-up is necessary to determine whether resistance rates will remain stable, and studies are needed to balance the clinical benefits and drawbacks of using ceftriaxone to treat suspected bacterial infections of the urinary tract and other areas of the body.

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Running title: Ceftriaxone usage and resistance rates

Introduction

Ceftriaxone has a favorable safety and tolerability profile, and there are recommendations for its' empiric use for complicated urinary tract infections in the inpatient setting[1], for first line empirical parenteral antimicrobial therapy in uncomplicated pyelonephritis[2], and for community acquired pneumonia that is not severe.[3]

However, there are concerns regarding the overuse of ceftriaxone and the potential for increased bacterial resistance rates.[4][5] There are claims that nearly 50% of ceftriaxone prescriptions are inappropriate, including nearly all lower respiratory tract infections[5], based on the assumption that limiting the use of ceftriaxone will reduce the prevalence of ESBL producing organisms, that is without conclusive evidence. [6]

Despite concerns of increasing resistance rates, ceftriaxone is used widely for empiric treatment of urinary and respiratory tract infections in patients who are hemodynamically stable.[7] Treatment is convenient, requiring only one intravenous dose per day, and most patients respond to initial treatment despite in-vitro bacterial resistance.[8] Ceftriaxone is the antibiotic with the highest usage in our hospital and it is unclear whether the continued widespread use of ceftriaxone has increased our resistance rates over the last three years.

Methods

We included all patients hospitalized in internal medicine departments not including cardiology and intensive care units from 2019-2021. the following variables were electronically obtained: antibiotic treatment entered by the nurses; urine culture results (>100,000 CFU/mL) including sensitivities to antibiotics; the age and gender of the patients; year of hospitalization; and discharge diagnosis. We determined the proportion of various bacteria in positive urine cultures, the proportion of patients treated with antibiotics and the proportion of hospital days with antibiotic treatment. We then compared the yearly proportion of patients treated with various antibiotics and the resistance rates of urine and blood pathogens.

The Laniado ethics committee approved this study (0065-22 LND) without the need for patient consent.

Results

The mean age of the patients was 72±19 years, and 10912/21504 (50.7%) were females. The median days of hospitalization was 3 with 25-75% quartiles of 2-5 days.

There were 29.7% of the patients with a diagnosis on discharge of an infectious disease. (Table 1). The 44.1% treated with antibiotics included those without a diagnosis of an infectious disease (Table 2), including those with other nonspecific symptoms, such as shortness of breath, general deterioration, and other diagnosis where the physician thought there might be an infectious component such as in those with aggravation of chronic obstructive lung disease. Antibiotics were given during 63.3% of the total hospital days.

Diagnosis	number	%
Respiratory tract infections	2744	12.8
Urinary tract infections	1721	8.0
Skin/subcutaneous infections	1278	5.9
Sepsis/shock	759	3.5
Viral infections/fever	408	1.9
Other infections	233	1.1
Antibiotics given in those without infections	2349	10.9
Total	7133	44.1

Table 1. Infectious diseases in 21504 internal medicine department patients

Antibiotic	Days N=103864 N (%)	Patients treated with antibiotic N=21504
Ceftriaxone	21698(20.9)	5677(26.4)
Piperacillin/tazobactam	6133(5.9)	1012(4.7)
Chloramphenicol	5849(5.6)	1036(4.8)
Cefazolin	5599(5.4)	1419(6.6)
Flagyl	5445(5.2)	927(4.3)
Vancomycin	4378(4.2)	737(3.4)
Doxycycline	4313(4.2)	1549(7.2)
Ceftazidime	3858(3.7)	298(1.4)
Ertapenem	2039(2.0)	432(2.0)
Meropenem	1652(1.6)	295(1.4)
Gentamicin	1203(1.2)	593(2.8)
Clindamycin	808(0.8)	211(1.0)
Augmentin	643(0.6)	166(0.8)
Erythromycin	457(0.4)	26(0.1)
Penicillin	445(0.4)	106(0.5)
Amikacin	335(0.3)	119(1.4)
Azithromycin	323(0.3)	161(0.7)
Trimethoprim/Sulfamethoxazole	205(0.2)	35(0.2)
Cloxacillin	199(0.2)	27(0.1)
Colistin	783(0.8)	118(0.5)
Levofloxacin	154(0.2)	68(0.3)
Total treatment days	65736(63.3)	9482(44.1)

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Table 2. Total days of antibiotic use during the 3 -year period total days

Over 80% of the positive urine cultures were due to *Escherichia coli*, *Klebsiella pneumonia*, *Proteus mirabulis* or *Pseudomonas aerogenes*, with little change over the three years (table 3).

Ceftriaxone was given to 22% of patients in 2019 and increased to around 30% in 2020 and 2021 (Table 4). Resistance rates to ceftriaxone were approximately 30% for *Escherichia coli*, and 40-50% for *Klebsiella pneumonia* and *Proteus mirabulis* without significant changes over the three-year period. Overall, for all urinary tract organisms, ceftriaxone had a resistance rate of 40.6% (1106/2693). The overall usage of carbapenems and amikacin were respectively 3.4% and 1.4%, and the resistance rates were ≤10% for all the urinary tract organisms, but amikacin had the lowest resistance rates overall. The only increase in resistance rates was piperacillin/tazobactam for the proteus mirabilis organism. The resistance rates of blood cultures were nearly identical to those of bacteria found in the urine.

Urine bacteria	**2019** **N=909**	**2020** **N=776**	**2021** **N=792**
Escherichia coli	459(50.5)	364(46.9)	366(46.2)
Klebsiella pneumonia	137(15.1)	151(19.5)	138(17.4)
Proteus mirabulis	101(11.1)	84(10.8)	87(11.0)
Pseudomonas aeruginosa	67(7.4)	59(7.6)	58(7.3)
Other	145 (16.0)	118 (15.2)	143(18.0)

Table 3. Urine bacteria 2019-2021 internal medicine departments

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Antibiotic-treatment and urine cultures	2019 N=8722	2020 N=6796	2021 5986	Blood cultures
Ceftriaxone*	1922(22.0)	1871(29.0)	1784(29.8)	
Escherichia coli	143/449(31.2)	125/363(34.4)	120/366(32.8)	85/280(30.4)
Klebsiella pneumonia	64/137 (46.7)	77/151(51.0)	60/138(43.5)	28/68 (41.2)
Proteus mirabulis	44/101(43.6)	33/84(39.3)	45/87(51.7)	16/47 (34.0)
Cefazolin*	588(6.7)	466(6.9)	365(6.1)	
Escherichia coli	Not done	133/322(41.3)	135/366(36.9)	45/128(35.2)
Klebsiella pneumonia		72/135(53.3)	62/137(45.3)	14/30 (46.7)
Proteus mirabulis		35/74(47.3)	52/87(59.8)	17/20(85.0)
Piperacillin/tazobactam*	367(4.2)	376(5.5)	269(4.5)	
Escherichia coli	30/459(6.5)	40/361(11.0)	27/366(7.4)	19/280(6.8)
Klebsiella pneumonia	31/137(22.6)	25/150(16.7)	20/137(14.6)	9/69(13.0)
Proteus mirabulis	4/101(4.0)	1/84(1.2)	20/137(14.6)*0.0013	1/48(2.1)
***Pseudomonas* aeruginosa**	7/66(10.6)	6/57(10.5)	10/58(17.2)	13/59(22.0)
Ertapenem*	156(1.8)	167(2.5)	109(1.8)	
Escherichia coli	1/458(0.2)	2/364(0.5)	365/366(0.3)	1/279(0.4)
Klebsiella pneumonia	0/136(0.0)	1/151(0.7)	4/138(2.9)	1/67 (1.5)
Proteus mirabulis	0/100(0.0)	1/83(1.2)	0/87(0.0)	0/48 (0.0)
***Pseudomonas* aeruginosa**				
Merapen*	101(1.2)	121(1.8)	73(1.2)	
Escherichia coli	1/459(0.2)	0/364(0.0)	0/366(0.0)	2/280(0.7)
Klebsiella pneumonia	1/137(0.7)	3/151(2.0)	5/138(3.6)	2/69(2.9)
Proteus mirabulis	1/101(1.0)	2/84(2.4)	1/87(1.1)	0/48(0.0)
***Pseudomonas* aeruginosa**	5/67(7.5)	0/58(0.0)	6/58(10.3)	7/62(11.3)
Gentamycin*	266(3.0)	151(2.2)	176(2.9)	
Escherichia coli	60/459(13.1)	42/363(11.6)	43/366(11.7)	28/280(10.0)

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Antibiotic-treatment and urine cultures	2019 N=8722	2020 N=6796	2021 5986	Blood cultures
Klebsiella pneumonia	35/136(25.7)	33/151(21.9)	20/138(14.5)*0.0216	16/69(23.2)
Proteus mirabulis	40/101(39.6)	34/84(40.5)	37/87 (42.5)	19/48(39.6)
***Pseudomonas* aeruginosa**	15/67 (22.4)	10/59(16.9)	7/57(12.3)	7/62 (11.3)
Amikacin*	46(0.5)	39(0.6)	34(0.6)	2/279(0.8)
Escherichia coli	1/459(0.2)	0/364(0.0)	0/366(0.0)	0/68(0.0)
Klebsiella pneumonia	1/137(0.7)	0/151(0.0)	1/138(0.7)	1/48(2.0)
Proteus mirabulis	0/101(0.0)	0/83(0.0)	0/75(0.0)	1/59(1.7)
Pseudomonas	0/67(0.0)	2/59(3.4)	3/58(3.4)	
Total treated	3661(42.0)	3111(45.8)	2710(45.3)	

Table 4. Antibiotic treatment (% of patients) and concomitant bacterial resistance 2019-2021.

**Proportion of patients treated*

Discussion

The main finding of this study was that resistance rates did not increase over the 3-year period in a hospital despite a 63.3% total daily use of antibiotics due to treatment of 44.1% of the hospitalized patients, 26% treated with ceftriaxone. Furthermore, the resultant low carbapenem and amikacin usage rates were associated with low rates of resistance to those antibiotics. A strength of this study was that antibiotic usage was based on what patients received rather than what was dispensed, commonly used in other studies.[9][10]

It is unclear if the empiric treatment with ceftriaxone was warranted given the high resistance rates. On one hand, Ceftriaxone treatment is very convenient to both the patient and nursing staff, and might partly explain the reduced catheter adverse event rates, since treatment is once a day and the intravenous line time can be minimized.[11] On the other hand, there are claims that the accepted treatment for cystitis is antibiotics with resistance rates of <20% and for pyelonephritis rates of <10%.[12][13] The

evidence for those recommendations however, is weak based on clinical experience, descriptive studies, and reports of expert committees.[14] An alternative is to use broader-spectrum antibiotics if there are risk factors for resistant organisms[15][16], but reported models to predict antibiotic susceptibility for urinary tract infections to ceftriaxone were poor with c-statistics <0.70.[15][17]

In order to use first-line empirical therapy that results in resistance rates less than 20%, third-generation cephalosporins would not be used in our hospital or in most other areas of the world as first-line empiric therapy for suspected urinary and respiratory tract infections. Ceftriaxone-resistance rates vary widely across different regions.[7][9][10][15][18][14][19][20] Patients admitted to Northern California emergency departments in 2017-2019 had 12.9% resistance rates to third-generation cephalosporin in those admitted with fever and a positive urine culture.[14] Ceftriaxone-resistant uropathogens rate was 43% in Turkish patients with pyelonephritis[19], and 29%[15] of patients admitted to the hospital in Singapore. In Mexico[20] the prevalence of *Escherichia coli* resistant organisms was 32.1%, and the average resistant rate for all the Enterobacteriaceae in University hospitals affiliated with the Center for Disease Control research network in the USA was 21%[7] ranging from around 5% to 45%. Ceftriaxone *Escherichia coli* resistance rates worldwide ranges from 5% to over 90% with a median of 45%.[9]

However, despite high resistance rates, we and many other hospitals use empiric therapy with cephalosporins [7][9][14][19][21][22] and their use has not been associated with increasing short-term mortality in patients with urinary tract infections [8], acute pyelonephritis[19] or urosepsis[21] but longer hospitalizations[8][14] and an increase in 90-day mortality rates.[14] In short, the overall risks and benefits of increasing the use of broader-spectrum antibiotics are unclear.

The study has several limitations. First, resistance rates may be influenced by antibiotic usage in other Israeli hospitals, but other Israeli hospitals have reported antibiotic usage not significantly different from our hospital. [10][22] Secondly, it is important to note that extrapolation of our results to areas with lower resistance rates may not be appropriate, and resistance rates could potentially increase over a longer follow-up period. Finally, while this study provides insight into resistance rates, it does not address other risks and benefits associated with this policy.

We conclude that despite increased usage, resistance rates to ceftriaxone have remained stable over the past three years, and rates of resistance to broader-spectrum antibiotics have remained low. For unstable patients, the empiric use of either a carbapenem or amikacin is appropriate until culture results are available (18). Longer follow-up is necessary to determine whether resistance rates will remain stable,

and studies are needed to balance the clinical benefits and drawbacks of using ceftriaxone to treat suspected bacterial infections of the urinary tract and other areas of the body.

Statements and Declarations

COI: none.

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Declarations

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