Ceftriaxone Usage and Resistance Rates in Internal Medicine Departments

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Abstract

Introducton: Ceftriaxone has been recommended for empiric treatment for urinary tract and respiratory tract infections, but there are recommendations to limit its' use in order to prevent an increase in resistance rates. It is unclear however, whether the continued widespread use will increase resistance rates.

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 various antibiotics and the resistance rates of urine and blood pathogens.

Results: 44.1% of patients were treated with antibiotics during 63.3% of the total hospital days. Ceftriaxone was given to 22% of patients in 2019 and increased to around 30% in 2020 and 2021. There were however, no significant changes over the three-year period in resistance rates to Ceftriaxone that was around 30% for E coli, and 40-50% for klebsiella pneumonia and proteus mirabulis. The overall usage of carbapenems and amikacin were 3.4% and 1.4% respectively and resistance rates did not increase over the follow-up period. The resistance rates for blood cultures were the same observed for urine bacteria.

Conclusion: We conclude that resistance rates have been stable over the past three years despite the increasing use of ceftriaxone. Further follow-up is required to see if the resistance rates do not increase over the longer-term, and studies of the clinical utility and disutility of empiric treatment with ceftriaxone in patients with suspected bacterial infections of the urinary tract and elsewhere will determine recommended antibiotic policies.

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Introduction

Ceftriaxone has a favorable safety and tolerability profile, and has been recommended for empiric treatment 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]. In fact, there are those who calculated, that nearly 50% of ceftriaxone prescriptions are inappropriate and included nearly all lower respiratory tract infections in that calculation [5]. They assumed that limiting the use of ceftriaxone will reduce the prevalence of ESBL producing organisms although the evidence is inconclusive [6].

Despite concerns of increasing resistance rates, ceftriaxone continues to be widely used for empiric treatment of urinary and respiratory tract infections in patients who are hemodynamically stable [7]. This in part is due to convenience, since ceftriaxone requires only one intravenous dose per day. Also, most patients respond to initial treatment despite bacterial resistance [8] perhaps due in part to overdiagnosis. In our hospital, ceftriaxone is the antibiotic with the highest usage. It is unclear however, whether the continued widespread use of ceftriaxone has increased our resistance rates over the last three years, and in fact whether resistance rates to both urine and blood cultures have changed or remained stable. This is important when considering antibiotic treatment policies.

Methods

We included all patients hospitalized in internal medicine departments excluding cardiology and intensive care units from 2019-2021. Administered antibiotics were recorded daily by the nursing staff in the computerized data base. Urinary cultures and resistance to the various antibiotics were also extracted, as was age and gender of the patients, year of hospitalization and discharge diagnosis.

First, we determined the proportion of various bacteria in positive urine cultures. Second, we determined the proportion of patients treated with antibiotics and the proportion of hospital days treated. Thirdly, we determined the proportion of patients treated with antibiotics and the proportion of hospital days treated. Finally, we 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 (0065-22LND) 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). Others that were treated with antibiotics without a diagnosis that resulted in the 44.1% overall frequency (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.

Table 1. Infectious diseases in the 21504 internal medicine departments

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 2. Total days of antibiotic use during the 3 -year period total days – internal medicine departments only.

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)
Doxylin	4313(4.2)	1549(7.2)
Ceftazidine	3858(3.7)	298(1.4)
Ertopenim	2039(2.0)	432(2.0)
Meripenim	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)
Pencillin	445(0.4)	106(0.5)
Amikacin	335(0.3)	119(1.4)
Azithromycin	323(0.3)	161(0.7)
Resprim	205(0.2)	35(0.2)
Cloxicillin	199(0.2)	27(0.1)
Colistin	783(0.8)	118(0.5)
Levoflox	154(0.2)	68(0.3)
Total treatment days	65736(63.3)	9482(44.1)

Over 80% of the positive urine cultures over the three-year period were due to E coli, klebsiella pneumonia, proteus mirabulis, or pseudomonas aerogenes. There was little change over the three-year period (Table 3). Around 40% of patients were treated with antibiotics with a rate of 63.3% of the total hospital days.

Table 3. Urine bacteria 2019-2021 internal medicine departments

Urine bacteria	2019 N=909	2020 N=776	2021 N=792
E 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 4. Antibiotic treatment (% of patients) and concomitant bacterial resistance 2019-2021.

Antibiotic-treatment and urine	2019 N=8722	2020 N=6796	2021 5986	Blood cultures
Ceftriaxone*	1922(22.0)*	1871(29.0)	1784(29.8)	
Ecoli	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 mirabilus	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)	
Ecoli	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 mirabilus		35/74(47.3)	52/87(59.8)	17/20(85.0)
Piperacillin/tazobactam	367(4.2)*	376(5.5)	269(4.5)	
Ecoli	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 mirabilus	4/101(4.0)	1/84(1.2)	20/137(14.6)*0.0013	1/48(2.1)
Pseudomonas aeru	7/66(10.6)	6/57(10.5)	10/58(17.2)	13/59(22.0)
Ertopenem	156(1.8)*	167(2.5)	109(1.8)	
Ecoli	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 mirabilus	0/100(0.0)	1/83(1.2)	0/87(0.0)	0/48 (0.0)
Pseudomonas aeuro				
Merapen	101(1.2)*	121(1.8)	73(1.2)	
Ecoli	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 mirabilus	1/101(1.0)	2/84(2.4)	1/87(1.1)	0/48(0.0)
Pseudomonas aeuro	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)	
Ecoli	60/459(13.1)	42/363(11.6)	43/366(11.7)	28/280(10.0)
Klebsiella pneumonia	35/136(25.7)	33/151(21.9)	20/138(14.5)*0.0216	16/69(23.2)
Proteus mirabilus	40/101(39.6)	34/84(40.5)	37/87 (42.5)	19/48(39.6)
Pseudomonas aeuro	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)	
Ecoli	1/459(0.2)	0/364(0.0)	0/366(0.0)	2/279(0.8)
Klebsiella pneumonia	1/137(0.7)	0/151(0.0)	1/138(0.7)	0/68(0.0)
Proteus mirabilus	0/101(0.0)	0/83(0.0)	0/75(0.0)	1/48(2.0)
Pseudomonas	0/67(0.0)	2/59(3.4)	3/58(3.4)	1/59(1.7)
Total treated	3661(42.0)	3111(45.8)	2710(45.3)	

**proportion of patients treated*

Ceftriaxone was given to 22% of patients in 2019 and increased to around 30% in 2020 and 2021 (Table 3). There were no significant changes over the three-year period in ceftriaxone resistance rates, that was around 30% for E coli, and 40-50% for klebsiella pneumonia and proteus mirabulis. Overall, for all urinary tract organisms, ceftriaxone had a resistance rate of 40.6% (1106/2693). The overall usage of carbapenems and amikacin were 3.4% and 1.4% respectively 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 mirabulis organism. The resistance rates of blood cultures were nearly identical to those of bacteria found in the urine.

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 40% of the hospitalized patients, 26% who were treated with ceftriaxone. Furthermore, the low rate of carbapenem and amikacin usage was associated with a continued low rate of resistance to those antibiotics. This suggests that we do not have to consider increasing resistance rates when empirically treating patients with ceftriaxone. 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].

Ceftriaxone had a 32% resistance rate to E coli. Ceftriaxone is very convenient to both the patient and nursing staff and might partly explain the reduced rates of catheter adverse events, since it is given only once a day and the intravenous line time can be minimized [11]. However, there are those who believe that the accepted treatment for cystitis are 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]. Others, have suggested that more wide spectrum antibiotics can be given if there are risk factors for resistance organisms [15][16]. However, models to predict antibiotic susceptibility for urinary tract infections in a hospital setting, have been poor with c-statistics <0.70 for ceftriaxone [15][17].

If those recommendations were adopted, 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. Resistance rates to ceftriaxone in hospitalized patients have been found to vary widely across different regions [7][9][10][14][15][18][19][20]. In California in 2017-2019 third generation cephalosporin resistance rates in those admitted to the emergency department with fever and a positive urine cultures was 12.9% [14]. In Turkey in patients hospitalized with pyelonephritis, the Ceftriaxone resistance rate was 43% [19]. In Singapore, the presence of Ceftriaxone-resistant uropathogens on admission to the hospital was 29% [15] and in Mexico [20] the prevalence of E coli ESBL organisms was 32.1%. In the United States, University hospitals affiliated with the Center of Disease control research network, the resistant rate for all the enterobacteriaceae was 21% [7] ranging from around 5% to 45%. Worldwide, resistance rates of E. coli in those treated with ceftriaxone was reported to range from 5% to over 90% with a median of 45% [9].

However, despite high resistance rates, many centers continue to use empiric therapy with cephalosporins [7][9][19][21][22] and their use has not been associated with increasing mortality in patients with urinary tract infections [8], acute pyelonephritis [19] or urosepsis [21]. However, the overall risks and benefits of increasing the use of broader-spectrum antibiotics is unclear.

The study has several limitations that need to be considered. While our hospital is regional, resistance rates may still be influenced by antibiotic usage in other hospitals in Israel. However, 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. Furthermore, 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. The advantages of ceftriaxone treatment need to be balanced by the high but stable rate of resistance. For unstable patients the empiric use of either a carbapenem or amikacin is appropriate until culture results are available, where resistance rates have also remained unchanged. Further 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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