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Antibiotics requiring dosage adjustment in community acquired pneumonia patients with renal impairment

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ORIGINAL RESEARCH ARTICLE

ABSTRACT

Aim: To determine the antibiotics requiring dosage adjustment in community-acquired pneumonia patients with renal impairment and to assess in-hospital mortality in the patients requiring dosage adjustment.

Subjects and methods: A prospective and observational study was carried out in a tertiary care hospital. All community-acquired pneumonia patients with mild to moderate renal impairment were included. The Cockroft-gault formula or MDRD equation was used to calculate creatinine clearance. The mean creatinine clearance values were calculated by t-test and chi-square test was used to test categorical variables. The odds ratio and relative risk were estimated to test the association between antibiotics requiring dosage adjustment and mortality.

Results: Fifty-two of the 136 pneumonia patients were found to have renal impairment. The mean serum creatinine in all patients was 2.4 mg/dL and calculated creatinine clearance was 36.3 ml/min/m^2 (SD, 16.45). Approximately 46% of the patients received antibiotics that required dose adjustment with 34% of patients had their antibiotics appropriately adjusted; 12% of patients were required to be adjusted appropriately. The antibiotics requiring dosage adjustment when compared with mortality did not show any significance (P = 0.91) and odds ratio [0.92 (95%CI 0.22 – 3.92)]. The relative risk of patients requiring dosage adjustment was 0.96 (95%CI 0.5 – 1.84).

Conclusion: The proportions of antibiotics requiring adjustment in Community-acquired pneumonia patients with renal impairment were high in the present study. However, the risk of mortality in the inappropriately adjusted patients was found to be non-significant. Further large randomized studies particularly focusing on in-hospital mortality of the patients with renal impairment is warranted.

Keywords: Community-acquired pneumonia, renal impairment, antibiotics dose adjustment, mortality.

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INTRODUCTION

Pneumonia is the significant cause of infection-related mortality and the risk of death further increases with worsening glomerular filtration rate (GFR) (McDonald et al., 2015). Moreover, patients on antimicrobial regimens often have some extent of impaired renal function and many commonly used antibiotics are excreted through renal route. Hence, it is often necessary to alter the dosing schedule in patients with impaired renal function (National Kidney Foundation., 2002). Drug dosing in renal insufficiency needs to be individualized whenever possible to optimize therapeutic outcomes and to

minimize toxicity. Drug dosage adjustment for patients with renal impairment is an assent standard of care, though the discrepancy to adjust drug dosing in renal dysfunction still exist. Many approaches have been proposed to determine renal function, amongst which the Cockcroft-Gault (CG) equation, provides an estimate of creatinine clearance (CrCl). However, a minor increase in serum creatinine (SCr) may exhibit a marked fall in GFR. Therefore, the estimation of GFR through the calculation of CrCl or eGFR using validated formula is required in every patient (Patel et al., 2010). The Modification of Diet in Renal Disease (MDRD) Study equation have been widely recognized as it provide more accurate estimates of glomerular filtration rate (GFR) when compared with Cockcroft-Gault (CG) equation (Stevens et al., 2009). Appropriate dosage adjustment in patients with renal impairment, may result in fewer adverse drug effects and mortality while maintaining therapeutic effectiveness (Fahimi et al., 2012). We aim to determine the percentage of antibiotics requiring dosage adjustment in patients with community-acquired pneumonia and/or kidney disease according to the available guidelines and to analyze whether the appropriate dosage adjustment is related to reduced in-hospital mortality.

SUBJECTS AND METHODS

A prospective and observational study was carried out in tertiary care hospital with the duration of six months. The study was approved by institutional ethics committee.

The study included all consecutive patients admitted to the hospital with age group more than 18 years, with clinical diagnosis of pneumonia, or signs consistent with pneumonia on physical examination and on chest radiography obtained within 24 hours of admission, patients with clinical diagnosis of mild to moderate renal impairment. To restrict the study, the following patients were excluded: admission from a nursing home or other long-term care facility, treated in outpatient setup, pediatric population and pregnant women, or history of chronic kidney disease were excluded.

Our primary outcome variable was to determine the percentage of antibiotics requiring dosage adjustment in patients with community-acquired pneumonia. The data was collected from the hospital case record and all the patient demographics, past medical and social history, co-morbidities, clinical parameters and treatment were recorded. Creatinine clearance was calculated using Cockroft-gault formula or MDRD equation (National Kidney Foundation., 2002). The prescribed dosages were then compared with available guideline dose recommendations (Bennett et al., 1983). When the drug regimen was adjusted based on the patient's CrCl as recommended by the guideline, were termed as appropriate or the dosage prescribed was not in conformity to the patient's CrCl as recommended by the guideline were termed as inappropriate.

Cockroft-Gault Formula:*

$$Creatinine\ clearence = \frac{[Age - 140] \times Body\ Weight}{Serum\ Creatinine \times 72} \ (\times 0.85 \text{ if female})$$

MDRD Equation:*

$$eGFR((mL/min)/1.73m^2) = 175 \times S_{cr}^{-1.154} \times (Age)^{-0.203} \times (0.742^{a}) \times (1.212^{b})$$

a: if females and b: if african American

*(National Kidney Foundation., 2002)

Descriptive statistics were used to examine the normality of data and describe the analysis. Data for the CG and MDRD equations are expressed in ml/min/1.73m^2. The Student's t-test was used to compare differences in mean creatinine clearance values between dead and alive patients. A categorical comparison was tested by using chi-square test between mortality and antibiotics requiring dosage adjustments. The Odds ratio and relative risk were estimated to relatively measure the association between antibiotics requiring dosage adjustment and mortality. Sub-group analyses were conducted to test the significance of various clinical characteristics with serum creatinine and estimated creatinine clearance using ANOVA. The SPSS statistical package (version 20.0, IBM-SPSS Inc) was used for the statistical analysis.

RESULTS

Out of one hundred and thirty six patients with pneumonia, 52 patients met the inclusion and exclusion criteria. The patient's demographics and clinical characteristics are shown in Table 1. The mean age was 48.1 years with a standard deviation of 18 years. Of the population, 65% were male and 35% were female, 69% were admitted to emergency department, and 31% were admitted to the General ward, within 24 hrs of hospitalization. The major co-morbidities in the present cohorts were lungs diseases such as COPD and TB, followed by stroke and heart diseases. Based upon Pneumonia Severity Index (PSI), 63% were at mild to moderate risk (Class I and II) and 37% were at high risk (Class III and IV). Patient stratified by CURB-65 scores include individuals with low risk (48%) and intermediate to high risk (52%).

Table 1. Patients sociodemographic and clinical characteristics.

Characteristics	Patients
	[n = 52] (%)
Sociodemograhics details	
Age, years [Mean (SD)]	48.13(18.4)
Male	34(65.4)
Alcoholic	21(40.4)
Smoker	18(34.6)
Clinical Characteristics	
Admitted to ICU	36(69.2)
Admitted to Gen. Wards	16(30.8)
Mechanical Ventilation	14(26.9)
Co Morbidity	
CNS disorders	1(1.9)
Heart Disease	5(9.6)
Hepatic Disease	3(5.8)
Lungs disorder	19(36.5)
Renal Disease	4(7.7)
Sepsis	4(7.7)
Stroke	5(9.6)
Other	2(3.8)
Physical and Laboratory data	
Altered mental status	13(25)
Pulse rate > 125/min	1(1.9)
Respiratory Rate > 30/min	14(26.9)
Systolic BP < 90 mm of Hg	11(21.2)
Temperature <95F or >102F	12(23.1)
BUN > 30 mg/dl	16(30.8)
Serum Sodium < 130 mEq/L	24(60)
Serum creatinine, mg/dL	
Mean (SD)	2.4(1.36)
Median (Range)	1.8(1.4 - 7.0)
Creatinine clearance, ml/min/1.73 m^2	
Mean (SD)	36.33(16.45)
Median (Range)	36.35(9.9 – 72.7)
Severity Assessment Tool	
Pneumonia Severity Index	
Grade I-II	33(63.4)
Grade III-IV	19(36.6)
CURB-65	
Class 0-1	25(48)
Class 2-3	27(52)

The mean serum creatinine in all patients was 2.4 mg/dL and calculated creatinine clearance was 36.3 ml/min/m^2 with 16.45 SD. The table 2 shows the serum creatinine and calculated creatinine clearance of different antibiotics prescribe in pneumonia patients with renal impairment. The estimated GFR of >60 ml/min/m^2 was observed 37%, 30-59 ml/min/m^2 in 56% and <30 ml/min/m^2 in 8% of patient population.

Table 2. The rate of prescribed antibiotics which needed dose-adjustment using standard references.

Antibiotics	Prescribed (%)	Adjusted (%)	Requiring dose adjustment (%)
Ceftriaxone	75	-	-
Piperacillin-Tazobactam	33	-	-
Azithromycin	38	-	-
Amoxicillin-clavulanate	8	4	4
Amikacin	8	4	4
Levofloxacin	12	12	0
Ciprofloxacin	8	6	2
Amoxicillin	4	2	2
Others	6	6	0

Table 3. Serum creatinine and calculated creatinine clearance of Antibiotics prescribed in Community-acquired pneumonia patients with renal impairment

Antibiotics	Serum creatinine (mg/dL)		Creatinine clearance (ml/min/m^2)	
	Mean	SD	Mean	SD
Ceftriaxone	2.33	1.36	38.18	17.28
Piperacillin-tazobactam	2.96	1.67	30.4	16.46
Azithromycin	2.42	1.46	37.31	18.32
Amoxicillin-clavulanate	1.85	0.65	44.45	17.04
Amikacin	1.48	0.15	50.75	10.27
Levofloxacin	2.12	0.52	30.27	5.79
Ciprofloxaccin	3.38	2.44	24.9	10.18
Others	2.24	0.5	32.32	11.33

Table 4. Comparison of Risk factors associated with mortality.

	Alive n (%)	Death n (%)	*P* - value	Odds Ratio (95%CI)	Relative risk (95%CI)
Requiring dose adjustment	23(82.14)	4(17.86)	0.059*	0.92 (0.217-3.920)	0.963 (0.5 – 1.84)
Dose adjusted	20(83.33)	5(16.67)			
eGFR ≤ 30 ml/min/m^2	18(90)	2(10)	0.027*	2.52 (0.47-13.58)	1.89 (0.53 – 6.72)
eGFR > 30 ml/min/m^2	25(78.1)	7(21.9)			

**P* value estimated by chi-square test (2-sided)

The antibiotic prescribed for patients with Community-acquired pneumonia with renal impairment includes Ceftriaxone (75%), Piperacillin-Tazobactam (33%), Azithromycin (38%), Amoxicillin-clavulanate (8%), Amikacin (8%), Levofloxacin (12%), Ciprofloxacin (8%), Amoxicillin (4%) and others (6%). The patient population requiring dosage adjustment as calculated from creatinine clearance using standard references are listed in table 2. Among antibiotics requiring dosing adjustment, 75% were adjusted appropriately and 25% were prescribed without any adjustment. The most inappropriately prescribed antibiotics in the entire cohort include Amikacin (4%), Amoxicillin-clavulanate (4%), ciprofloxacin (2%), and amoxicillin (2%). The figure 1 shows the rate of adjusted antibiotics or requiring adjustments in patients with pneumonia with renal impairment.

The mean serum creatinine also varied in patients taking different antibiotics (Table 3). The patients receiving ciprofloxacin and amikacin have the highest and lowest mean serum creatinine of 3.38 and 1.48 mg/dL, respectively. The calculated mean creatinine clearance was highest in patients receiving amikacin 36.3 ml/min/m^2 and lowest in patients receiving ciprofloxacin 24.9 ml/min/m^2.

The mortality rate was 18% (9/52) and 82% are still alive (43/52). The antibiotics requiring dosage adjustment was compared with mortality (Table 4), but was non-significant (*P* = 0.91) with odds ratio of 0.92 (95%CI 0.22-3.92). The relative risk of patients requiring dosage adjustment was 0.96 (95%CI 0.5 – 1.84). The estimated GFR ≤ 30 ml/min/m^2 vs > 30 ml/min/m^2, showed a significant risk factor for mortality with odds ratio of 2.5

(95%CI 0.47 – 13.58). The relative risk of patients with ≤ 30 ml/min/m^2 was 1.89 (95%CI 0.53 – 6.72).

The clinical characteristics of community acquired pneumonia patients with renal impairment did not show any significant difference (Table 5). The mean serum creatinine for patients with age ≤ 50 years was 2.7 mg/dL compared with 2.12 mg/dL for age > 50 years, *P* = 0.122. The mean estimated creatinine clearance for male patients was 39.55 ml/ min/ m^2, whereas the mean estimated creatinine clearance for female patients was 30.26 ml/min/m^2 (*P*= 0.052).

Table 5. Sub group analyses comparing clinical characteristics with serum creatinine and calculated creatinine clearance.

Characteristics	Serum creatinine (mg/dL)		*P - value*	Creatinine clearance (ml/min/m^2)		*P* - value
	Mean	**SD**		**Mean**	**SD**	
Age			*0.122*			
Age ≤ 50 yrs	2.7	1.7		37.46	20.46	*0.625*
Age > 50 yrs	2.12	0.87		35.2	11.43	
Gender						
Male	2.29	1.18	*0.384*	39.55	15.93	*0.052*
Female	2.64	1.67		30.26	16.11	
Alcoholic						
No	2.37	1.38	*0.791*	36.25	17.13	*0.967*
Yes	2.47	1.38		36.45	15.81	
Smoker						
No	2.53	1.53	*0.379*	34.25	16.71	*0.213*
Yes	2.18	0.98		40.26	15.65	
Site of Care						
ICU	2.27	1.06	*0.272*	36.18	14.78	*0.919*
Non ICU	2.73	1.9		36.69	20.26	
CURB						
High risk	2.23	1.09	*0.298*	36.61	14.15	*0.898*
Low risk	2.63	1.63		36.01	19.1	
PSI			*0.407*			
Mild to Moderate risk	2.53	1.55		36.08	17.88	*0.885*
Severe risk	2.2	0.98		36.77	14.07	
Respiratory Rate > 30/min						
No	2.41	1.47		36.69	16.11	*0.801*
Yes	2.42	1.1	*0.970*	35.37	17.93	
Pulse rate > 125/min						
No	2.24	1.37	*0.605*	36.92	16.95	*0.678*
Yes	1.7	NE		34.14	14.97	
Systolic BP < 90 mm of Hg						
No	2.38	1.28	*0.751*	36.92	16.95	*0.623*
Yes	2.53	1.74		34.14	14.97	
Temperature <95F or >102F						
No	2.38	1.24	*0.761*	35.7	15.14	*0.616*
Yes	2.52	1.8		38.45	20.87	
BUN > 30 mg/dl						
No	2.16	1.28	*0.329*	40.34	15.88	*0.186*
Yes	2.55	1.41		34.03	16.57	
Serum Sodium < 130 mEq/L						
No	2.37	1.36	*0.754*	35.88	15.19	*0.77*
Yes	2.5	1.43		37.35	19.51	

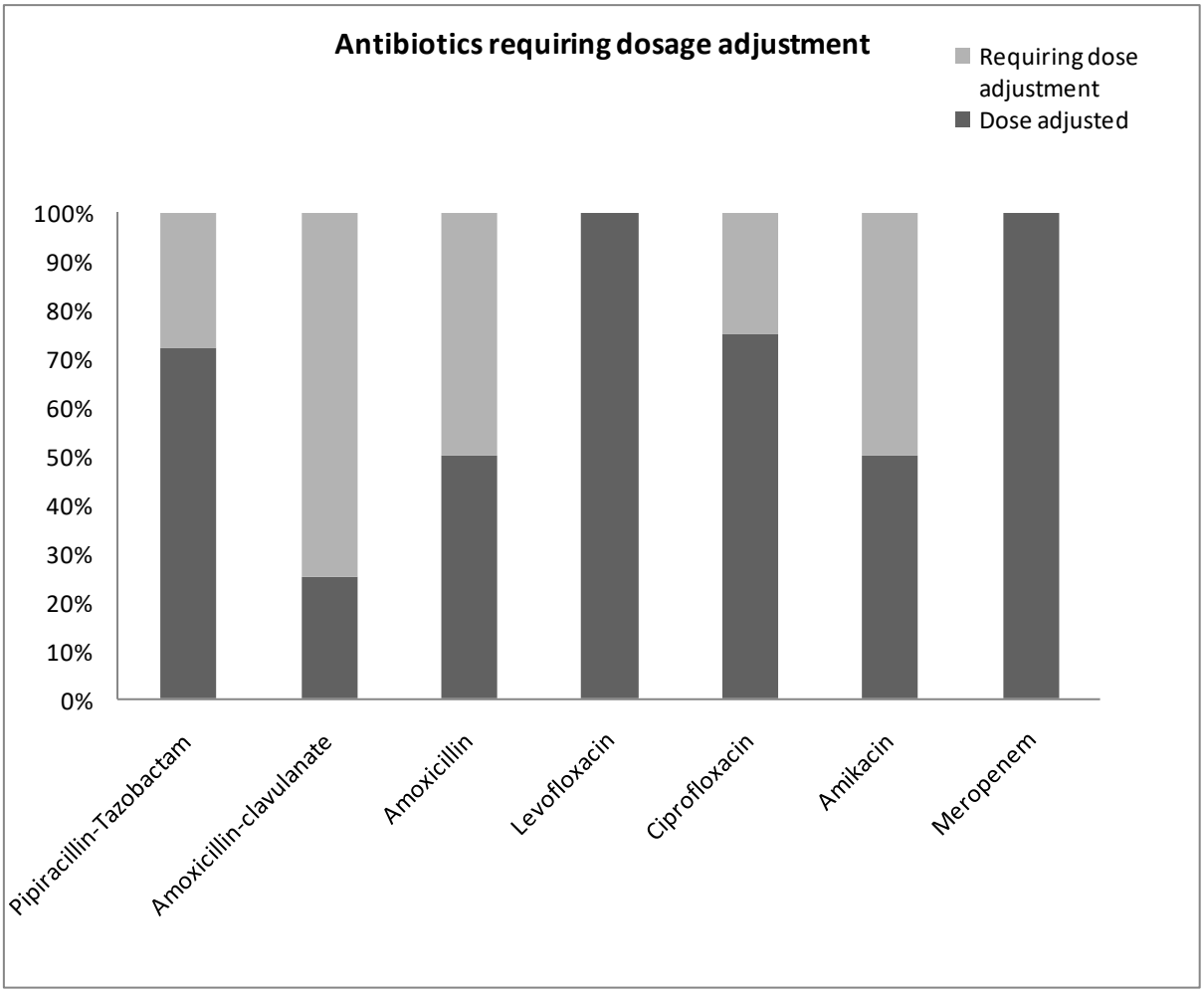

Figure 1. The rate of prescribed antibiotics requiring dosage adjustment in community-acquired pneumonia patients with renal impairment.

DISCUSSION

Community-acquired pneumonia is the recognized cause of mortality, with risk being increased with reduced eGFR and renal dysfunction. Not all patients with community-acquired pneumonia are at risk of developing complication such as acute kidney injury, but it may act as add-on risk factor for in-hospital mortality. Many physicians prefer to use empirical broad spectrum antibiotics particularly in primary care as immediate access to laboratory data is very limited, but this may lead to further deterioration of renal function if the patients are presented with pre-existing CKD (McDonald et al., 2015). Hence more focused is to be given for patients with known renal disorders and antibiotics prescribed should be adjusted appropriately.

The present study evaluates the proportion of antibiotics requiring adjustment in Community-acquired pneumonia patients with renal impairment. In current study, 46% received antibiotics that required dose adjustment and about 54% of patients did not require any dosage adjustment. These mean that the patients might have not required any dosage adjustment or the antibiotics prescribed might be non-nephrotoxic. Among the patients who received antibiotics that required dose adjustment, 75% of patients had their antibiotics appropriately adjusted; 25% of patients were required to be adjusted appropriately.

The appropriateness of the antibiotics prescribed is associated with serum creatinine, as the physicians become more cautious while prescribing antibiotics among the patients with elevated serum creatinine. The use of serum creatinine might sometimes result in underestimation of renal function especially in elderly, which might increase the number of inappropriate prescriptions (Modig et al., 2011). In present study the mean serum creatinine was significantly high (2.4 mg/dL) with nearly 8% of patient population had estimated creatinine clearance < 30 ml/min.

In our study we used the Cockroft-Gault(CG) formula and/or MDRD equations for estimation of Creatinine Clearance. No equation has proven superiority over the other. However, the use of MDRD equation for adjustment of dosages often calculates higher doses than the CG equation. On the other hand, CG classically gives a more conventional estimate and may suggest the need for dose adjustment more often (Moranville et al., 2009).

The patient population with high risk of developing renal dysfunction should be given more attention and emphasis should be given to calculate creatinine

clearance for estimation of renal function in addition to serum creatinine alone. Interventional randomized studies focusing on dosage adjustment in patients with renal failure are warranted. Perhaps, such studies might show a significant impact of dosage adjustment on mortality (van Dijk et al., 2006).

The present study has some limitations. Firstly, the sample size was small and the design of the study was prospective in nature. The study could not assess the extent of renal dysfunction and could not differentiate between acute and chronic kidney diseases. In addition to renal function, the physician might have used other parameters like electrolyte levels, blood pressure, heart rate etc. Secondly, the MDRD equation used in our study, did not take the patient's weight or height into consideration and as a result, it might have fail to make an accurate prediction of GFR. Lastly, the physicians might have used guidelines to make dosage adjustment other than the guidelines used by the investigators in the present study.

CONCLUSION

The proportions of antibiotics requiring adjustment in Community-acquired pneumonia patients with renal impairment were high in the present study. However, the risk of mortality in the inappropriately adjusted patients was found to be non-significant. Further large randomized studies particularly focusing on in-hospital mortality of the patients with renal impairment is warranted.

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CONFLICT OF INTEREST

None declared.

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