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Appropriateness of Amikacin Dose Prescription, Monitoring and Safety during Hospitalization as an Impact of Clinical Pharmacologist Intervention, in the Israeli Regional Hospital

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Abstract

Background: Use of inappropriate amikacin dose is one of the most important factors in inducing toxicity, prolonged hospitalization as well as in increasing patient's mortality. **Objective:** The aims of this study are the analysis of amikacin dose, serum level and the examination of the effectiveness of the clinical pharmacologist (CP) therapeutic drug monitoring (TDM) intervention to guarantee the safety of amikacin use. **Methods:** This is a one-year retrospective observational chart review study, which evaluates amikacin dose, serum drug level, development of adverse effects in patients on amikacin with or without CP TDM consultation. **Results:** Amikacin was prescribed for 393 complex patients, with median age 83. Amikacin group (AG) included 140 (32%) courses with CP consultation (AG1) and 292 (68%) courses without CP consultation (AG2). The distribution of most study characteristics in both groups was similar including amikacin dose (9 - 10 mg/kg/day), renal failure (14%) and mortality (12%). Acceptance for CP consultation was in 46% of amikacin courses and dose changes were done in 63% after CP intervention. Prolonged antibiotic course (4.6 ± 1.5 vs 3.8 ± 1.6 days, $p < 0.0001$) and the patient's hemodynamic instability (15% vs 7%, $p = 0.01$) were more frequent in the AG1 compared to the AG2. There was a strong association between CP consultation and prolonged hospitalization ($p = 0.005$), while no association between it and amikacin adverse effects, renal failure or mortality. **Conclusions:** There was no trend to reducing amikacin toxicity,

days of hospitalization or mortality in patients with CP consultation. CP TDM intervention was more in the management of complicated clinical situations. However, it is necessary to optimize it.

Keywords

Amikacin, Therapeutic Drug Monitoring, Appropriate, Clinical Pharmacologist, Safety, Adverse Effects

1. Introduction

In recent years, the use of aminoglycosides antibiotics during hospitalization has been increased, due to increasing the development of antibiotic resistance. The toxicity of these antibiotics assumes the individual approach to their use together with therapeutic drug monitoring (TDM). Using TDM in the antibiotic's management has been known since the early 1970s. Today, TDM of aminoglycosides in hospitals has become a standard strategy for maximizing therapeutic efficacy and minimizing adverse events [1]-[6]. The hospital TDM approach must be education-based and multidisciplinary which means involving infection disease unit, clinical pharmacology unit with clinical pharmacy specialist, a microbiological laboratory and hospital departments. The hospital TDM for antibiotic dose adjustment is usually included with dosing regimen, time of drug level monitoring, microbial MIC (minimum inhibitory concentrations) and treatment duration [4] [6]-[13]. Randomized controlled trials demonstrate a reduction in mortality, days of hospitalization and toxicity by using antimicrobial TDM [7] [8].

Antibiotic TDM service in our hospital has been functioning on a multidisciplinary approach for many years. Since 2004 the clinical pharmacology unit of our hospital was the first one in Israel to start giving regular TDM consultations to the physicians by clinical pharmacologist (CP). They are responsible for and taking care about the appropriate use of TDM antibiotics for today, their annual number being from 250 to 480. The 70% of these consultations are for amikacin. Amikacin is a widely used antibiotic in our hospital with DDD (defined daily dose) 2.6 - 2.3 per 100 patient days or DOT (days of therapy) 3.2 - 2.7 per 100 patient days in recent years till today. Despite a prescriber awareness of TDM consultation, it has barriers in successful uptake and free integration into routine workflow. These barriers are known in most cases, but difficult to overcome in real life and as a result, the TDM intervention has variable success [14] [15].

Therefore, this study has several objectives. First of all, we hypothesized that the amikacin adverse effects (AAEs) appear most frequently in patients who did not receive CP TDM consultation. So, the aim of this study is to examine: amikacin dose; amikacin serum TDM; the effectiveness of the CP intervention in getting appropriate doses of aminoglycosides for preventing toxicity, decreasing the days of hospitalization and mortality; to find specific patients characteristics that really require CP TDM intervention during hospitalization, for improving

of CP consultations.

2. Methods

2.1. Description of Hospital Clinical Pharmacologist Service for TDM

The Israeli Kaplan academic tertiary hospital in Rehovot is a 581-bed medical institution with an average of 43,000 admissions per year. The hospital has an electronic medication management system in all clinical areas. The clinical pharmacology unit was established in 2003 and continuous it functions for today, the staff constitution of two clinical pharmacologists. The TDM service in clinical pharmacology units is only part of full CP service for inpatient and sometimes for outpatient departments. CP TDM intervention includes: physician's education, TDM protocols and individual consultation for dose calculation according to patient clinical/laboratory parameters. Electronic consultation is given routinely 24 hours, 7 days a week for all hospital departments with consultation follow-up during the whole course of antibiotic therapy. In addition, once a week the CP reviewers electronic charts for medication management in all departments and gives electronic consultation for drugs management including the TDM service for all patients on aminoglycosides or other antibiotic therapy. Serum amikacin level is generally collected on trough level in our hospital. Amikacin dose calculation is done by using Rx-Kinetics program with adaptation for each patient. The CP consultation is just a recommendation. Therefore, decision to accept or to not accept it is directly dependent on physicians experience and dynamic clinical situation.

2.2. Study Design and Population

The study is a retrospective observational chart review from 01.01.2019 to 01.01.2020. Approval was obtained from the hospital's Research Ethics Committee. The study population consisted of 18 year olds and older patients who received amikacin during hospitalization. This Amikacin Group (AG) was divided into: patients who received CP TDM consultation (AG1) and those who did not (AG2).

Patients who were ≤ 18 years old, who received hemo or peritoneal dialysis and received antibiotic therapy only once or multiple single doses once every 4 or more days and non-intravenous amikacin use were excluded.

2.3. Collected Data

General patient's characteristics include demography, medical diagnoses and comorbidities. Charlson Comorbidity Index and Chronic Disease Score calculation were done for every patient. General laboratory tests and hemodynamic states were extracted from electronic data on the day of admission as baseline (T1), on the third day of hospitalization (T2) and before discharge (T3). Glomerular Filtration Rate (GFR, mL/min/1.73m^2) was calculated with three GFR equations: Modification of Diet in Renal Disease (MDRD), Cockroft\Gaul and

CKD-EPI equation [16]. Definition of creatinine instability and acute renal failure (ARF) are given in Supplement 1.

Amikacin courses include the patient's doses and CP-recommended doses, the days of therapy duration and the number of administrations. Normal amikacin doses per GFR were calculated for every patient (creatinine of time T1 and T2). All drug dose adjustments were correlated with CP consultation, GFR and TDM blood tests. Normal amikacin dose per GFR level, risk factors for toxicity and development of amikacin adverse effects (AAEs) described in Supplement 1.

CP consultation includes the day of consultation on antibiotic therapy, recommendation for the antibiotic dose and for TDM blood samples collection as well as the examination of whether this recommendation was accepted. Antibiotic dose was calculated using Rx-Kinetics program and adapted for each patient (http://www.rxkinetics.com). The group of patients with recommendation to make changes of amikacin dose was called interventional AG1 and acceptance of the recommendation was examined.

TDM drug laboratory service includes serum amikacin report and the number of tests per each patient, correlation between the time of blood sample collection, the time of drug administration and the time of the CP consultation. Serum concentration was interpreted as high, normal or low. For patient with high serum drug levels the correlation between having the second serum TDM sample and changing or stopping amikacin therapy was done.

Statistical analysis of parameters of patients groups was compared by Pearson's χ^2 test, Chi-squared test, Fisher exact test and Student's t-test. Linear regression was conducted on the number of days of hospitalization and logistic regression was conducted on other dichotomous-dependent variables. Multiple logistic regression was used in order to compare groups to determine the impact of CP consultation and the variables independently associated with significant risk factors of renal failure, days of hospitalization and death. P value < 0.05 is considered statistically significant (Supplement 1).

3. Results

3.1. Description Data Collection

The main electronic data included 686 amikacin courses. From them were excluded: 20 patients on hemodialysis, 178 patients who received antibiotic therapy only once and 56 patients who had amikacin prescriptions more than one time once in the period of more than 4 days. The final study included 432 amikacin courses administrated to 393 patients, 294 (75%) of them beeing females. The mean age of the whole group was 80 ± 13.2 years old (median 83). AG1 included 131 patients (140 (32%) courses) and AG2 included 265 patients (292 (68%) courses).

3.2. Patient's Characteristics

General (Table 1).

No differences in mean age and sex distribution were found. The total number

Table 1. General groups characteristics.

	AG1* (n = 140)	AG2* (n = 292)	P value
Age (years)	80 ± 12.9	80 ± 13.3	1.0
Female sex	53 (66)	188 (64)	0.8
Body weight (kg)	67 ± 2	67 ± 3	0.6
Days of hospitalization	15 ± 18	11 ± 10	0.002
Indication for treatment with amikacin**			
Presence of sepsis	18 (13)	39 (13)	1.0
Urinary tract infection	125 (90)	254 (87)	0.6
Bacteremia	8 (6)	21 (7)	0.7
Pneumonia	39 (28)	49 (17)	0.02
Other infections diseases[1]	27 (19)	52 (18)	0.9
Total number indications for treatment with amikacin per one patient	1.3 ± 0.6	1.3 ± 0.5	0.3
Concomitant comorbidities**			
Total number of other active disease during hospitalization per one patient[2]	2.0 ± 1.8	2.0 ± 1.7	0.9
Total number of chronic disease per one patient	8.6 ± 4.4	8.6 ± 5.1	1.0
Total number of chronic medications and others per one patient	7.0 ± 3.2	7.2 ± 4.3	0.7
Total number of medications and others during hospitalization per one patient[3]	11.1 ± 5.1	11.4 ± 5.6	0.6
Charlson Comorbidity Index	5.9 ± 2.6	5.9 ± 2.6	1
Chronic Disease Score	7.9 ± 4.5	8.2 ± 4.4	0.7
Death during hospitalization	19 (14)	33 (11)	0.6
Acute renal failure (ARF) per study definitions			
Unstable renal function[4]	53 (41)	105 (39)	0.7
ARF per Creatinine calculation[5]	18 (14)	40 (15)	0.8
ARF per MDRD equation[6]	19 (15)	39 (14)	0.9
ARF per Cockroft\Gaul equation[6]	18 (14)	37 (14)	0.9
ARF per CKD-EPI equation[6]	18 (14)	36 (13)	0.9

Data are expressed as mean ± SD or number (%). *Amikacin hospitalization Group with therapeutic drug monitoring (TDM)drug consultation = AG1; Amikacin hospitalization Group without therapeutic drug monitoring (TDM) drug consultation = AG2. ** One patient may have more than one diagnosis. [1]Other infectious diseases: Skin and soft tissue infection (Cellulitis, Gangrene/decubitus ulcer) AG1-19(14)/AG2-24(8); Intra-abdominal problems (Abdominal pain, Diarrhea) AG1-7(5)/AG2-18(6); Neutropenic fever AG1-1(0.7). [2]Describtionof other active diseases during hospitalizationare in Supplement 2. [3]Others: fluids, nutrition and alternative medication. [4]Unstable renal function: any increase in creatinine (differences between study periods on admission (T1)/on third day of hospitalization (T2)/on discharge (T3)). [5]Acute renal failure per creatinine: increase in Serum Creatinine by ≥0.3 mg/dL. [6]Acute renal failure per GFR (Glomerular Filtration Rate): decrease in GFR by ≥25%. MDRD (Modification of Diet in Renal Disease equation); CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration equation).

of hospitalization days was higher in the AG1 than in the AG2 (15 ± 18 vs 11 ± 10, p = 0.002). The main patients' diagnosis for amikacin therapy was urinary tract infection in 90% in both groups. Incidence of pneumonia was higher in theAG1 (28% vs 17%, p = 0.02). Patients in both groups had about nine con-

comitant comorbidities and about seven chronic medications per one patient on admission. During hospitalization patients received about twelve medications per patient. Patients' mortality was about 12% in each group. Charlson Comorbidity Index and Chronic Disease Score were not different in both groups. Linear/logistic regressions analysis was done for detecting variables associated with death and days of hospitalization. There was association between the days of hospitalization and CP consultation (OR 3.7, 95% CI: 1.3 - 6.4, p = 0.005), low systolic BP (OR 9.6, 95% CI: 4.9 - 14.5, p = 0.0001), high systolic or diastolic BP (OR 3.4, 95% CI: 0.9 - 6.0, p = 0.008) and pneumonia (OR 9.2, 95% CI: 6.0 - 12.1, p < 0.0001). Death was associated with renal failure (OR 12.9, 95% CI: 7.0 - 37.8, p < 0.0001), low systolic BP (OR 11.5, 95% CI: 4.1 - 40.7, p < 0.0001), low or high pulse (OR 2.4, 95% CI: 1.1 - 5.1, p = 0.03) and pneumonia (OR 3.6, 95% CI: 1.6 - 8.1, p = 0.002) (Table 2).

Clinical and laboratory parameters (*Supplement* 2).

Systolic pressure has tended to increase in 23% of patients prior to their discharge. Low diastolic pressure was specific for AG1 in the T1 admission period

Table 2. Regression analysis of risk factors for amikacin associated renal failure, days of hospitalizations and death.

Covariates	Renal failure			Days of hospitalizations			Death		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Clinical pharmacologist consultation	1.7	0.3 - 4.6	0.4	3.77	1.3 - 6.4	**0.005**	0.73	0.31 - 1.71	0.6
Acceptance of clinical pharmacologist recommendation	−0.78	−14.59 - 13.03	0.9	4.88	−2.14 - 11.88	0.2	3.94	−4.94 - 12.82	0.4
Previous exposure to aminoglycosides	14.2	2.39 - 85.51	**0.004**				0.26	1.3 - 2.33	0.8
Amikacin courses on high dose	0.21	0.04 - 1.04	0.6	3.14	−0.87 - 7.12	0.1	0.25	0.08 - 10.2	0.82
Amikacin courses more than 5 days	0.36	0.08 - 1.51	**0.08**				0.07	0.4 - 2.45	0.87
Amikacin high serum TDM level	1.01	0.71 - 12.17	0.12	−0.02	−1.23 - 0.08	0.7	0.26	0.19 - 8.95	0.78
Renal failure				−3.94	−8.97 - 1.09	0.1	2.8	6.78 - 37.8	**<0.001**
Amikacin Adverse Effects (AAEs)				0.5	0.14 - 1.79	0.3	6.24	−4.88 - 17.35	0.2
Hemodynamic instability and sepsis*	31.3	2.89 - 336.99	**0.005**	8.59	3.49 - 18.5	**0.001**	2.5	2.05 - 38.65	**0.001**
Pneumonia	3.94	−4.94 - 12.82	0.38	9.2	6.06 - 12.25	**<0.001**	3.6	1.59 - 8.11	**0.002**
Use of cardiovascular drugs	4.8	1.33 - 17.52	**0.01**						
Number hospitalizations without fluids administration	0.22	0.48 - 176.62	0.14						

*Hemodynamic instability and sepsis: combination of hypotension, hypertension, bradycardia, tachycardia and sepsis; CI = confidence interval; OR = Odds Ratio.

(65 ± 14 vs 67 ± 16, p = 0.05) and in T3 discharge period (15% vs 7%, p = 0.01). However, when comparing all these variables during the whole study period the statistical differences between the groups disappeared. As for the variables of laboratory parameters, there were no differences between the groups.

Kidney function (Table 1; *Supplement* 2).

Kidney parameters such as creatinine and GFR calculated using three different equitation formulas at the three timepoints were not different. Kidney function per all three GFR calculations improved significantly in both groups prior to discharge. The instability of the renal function and the incidence of acute renal failure (ARF) per creatinine definition was more significant in AG1 than in AG2 on the first three days ((34 (24%)/30 (10%); p < 0.001) and (8 (6%) vs 6 (2%), p = 0.08)). On discharge only 6 (4%) patients in AG1 were with ARF (per creatinine) while in AG2 there were 33 (12%), p = 0.02. But all this differences disappeared in the groups, when comparing the whole study period. The fluctuation in the ARF development per GFR definition in all GFR equations was the same and did not differ in the both groups. About 14% of the patients have ARF during the whole study period and 10% of the patients were discharged with ARF in AG1 and AG2. On logistic regression analysis no relationship was found between renal failure and CP consultation (OR1.7, 95% CI: 0.3 - 4.6, p = 0.4). Even such variables as duration of amikacin therapy for more than 6 days (p = 0.06), large daily dose of amikacin and non-acceptances of CP recommendation were not associated with renal failure. But renal failure was associated with hemodynamic instability or sepsis (OR 31.3, 95% CI: 2.9 - 337, p = 0.005), the use of cardiovascular drugs (OR 4.8, 95% CI: 1.3 - 17.5, p = 0.01) and previous exposure to aminoglycosides (OR 14.2, 95% CI: 2.4 - 85.5, p = 0.004) (Table 2).

3.3. Amikacin Courses Characteristics (Table 3; Supplement 2)

Amikacin therapy began during the first three days of hospitalization for 70% of the patients, on the fourth up to the tenth day for 20% and during the following days of hospitalization for 10% of the patients in both groups. Total daily amikacin dose per patient in each group was about 9 - 10 mg/kg/day. For most patients amikacin therapy continued for 5 or less days. For 20% in AG1 and 13% in AG2 (p = 0.03) antibiotic therapy continued for more than 5 days. Therefore, AG1 was characterized with prolonged antibiotic courses (4.6 ± 1.5 vs 3.8 ± 1.6 days, p < 0.0001) and the larger total dose of amikacin per course (2709 ± 1256 vs 2327 ± 1181 mg, p < 0.002). More changes of the dose were made in AG1 than in AG2 (29% vs 20%, p = 0.03). The changed dose in AG1 decreased more significantly than that in AG2 (8.9 ± 2.7 vs 9.9 ± 4.2, mg/kg/day; p = 0.05). The doses that patients in AG1 and AG2 received in most cases were significantly smaller than those calculated by GFR level periods T1 and T2 (p < 0.0001). One-third of them received amikacin doses higher than the ones calculated by GFR which was not statistically different between the groups. Multivariable analysis showed no relationship between higher amikacin dose and CP consultation (OR 0.3, 95% CI: 0.1 - 1.5, p = 0.2) (Table 2).

Table 3. Amikacin course characteristics.

	AG1* (n = 140)	AG2* (n = 292)	P value
Days of hospitalization before starting amikacin course therapy.	4.7 ± 9.4	3.8 ± 6.4	0.2
Total days of amikacin course (N)	4.6 ± 1.5	3.8 ± 1.6	<0.0001
Total amikacin doses per course (mg)	2709 ± 1256	2327 ± 1181	0.002
mg/day (per 24 hours)	600 ± 220	624 ± 207	0.2
mg/kg/day (per 24 hours)	9 ± 3.3	9.4 ± 3.4	0.3
Number courses changed amikacin dose	41(29)	57(20)	0.03
The day of the course changed amikacin dose	3.8 ± 1.6	3.2 ± 1.5	0.07
Starting amikacin doses			
Number doses	3.5 ± 1.6	3.1 ± 1.5	0.02
Dose mg /day (per 24 hours)	648 ± 220	627 ± 197	0.7
Dose mg /kg/day (per 24 hours)	9.8 ± 3.4	10 ± 3.6	0.1
Changed amikacin dose			
Number doses	2.6 ± 1.4	2.8 ± 1.6	0.6
Dose mg /day (per 24 hours)	567 ± 172	616 ± 211	0.4
Dose mg /kg/day (per 24 hours)	9.2 ± 3.0	9.9 ± 4.2	0.05

Data are expressed as mean ± SD or number (%); *Amikacin Group with TDM drug consultation = AG1; Amikacin Group without TDM drug consultation = AG2.

3.4. Laboratory TDM (Supplement 2)

More patients in AG1 than in AG2 had either one or two serum amikacin samples collections (77 (55%) vs 109 (37%), p = 0.001; 20 (14%) vs 15 (5%), p = 0.002). Amikacin blood tests (first and second) were done much earlier in AG2 (1.9 ± 0.7; 4.4 ± 3.1 days) than in AG1 (2.9 ± 1.5; 5 ± 2 days) (p < 0.001). Amikacin level was much lower in the first tests in AG2 than in AG1 (18% vs 7%, p = 0.03). About 60% of patients in both groups had the level higher than normal and in 40% of these patients a second test was not collected. If it was collected the patients had both first and second amikacin level higher than normal (17% of AG1 vs 4% of AG2, p = 0.01).

In both groups, about one-third of patients with high TDM level stopped amikacin, the second third continued therapy without changing amikacin dose and for the last third, the dose was changed. Multivariable analysis showed no association between the high amikacin serum level and renal failure, other AAEs or death (Table 2).

3.5. CP Consultation Characteristic in AG1 (n = 140) (Table 4)

CP consultation in AG1was given on the 3.1 ± 1.5 day from the start of treatment or 1.5 ± 1.8 day before stopping amikacin. All patients received one consultation and 2% of them two consultations. In the 55 (39%) courses, amikacin dose or other management was appropriate, therefore there were no recommendations.

Table 4. Characteristics of clinical pharmacologist (CP) consultation.

Number patients with CP consultation (AG1)	n = 140
Day consultation after start Amikacin	3.1 ± 1.5
Day consultation before stop Amikacin	1.5 ± 1.8
Number patients with two CP consultations	3 (2)
Number CP consultation with recommendation to change Amikacin dose or other management:	85 (61)
Recommendation was accepted	39
Recommendation was NOT accepted	46
Number courses with changed Amikacin dose:	41 (48)
Dose changes after CP consultation	26
Total Number of course with TDM tests:	77 (55)
Test done before CP consultation (*single or first*)	41
Test done after CP consultation (*single or first*)	36
Number patients with two TDM laboratory tests:	20 (14)
Second Blood test done before CP consultation	2
Second Blood test done after CP consultation	18

Data are expressed as mean ± SD or number (%).

In the remaining 85 amikacin courses the CP recommended to change amikacin dose or to do other therapeutic management. These recommendations were accepted in 39 (46%) of them. The amikacin doses changes were made in 41 (48%) of these 85 courses. In 26 (63%) of this 41 courses the changes were made after CP consultation and in 15 (37%) by a physician himself.

Comparing the CP recommended dose (617 ± 204 mg/day, 9.2 ± 3.1 mg/kg/day) with a starting dose (648 ± 220 mg/day, 9.8 ± 3.4 mg/kg/day) and a changed dose (567 ± 172 mg/day, 9.2 ± 3 mg/kg/day), did not lead to statistic differences.

As to the TDM tests of AG1 (n = 77), half of them were done after CP consultation. Twenty courses of AG1 had two TDM tests, the second TDM test being done in 90% after CP consultation.

3.6. Risk Factors of Amikacin Toxicity and AAEs. (Table 5, Supplement 2)

Risk factors in AG1 and AG2 were the same, except for three factors in AG1: prolonged antibiotic therapy (22% vs 13%, p = 0.02), elevated Amikacin serum trough level (36% vs 20%, p = 0.001) and combination therapy with Vancomycin (10% vs 3%, p = 0.07). AAEs were found more in patients of AG1 where recommendations were not accepted (18 (45%)/9 (3%), p = 0.03). Logistic regressions analysis did not detect statistic relationship between AAEs and CP consultation, non-acceptance of CP recommendation, amikacin treatment for more than 6 days, elevated amikacin trough serum levels, previous exposure to aminoglycosides and high amikacin doses (Table 2).

Table 5. Major risk factors for development of amikacin toxicity.

Factors related to Amikacin toxicity		AG1* (n = 140)	AG2* (n = 292)	P value
Duration of Amikacin treatment (≥6 days)		31 (22)	38 (13)	0.02
High Amikacin dose **		47 (34)	102 (35)	0.8
Sepsis		18 (13)	39 (13)	1.0
Septic shock or Hypotension		29 (21)	58 (20)	0.1
Age	70 - 80 years	32 (23)	66(23)	1.0
	81 - 90 years	59 (42)	130(46)	0.7
	>90 years	25 (18)	47(16)	0.7
Dehydration (and nausea/vomiting)		6 (4)	12 (4)	0.6
Elevated Amikacin trough serum level		50 (36)	61 (21)	0.001
Previous exposure to aminoglycosides (recurrent therapy)***:				
During one year before hospitalization		37 (29)	75 (28)	0.9
During study period recurrent course		12 (9.3)	28 (10.2)	0.9
Number of hospitalizations without fluids administration		25 (18)	58 (20)	0.7
Concomitant medications[1]:				
Vancomycin		8 (6)	13 (4.5)	0.7
NSAIDS		-	2 (0.7)	1.0
ACE and ARBs		58 (41)	118 (40)	0.4
Diuretics:		57 (41)	107 (37)	0.5
Furosemide		46	92	0.8
Hypertension (without diuretics, ACE\ARBs)		72 (51)	135 (46)	0.4
Antiarrhythmic (without CCB\BB):		8 (6)	23 (8)	0.6
Digoxin		6	15	0.8
Chemotherapy		1 (0.7)	0	0.3
Ears disorders per history		6 (4)	16 (6)	0.9
Obesity per history		20 (14)	46 (16)	0.6

Data are expressed as number (%); ACE—Angiotensin-converting enzyme inhibitors, ARBs—Angiotensin receptor blockers, BB—Beta Blockers, CCB—Calcium channel blockers, NSAIDs—Nonsteroidal anti-inflammatory drugs. *Amikacin Group with therapeutic drug monitoring (TDM) drug consultation = AG1; Amikacin Group without therapeutic drug monitoring (TDM) drug consultation = AG2. **High Amikacin dose = patient amikacin dose was more than ≥50 mg/day, as a differences between patient's study dose and calculated patient's dose per one of three calculated GFRs. ***Number patients received more than one courses therapy, during one year before hospitalization and patients how received amikacin twice or more during study period. Calculation percentage from number of patients (140 courses = 128 patients of AG1; 292 courses = 265 patients of AG2). [1]Concomitant medication: chronic medication or medication during hospitalization or both, total number of courses.

4. Discussion

Precision in dosing amikacin is a multifaceted process that requires an understanding of prescribing practices. Intervention of clinical pharmacology unit in the TDM audition has been shown to improve the antibiotics use and patient's outcome [1]-[6]. But the busy hospital environment and difficult clinical situations have been postulated to contribute to the poor compliance with the amikacin guidelines [14] [15]. Therefore, we are bringing our results for discussion.

4.1. General Patients Characteristics

Our population consists of frail older patients with a multiple number of chronic diseases and severe polypharmacy, a high percent of them being women. All this increases the risk of prolonged hospitalization, multiple courses of antibiotic therapy and mortality [17] [18] [19]. In our cohort the main active infection for amikacin use was UTI (90%) and all these patients had about three additional active diseases. The amikacin group with CP consultation (AG1) was characterized by presence of pneumonia ($p = 0.002$) in addition to UTI, prolonged hospitalization ($p = 0.02$) and low diastolic pressure ($p = 0.01$). Previous aminoglycosides studies demonstrated, that hospitalization was shorter for patients who underwent guided TDM [6] [7] [8] [9] [20], but this was not the case in our study.

Renal function is a main parameter for selecting the amikacin dose in patients with decreased renal function, especially in the elder patients [20]. Half of our patients in both groups had GFR less than 50 mL/minute on admission by Cockroft/Gault equation and about one third of them by other equations. The definition of renal failure is relative taking into account the age and the creatinine level, which is generally low in the elderly [21] [22] [23]. So, we added another parameter such as unstable renal function. We found that AG1 patients had unstable renal function ($p = 0.0002$) on admission, while patients in AG2 developed more acute renal failure by creatinine definition on discharge (6 (4); 33 (12), $p = 0.02$) (Supplement 2). But the statistic difference was non-significant in the whole study period may be because of the fluctuations of creatinine during AG1 prolonged hospitalization. The renal failure was more frequent in patients with previous exposure to aminoglycosides (OR 14.2, 95% CI: 2.4 - 85.5, $p = 0.004$). Taking into account the AG1 patients' instability during prolonged amikacin therapy and hospitalization, we found out that there was no increasing in the rate of mortality and AAEs in AG1 compared with amikacin group that did not receive CP consultation (AG2). As a result, CP consultation did not lead to the deterioration in the outcomes in of frail older complex unstable patients during prolonged hospitalization.

4.2. Amikacin Courses Characteristics

Amikacin dose was not different in the two study groups. We think that one of the main factors for this is that the TDM consultations in our hospital have been given since 2004 till today, therefore, physicians use their acquired knowledge and experience for selecting the correct dose. Amikacin therapy in AG1 was characterized by longer duration ($p < 0.0001$), larger total dose per patient ($p < 0.0002$) and the dose changes were more frequent in this group rather than in AG2 (29% vs 20%, $p = 0.03$). The second amikacin dose in AG1 was smaller than the first one and this decrease was more significant for AG1 that for AG2 (8.9 ± 2.7 vs 9.9 ± 4.2, mg/kg/day; $p = 0.05$). Comparing patient's doses and GFR guided doses, we can see that the former were lower than the latter ($p < 0.001$) in both groups. The second GFR guided dose in most cases must be bigger than the

first one, because of the GFR improvement during hospitalization, but the patient second dose was smaller than the first one. It is a known fact in the studies that aminoglycosides doses in the real time are much lower than the GFR guided doses [24] [25] [26]. In these studies, most patients were critically ill, not very old and had a very short duration of aminoglycoside therapy. In our study, only 20 % of the patients were critically ill, more than 80% of them were very old (83 years old) and duration of aminoglycoside therapy was longer than 3 days. An expression "start low, go slow" is generally accepted for geriatric patients and is not accepted for therapy of serious infections [27]. We think that it may be correct in infectious disease of geriatric population, who are not critically ill and in need of intravenous antibiotic therapy. For this rule to work, we must use CP TDM consultation for improving efficacy of the hospitalization and preventing AAEs. Other factors for use of low amikacin dose may be the lack of homogeneity in the GFR guided doses (in the different pharmaceutical sites for the borderline of GFR for every ten after 60 ml\min (Supplement 1)) and that the GFR is a relative parameter for elderly patients, therefore in practice the physicians generally use a decreased dose. So, the CP TDM consultation is recommended for the rightly corrected amikacin doses.

4.3. Laboratory Amikacin TDM

The main goal of TDM is the optimization of amikacin dosage, through maintaining blood drug concentrations within a therapeutic range. The regular TDM serum level of amikacin is not necessary to be performed in every patient, if the patient is clinically stable and the dose is safely effective [6]. In our cohort TDM serum samples were done more in AG1 (55%) than in AG2 (37%) ($p = 0.001$) and the TDM blood collections were done significantly earlier in AG2 than in AG1 ($p < 0.001$) and the first test was significantly lower in AG2 than in AG1 ($p = 0.03$). About 60% of patients have first or second amikacin levels higher than normal in both groups, but only patients in AG1 have both amikacin levels higher (17% vs 4%; $p = 0.01$). Those results showed us that patients in AG1 were more unstable and did not increase AAE, so TDM evaluation and CP audition are required as an assistance in choosing correct dosage and therapeutic strategy.

In our study amikacin management according to TDM level, was the same in the two groups. The blood TDM therapeutic range is generally used as a guide for choosing the optimal dose for a patient on amikacin therapy, but this range cannot be considered as an absolute one. The positive drug effect can be evident even in case where the serum concentration is too low or too high, without any symptoms of therapy failure or toxicity. Whereas toxic effects could appear even if the drug serum concentration is low or within therapeutic range. Hence, dosing of drug should be guided together by serum drug concentration, clinical response and CP TDM consultations, which help make the right decision.

4.4. CP consultation characteristics of AG1

CP intervention was in 32% of amikacin courses only. In 55 (39%) of CP con-

sultations the amikacin dose was appropriated, therefore there were no recommendations to make any dose changes or other interventions. Generally, if a dose is correct and a patient is stable, we do not recommend any dose management or collection of TDM test. We do recommend observing patient's renal or hemodynamic function and doing TDM test in case the patient is clinically unstable or in accordance with laboratory tests and if he received therapy for more than five days.

For example, in a survey-conducted study in French healthcare facilities the compliance with aminoglycoside guideline by dose was up to 60% and by therapy duration up to 90% of the patients [28]. In our study the CP recommendations were accepted only for 46% of the 85 AG1 courses needing intervention. There are some reasons why accepting the suggestion was not followed, in case when the treatment optimization suggestions might have been forgotten by the medical resident, a validation by his supervisor might have been required if the supervisor was not present during medical rounds or the clinical state of the patient was stable. In addition, because the aminoglycoside therapy is a short course for most patients, the decision for optimization of therapy must be fast and should be done on the day requiring optimization therapy.

The acceptance rate of the interventions by all clinical specialists (except CP specialist) asked for consultation, can be up to 90%. However, the outcome of the interventions by the CP specialist asked for consultation may be accepted in 50% to 98 % of the patient's consultation [29] [30] [31]. What is interesting is that, in all of these studies TDM consultation was given by clinical pharmacy specialist, because in most hospitals this consultation is given by clinical pharmacist. While in our study the consultation was given by a clinical pharmacologist. We did not find similar studies for comparison, but we found that the rate of acceptance of TDM recommendation was not increased in spite of the fact that it was given by clinical pharmacologist. In the 63% of the amikacin courses the dose changes and in the 47% of the amikacin courses the TDM serum level were found after CP consultation, that is not so bad at all. When comparing the CP recommended dose with the patient's dose the difference was not significant. The decision of the physicians to optimize the dose is based on their experience and on patient's clinical characteristics. Therefore, in some cases the dose may stay unchanged, in others there may be early discontinuation of amikacin and in still others the optimized dose may be smaller than the recommended dose. Under dosing of amikacin has been observed previously, however, the reasons for this remain unclear. It may be based on the clinical experience of prescribers or the concern for well-known amikacin toxicity [8] [31] [32] [33] [34]. Neither did our study make these reasons clear, which requires further clinical prospective studies and improvement of TDM hospital education.

4.5. Risk Factors of Toxicity and Amikacin Adverse Effects (AAE)

The major factors of amikacin toxicity are well known. Using pharmacokinetic dose calculation can reduce the risk of adverse effects, mainly nephrotoxicity, by

preventing administration of a high cumulative dose [8]. Our analysis found out that most risk factors of toxicity were the same in both groups, except for the prolonged antibiotic therapy (22% vs 13%, p = 0.02), the high Amikacin serum trough level (36% vs 20%, p = 0.001) and the combination with Vancomycintherapy (10% vs 3%, p = 0.07) which were more significant in AG1 than in AG2. In spite of that the incidence of AAE did not increase.

It is important that the patients, for whom CP recommendations were accepted developed less AAE than those for whom the recommendations were not accepted (p = 0.03), but logistic regression analysis found difficult to show this association, may be because of the small number of the patients in this group.

The reported incidence of nephrotoxicity varies widely due to variations in study design, toxicity definition, studies' population and concomitant risk factors. So, the reasonable estimate of renal toxicity might be found in 10 to 20% of the patients receiving amikacin, in spite of careful study patient selection and close toxicity monitoring [34]. The incidence of renal failure in our study was as frequent as in other studies (about 15% in both groups), not less than that, requires improvement of the CP intervention and the acceptance for CP recommendations. Taking into account that intervention in old complex patients must be early and recurrent.

5. Conclusions

We did not succeed in showing that intervention of the CP in amikacin appropriateness could decrease AAE, days of hospitalization or mortality. We did show that the CP TDM consultations were helpful in cases of complicated clinical situations in old complex patients with prolonged hospitalization.

For improvement of CP TDM consultations and their acceptance, it is necessary to do some interventions. The first is to improve a physicians' TDM education, an accent on amikacin appropriate dose calculation and practical use of drug laboratory monitoring. The second is to increase CP TDM intervention in old-complex patients with pneumonia, hemodynamic instability, history of previous exposure to aminoglycosides, inappropriate drug levels or dose and with the potential of prolonged amikacin course and hospitalization.

6. Limitations

We did not include in the study, what is done routinely for all patients, which is microbiological patient's analysis and dose calculation within MIC susceptibility. This study is retrospective so AAE are not well documented in the electronic data, especially with regard to toxicity. General parameters such as laboratory analysis and hemodynamic status in some patients did not correlate directly with days of amikacin therapy, however if these parameters were correlated, it did not change study conclusion. Another parameter that was not included in the study is dosage of concomitant medications.

So, for achieving more successful results we need to plan the prospective study

having chosen the non-interventional group in same other hospital without clinical pharmacologist or clinical pharmacy TDM service.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Rawson, T.M., Wilson, R.C., O'Hare, D., Herrero, P., Kambugu, A., Lamorde, M., Ellington, M., Georgiou, P., Cass, A., Hope, W.W. and Holmes, A.H. (2021) Optimizing Antimicrobial Use: Challenges, Advances and Opportunities. *Nature Reviews Microbiology*, **19**, 747-758. https://doi.org/10.1038/s41579-021-00578-9

[2] Arulkumaran, N., Routledge, M., Schlebusch, S., Lipman, J. and Morris A.C. (2020) Antimicrobial-Associated Harm in Critical Care: A Narrative Review. *Intensive Care Medicine*, **46**, 225-235. https://doi.org/10.1007/s00134-020-05929-3

[3] Ried, L.D., McKenna, D.A. and Horn, J.R. (1989) Meta-Analysis of Research on the Effect of Clinical Pharmacokinetics Services on Therapeutic Drug Monitoring. *American Journal of Health-System Pharmacy*, **46**, 945-51. https://doi.org/10.1093/ajhp/46.5.945

[4] Koren, G., Soldin, S.J. and MacLeod, S.M. (1985) Organization and Efficacy of a Therapeutic Drug Monitoring Consultation Service in a Pediatric Hospital. *Therapeutic Drug Monitoring*, **7**, 295-298. https://doi.org/10.1097/00007691-198507030-00010

[5] Tonkin, A.L. and Bochner, F. (1994) Therapeutic Drug Monitoring and Outcome. A Review of the Issues. *Clinical Pharmacokinetics*, **27**, 169-174. https://doi.org/10.2165/00003088-199427030-00001

[6] Zahar, J.-R., Rioux, C., Girou, E., Hulin, A., Sauve, C., Bernier-Combes, A., Brun-Buisson, C. and Lesprit P. (2006) Inappropriate Prescribing of Aminoglycosides: Risk Factors and Impact of an Antibiotic Control Team. *Journal of Antimicrobial Chemotherapy*, **58**, 651-656. https://doi.org/10.1093/jac/dkl288

[7] van Lent-Evers, N.A., Mathôt, R.A., Geus, W.P., van Hout, B.A. and Vinks, A.A. (1999) Impact of Goal-Oriented and Model-Based Clinical Pharmacokinetic Dosing of Aminoglycosides on Clinical Outcome: A Cost-Effectiveness Analysis. *Therapeutic Drug Monitoring*, **21**, 63-73. https://doi.org/10.1097/00007691-199902000-00010

[8] Bartal, C., Danon, A., Schlaeffer, F., Reisenberg, K., Alkan, M., Smoliakov, R., Sidi, A. and Almog, Y. (2003) Pharmacokinetic Dosing of Aminoglycosides: A Controlled Trial. *The American Journal of Medicine*, **114**, 194-198. https://doi.org/10.1016/S0002-9343(02)01476-6

[9] Kovačević, T., Avram, S., Milaković, D., Špirić, N. and Kovačević, P. (2016) Therapeutic Monitoring of Amikacin and Gentamicin in Critically and Noncritically Ill Patients. *Journal of Basic and Clinical Pharmacy*, **7**, 65-69. https://doi.org/10.4103/0976-0105.183260

[10] Roberts, J.A., Norris, R., Paterson, D.L. and Martin, J.H. (2012) Therapeutic Drug Monitoring of Antimicrobials. *British Journal of Clinical Pharmacology*, **73**, 27-36. https://doi.org/10.1111/j.1365-2125.2011.04080.x

[11] Avent, M.L., Rogers, B.A., Cheng, A.C. and Paterson, D.L. (2011) Current Use of Aminoglycosides: Indications, Pharmacokinetics and Monitoring for Toxicity. *Internal Medicine Journal*, **41**, 441-449.

https://doi.org/10.1111/j.1445-5994.2011.02452.x

[12] Streetman, D.S., Nafziger, A.N., Destache, C.J. and Bertino Jr., A.S. (2001) Individualized Pharmacokinetic Monitoring Results in less Aminoglycoside-Associated Nephrotoxicity and Fewer Associated Costs. *Pharmacotherapy*, **21**, 443-451. https://doi.org/10.1592/phco.21.5.443.34490

[13] Delattre, I.K., Musuamba, F.T., Nyberg, J., Taccone, F.S., Laterre, P.F., Verbeeck, R.K., Jacobs, F. and Wallemacq, P.E. (2010) Population Pharmacokinetic Modeling and Optimal Sampling Strategy for Bayesian Estimation of Amikacin Exposure in Critically Ill Septic Patients. *Therapeutic Drug Monitoring*, **32**, 749-756. https://doi.org/10.1097/FTD.0b013e3181f675c2

[14] Cox, Z.L., Nelsen, C.L., Waitman, L.R., McCoy, J.A. and Peterson, J.F. (2011) Effects of Clinical Decision Support on Initial Dosing and Monitoring of Tobramycin and Amikacin. *American Journal of Health-System Pharmacy*, **68**, 624-632. https://doi.org/10.2146/ajhp100155

[15] Yager, R.C., Taylor, N., Stocker, S.L., Day, R.O., Baysari, M.T. and Carland, J.E. (2022) Would they Accept it? An Interview Study to Identify Barriers and Facilitators to User Acceptance of a Prescribing Advice Service. *BMC Health Services Research*, **22**, Article No. 514. https://doi.org/10.1186/s12913-022-07927-1

[16] Pierrat, A., Gravier, E., Saunders, C., Caira, M.V., Aït-Djafer, Z., Legras, B. and Mallié, J.P. (2003) Predicting GFR in Children and Adults: A Comparison of the Cockcroft—Gault, Schwartz, and Modification of Diet in Renal Disease Formulas. *Kidney International*, **64**, 1425-1436. https://doi.org/10.1046/j.1523-1755.2003.00208.x

[17] Eliakim-Raz, N., Babitch, T., Shaw, E., Addy, I., Wiegand, I., Vank, C., Torre-Vallejo, L., Joan-Miquel, V., Steve, M., Grier, S., Stoddart, M., Nienke, C., Leo, V.D.H., Vuong, C., MacGowan, A., Carratalà, J., Leibovici, L., Pujol, M. and RESCUING Study Group. (2019) Risk Factors for Treatment Failure and Mortality among Hospitalized Patients with Complicated Urinary Tract Infection: A Multicenter Retrospective Cohort Study (RESCUING Study Group). *Clinical Infectious Diseases*, **68**, 29-36. https://doi.org/10.1093/cid/ciy418

[18] Gharbi, M., Drysdale, J.H., Lishman, H., Goudie, R., Molokhia, M., Johnson, A.P., Holmes, A.H. and Aylin, P. (2019) Antibiotic Management of Urinary Tract Infection in Elderly Patients in Primary Care and its Association with Bloodstream Infections and All Cause Mortality: Population Based Cohort Study. *The BMJ*, **364**, Article 364:l525. https://doi.org/10.1136/bmj.l525

[19] Kovesdy, C.P., Bleyer, A.J., Molnar, M.Z., Ma, J.Z., Sim, J.J., Cushman, W.C., Quarles, L.D. and Kalantar-Zadeh, K. (2013) Blood Pressure and Mortality in U.S. Veterans with Chronic Kidney Disease: A Cohort Study. *Annals of Internal Medicine*, **159**, 233-242. https://doi.org/10.7326/0003-4819-159-4-201308200-00004

[20] Crist, K.D., Nahata, M.C. and Ety, J. (1987) Positive Impact of a Therapeutic Drug—Monitoring Program on Total Aminoglycoside Dose and Cost of Hospitalization. *Therapeutic Drug Monitoring*, **9**, 306-310. https://doi.org/10.1097/00007691-198709000-00010

[21] Matzke, G.R., Aronoff, G.R., Atkinson Jr., A.J., Bennett, W.M., Decker, B.S., Eckardt, K.U., Golper, T., Grabe, D.W., Kasiske, B., Keller, F., Kielstein, J.T., Mehta, R., Mueller, B.A., Pasko, D.A., Schaefer, F., Sica, D.A., Inker, L.A., Umans, J.G. and Murray, P. (2011) Drug Dosing Consideration in Patients with Acute and Chronic Kidney Disease—A Clinical Update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney International*, **80**, 1122-1137. https://doi.org/10.1038/ki.2011.322

[22] Ostermann, M., Bellomo, R., Burdmann, E.A., Doi, K., Endre, Z.H., Goldstein, S.L.,

Kane-Gill, S.L., Liu, K.D., Prowle, J.R., Shaw, A.D., Srisawat, N., Cheung, M., Jadoul, M., Winkelmayer, W.C., Kellum, J.A. and Conference Participants. (2020) Controversies in Acute Kidney Injury: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. *Kidney International*, **98**, 294-309. https://doi.org/10.1016/j.kint.2020.04.020

[23] Clinical Practical Guideline for Acute Kidney Injury. http://www.kdigo.org/clinical_practice_guidelines/AKI.php.

[24] Jenkins, A., Thomson, A.H., Brown, N.M., Semple, Y., Sluman, C., MacGowan, A., Lovering, A.M. and Wiffen, P.J. (2016) Amikacin Use and Therapeutic Drug Monitoring in Adults: Do Dose Regimens and Drug Exposures Affect either Outcome or Adverse Events? A Systematic Review. *Journal of Antimicrobial Chemotherapy*, **71**, 2754-2759. https://doi.org/10.1093/jac/dkw250

[25] Ryan, A.C., Carland, J.E., McLeay, R.C., Lau, C., Marriott, D.J.E., Day, R.O. and Stocker, S.L. (2021) Evaluation of Amikacin Use and Comparison of the Models Implemented in Two Bayesian Forecasting Software Packages to Guide Dosing. *British Journal of Clinical Pharmacology*, **87**, 1422-1431. https://doi.org/10.1111/bcp.14542

[26] Fraisse, T., Gras, Aygon. C., Paccalin, M., Vitrat, V., De, Wazieres. B., Baudoux, V., Lechiche, C., Vicens, A., Sotto, A., Pagani, L., Gaillat, J., Forestier, E. and Gavazzi, G. (2014) Aminoglycosides Use in Patients Over 75 Years Old. *Age and Ageing*, **43**, 676-681. https://doi.org/10.1093/ageing/afu023

[27] High, K.P. (2017) Infection: General Principles. In: Halter, J.B., Ouslander, J.G., Studenski, S., High, K.P., Asthana, S., Supiano, M.A., Ritchie, C., Eds., *Hazzard's Geriatric Medicine and Gerontology*,

[28] Robert, J., Péan, Y., Alfandari, S., Bru, J.P., Bedos, J.P., Rabaud, C., Gauzit, R., Société de PathologieInfectieuse de Langue Française (SPILF), the Observatoire National de l'Epidémiologie de la Résistance Bactérienne aux Antibiotiques (ONERBA) and the Surveillance de la Prescription des Antibiotiques (SPA) group. (2017) Application of Guidelines for Aminoglycosides Use in French Hospitals in 2013-2014. *European Journal of Clinical Microbiology & Infectious Diseases*, **36**, 1083-1090. https://doi.org/10.1007/s10096-016-2892-5

[29] Janković, S.M., Milovanović, D., Zečević, D.R., Folić, M., Rosić, N. and Vulović, D. (2016) Consulting Clinical Pharmacologist about Treatment of Inpatients in a Tertiary Hospital in Serbia. *European Journal of Clinical Pharmacology*, **72**, 1541-1543. https://doi.org/10.1007/s00228-016-2141-y

[30] Guignard, B., Bonnabry, P., Perrier, A., Dayer, P., Desmeules, J. and Samer, C.F. (2015) Drug-Related Problems Identification in General Internal Medicine: The Impact and Role of the Clinical Pharmacist and Pharmacologist. *European Journal of Internal Medicine*, **26**, 399-406. https://doi.org/10.1016/j.ejim.2015.05.012

[31] Mas-Morey, P., Ballesteros-Fernández A, Sanmartin-Mestre E and Valle M. (2018) Impact of Clinical Pharmacist Intervention on Antimicrobial Use in a Small 164-Bed Hospital. *European Journal of Hospital Pharmacy*, **25**, e46-e51. https://doi.org/10.1136/ejhpharm-2017-001307

[32] Tabah, A., De Waele, J., Lipman, J., Zahar, J.R., Cotta, M.O., Barton, G., Timsit, J.F., Roberts, J.A. and Working Group for Antimicrobial Use in the ICU within the Infection Section of the European Society of Intensive Care Medicine (ESICM). (2015) The ADMIN-ICU Survey: A Survey on Antimicrobial Dosing and Monitoring in ICUs. *Journal of Antimicrobial Chemotherapy*, Sep; **70**, 2671-2677. https://doi.org/10.1093/jac/dkv165

[33] Roger, C., Nucci, B., Molinari, N., Bastide, S., Saissi, G., Pradel, G., Barbar, S., Aubert, C., Lloret, S., Elotmani, L., Polge, A., Lefrant, J.Y., Roberts, J.A. and Muller, L.

(2015) Standard Dosing of Amikacin and Gentamicin in Critically Ill Patients Results in Variable and Subtherapeutic Concentrations. *International Journal of Antimicrobial Agents*, **46**, 21-27. https://doi.org/10.1016/j.ijantimicag.2015.02.009

[34] Wargo, K.A. and Edwards, J.D. (2014) Aminoglycoside—Induced Nephrotoxicity. *Journal of Pharmacy Practice*, **27**, 573-577. https://doi.org/10.1177/0897190014546836

Supplement

https://drive.google.com/file/d/1fRMCTaf_lm53325oRwZPL3KpSjBLs2m9/view?usp=sharing