ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES SCHOOL OF MEDICINE

DEPARTMENT OF PEDIATRICS AND CHILD HEALTH

# TITLE: MAGNITUDE AND FACTORS ASSOCIATED WITH AUGMENTED RENAL CLEARANCE AND PRACTICE OF ANTIMICROBIAL PRESCRIPTION IN PEDIATRIC INTENSIVE CARE UNITS AMONG CHILDREN ADMITTED TO TASH AND ALERT CENTER

BY

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A RESEARCH THESIS TO BE SUBMITTED TO TIKUR ANBESSA SPECIALIZED HOSPITAL, DEPARTMENT OF PEDIATRICS AND CHILD HEALTH IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR FELLOWSHIP PROGRAM IN PEDIATRIC INFECTIOUS DISEASES

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RESEARCH THESIS

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## ABSTRACT

**Background** Augmented renal clearance (ARC) refers to a condition where there is an increased elimination of renal solutes, presenting notable challenges in the Pediatric Intensive Care Unit (PICU). This phenomenon can have a significant impact on various aspects of patient care, such as medication dosing, treatment effectiveness, and overall clinical outcomes.
In clinical practice, managing ARC necessitates close monitoring and individualized approaches tailored to each patient's unique renal status. ARC is associated with suboptimal exposure to critical medications, particularly hydrophilic antibiotics including ß-lactams, Vancomycin, Aminoglycosides leading to treatment failure and development of resistance. Mechanisms for ARC in critically ill patients are incompletely defined. Aggressive fluid resuscitation, presence of SIRS, capillary leak, use of vasopressors and inotropes, neuro hormonal changes, activation of renal functional reserve in young individuals lead to increase in renal perfusion and increase in GFR

**Methods** We conducted a prospective Follow up cross sectional study on patients admitted PICUs of two tertiary hospitals in Addis Ababa from July 2024-December 2024 . ARCwas assessed by measuring serum creatinine levels and calculating estimated glomerular filtration rate (eGFR) using the modified Schwartz formula during the first three days of PICU admission. Correlation analysis was done to assess conditions associated with ARC. Mann witney U test, independent samples t-test and one way ANOVA tests were done to compare different variables in relation to ARC.Logistic regression analysis was used to determine risk factors for ARC and deathat day7 of PICU admission.

**Results** This retrospective study examined the incidence and associated factors of augmented renal clearance (ARC) among 170 pediatric patients admitted to the Pediatric Intensive Care Units (PICUs) of two hospitals: TASH and ALERT. The cohort comprised 105 males and 65 females, with 108 patients admitted to TASH and 62 to ALERT. During the first three days of PICU admission, 66 patients (38.8%) experienced at least one documented episode of ARC. Of 438 serum creatinine measurements, 112 were indicative of ARC.Patients experiencing ARC exhibited a median estimated glomerular filtration rate (eGFR) that increased over the first three days of PICU admission: 108.59 mL/min/1.73m² on day one, 115.8 mL/min/1.73m² on day two, and 185.9 mL/min/1.73m² on day three. A statistically significant positive correlation was observed between eGFR and total fluid input on day one. Furthermore, specific diagnoses including febrile neutropenia, brain tumors, and admissions for surgical interventions were significantly associated with the occurrence of ARC.A Mann-Whitney U test revealed that patients without any record of ARC within the initial three days demonstrated significantly lower values for age, weight, height, and body surface area (BSA) compared to those with ARC. Older age, greater BSA, and the presence of febrile neutropenia, hematologic malignancies, brain tumors, and admission for surgical reasons were each independently associated with an elevated risk of ARC. Furthermore, higher PHOENIX scores, vasopressor use, hypotension and febrile neutropenia were associated with increased mortality by day seven of PICU admission.

**Conclusion** The magnitude of ARC in our setting  is high .Early recognition and dosing adjustments can improve outcomes in critically ill pediatric patients. Factors like age and laboratory markers influence ARC development, emphasizing the need for routine monitoring in high-risk groups. Personalized medicine is crucial in PICU care, with potential for future studies on dosing algorithms and risk factors. Clinical guidelines based on these findings can enhance care for vulnerable patients.

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## ABBREVIATION AND ACRONYMS

| | |
|---|---|
| ALERT | All Africa Leprosy TB Rehabilitation and Training Center |
| ARC | Augmented Renal Clearance |
| APACHE II score | Acute Physiology and Chronic Health Evaluation II score |
| AUC | Area Under the Curve |
| CKD | Chronic Kidney Disease |
| $C_{max}$ | Maximum Concentration |
| CrCl | Creatinin Clearance |
| C-RP | C- Reactive Protein |
| FIo2 | Fraction of Inspired Oxygen |
| *f*T >MIC | Function of Time above Minimum Inhibitory Concentration |
| GCS | Glasgow Coma Scale |
| eGFR | Estimated Glomerular Filtration Rate |
| GFR | Glomerular Filtration Rate |
| HAP-VAP | Hospital Acquired Pneumonia- Ventillator Associated Pneumoniae |
| HIV | Human Immunodeficiency Virus |
| IMV | Invasive Mechanical Ventilation |
| INR | International Normalized Ratio |
| IV | Intravenous |
| KDIGO | Kidney Disease Improving Global Outcomes |
| MDR | Multi Drug Resistant |
| MIC | Minimum Inhibitory Concentration |
| MSSA | Methicillin Sensitive Staphylococcus Aureus |
| Pao2 | Arterial Pressure of Oxygen |
| PICU | Pediatric Intensive Care Unit |
| PK/PD | Pharmacokinetics/Pharmocodynamics |
| SIRS | Systemic Inflammatory Response Syndrome |
| SOFA | Sequential Organ failure Assessement |
| Spo2 | Oxygen Saturation measured by pulse oxymetry |
| SPSS | Statistical Package for Social Science |
| TASH | Tikur Anbessa Specialized Hospital |

# Introduction

## Background

In critically ill patients, Acute Kidney Injury (AKI) is a common concern that healthcare professionals often consider. However, recent studies have shed light on the phenomenon of supra physiologic renal clearance in this particular patient population. This unexpected finding has sparked discussions and further research into the underlying mechanisms and implications for patient care. (1)

Moreover, the rise in multidrug-resistant (MDR) bacterial infections poses a significant challenge in healthcare settings. Pharmacokinetic/pharmacodynamic (PK/PD) factors have emerged as crucial determinants in the development of antimicrobial resistance. For example, inadequate dosing of antibiotics due to poor understanding of PK/PD principles can inadvertently promote the selection of resistant bacterial strains. Recognizing the importance of optimizing antibiotic regimens based on PK/PD considerations is paramount in combating the growing threat of MDR infections. (2).

Augmented renal clearance (ARC) refers to a condition where there is an increased elimination of renal solutes, presenting notable challenges in the Pediatric Intensive Care Unit (PICU). This phenomenon can have a significant impact on various aspects of patient care, such as medication dosing, treatment effectiveness, and overall clinical outcomes. Despite its importance, there is a lack of consensus, especially in the pediatric population, regarding the exact definition of ARC. In the majority of studies, ARC is characterized by a creatinine clearance (CrCl) exceeding 130 mL/min/1.73 $m^2$.

To further elaborate, consider an observational study conducted in children, which defined ARC as a measured glomerular filtration rate (GFR) surpassing 20% of the upper limit of normal values. This highlights the variability in defining ARC across different age groups and settings. The implications of ARC extend beyond mere numbers, as it requires clinicians to carefully adjust medication doses and treatment strategies to accommodate the enhanced renal function observed in these patients.

In clinical practice, managing ARC necessitates close monitoring and individualized approaches tailored to each patient's unique renal status. This underscores the importance of ongoing assessment and adjustment in the PICU setting to optimize care delivery and promote favorable patient responses. By addressing the complexities of ARC through comprehensive evaluation and tailored interventions, healthcare providers can navigate this phenomenon effectively and enhance the overall quality of care for pediatric patients.

Another study involving critically ill children in PICU defined ARC as GFR exceeding two SD above upper limit of normal for age (3)**.**

ARC is associated with suboptimal exposure to critical medications, particularly hydrophilic antibiotics including ß-lactams, Vancomycin, Aminoglycosides leading to treatment failure and development of resistance. Mechanisms for ARC in critically ill patients are incompletely defined. Aggressive fluid resuscitation, presence of SIRS, capillary leak, use of vasopressors and

inotropes, neuro hormonal changes, activation of renal functional reserve in young individuals lead to increase in renal perfusion and increase in GFR (4).

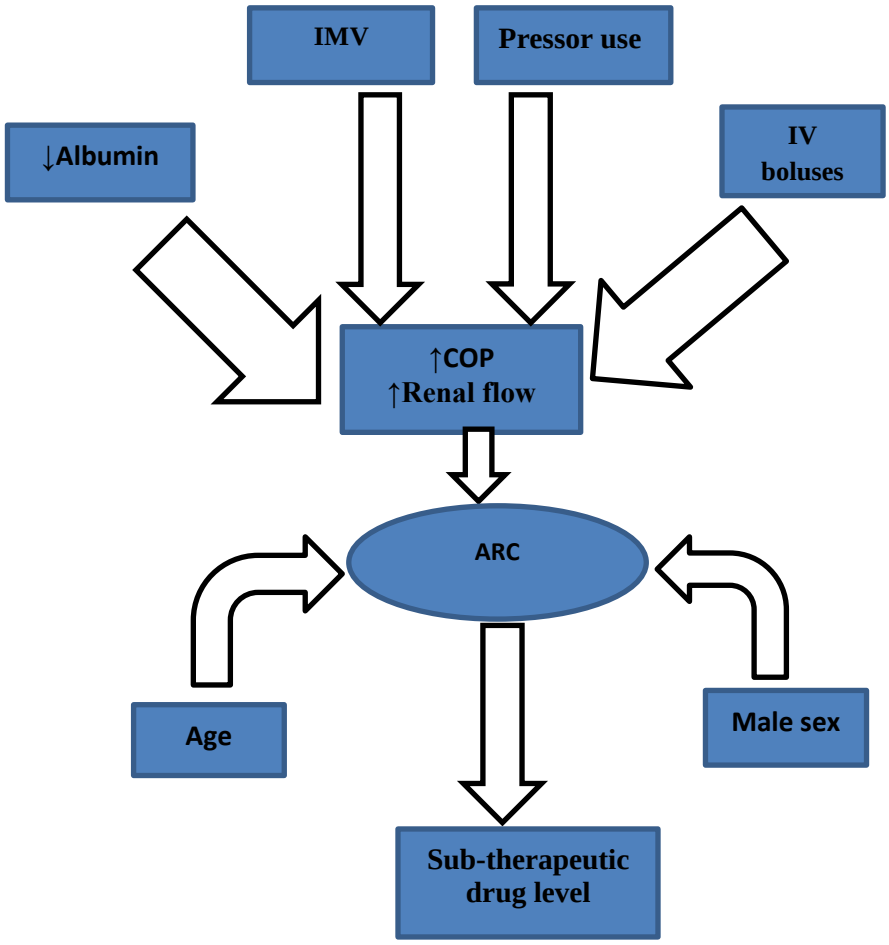


**Figure 1**: Factors associated with increased risk of augmented renal clearance(ARC)

Children admitted to PICUs usually have uncompromised renal function before admission, hence they are more prone to develop ARC in the setting of critical illness. The mechanism not solely involves increase in GFR, renal hyperperfusion also increases solute delivery to other renal drug eliminating pathways like tubular secretion.

During critical illness, physiological changes and therapeutic interventions can alter drug pharmacokinetics.There is increased volume of distribution for hydrophilic antimicrobials causing sub-therapeutic levels in blood. Hypoalbuminemia which is frequently found in this patients also affect pharmacokinetics of antimicrobials that are highly protein bound. Changes in PK of antimicrobials that take place in these patients can lead to treatment failure (5).

Risk factors for ARC include age under 50, lower severity of illness, acute neurotrauma, burns, major surgery, sepsis, hematological malignancies, male gender, being on mechanical ventilation, use of vasopressors, high cardiac index and febrile neutropenia.Onset and duration vary from patients to patients. In adult ICUs there are varying reports regarding onset and duration of ARC (6)

Data regarding ARC in children are scarce and understanding the prevalence and factors associated with ARC in critically ill pediatric patients is crucial for optimizing drug therapy and enhancing clinical management within Pediatric intensive care units(PICUs).

## Statement of the Problem

ARC is a common pathological phenomenon in critically ill patients, particularly children. It is associated with increased renal solute excretion, including water soluble antibiotics (4). Data regarding prevalence in pediatric population is scarce and the exact epidemiology in our setting is unknown. Knowledge of the magnitude and factors associated with ARC is helpful to consider and optimize antimicrobial dosages and administration methods in PICU patients. To assess this prospective cross sectional study will be conducted at two PICUs in tertiary hospitals in Addis Ababa, Ethiopia.

ARC is a common pathological phenomenon in critically ill patients, particularly children. This condition is characterized by an increased excretion of renal solutes, which includes water-soluble antibiotics. However, despite its significance, there is a lack of data on the prevalence of ARC in the pediatric population, and the exact epidemiology of this condition in our specific setting remains unknown. Understanding the extent of ARC and the factors contributing to it is crucial for effectively determining and optimizing the dosages and methods of administering antimicrobial medications to patients in the Pediatric Intensive Care Units (PICU).

To address this gap in knowledge, a prospective cross-sectional study will be conducted at two PICUs located in tertiary hospitals in Addis Ababa, Ethiopia. By undertaking this study, we aim to assess the prevalence of ARC, identify any associated risk factors, and explore the implications for antimicrobial treatment strategies in critically ill children. This research endeavor will involve collecting data on a range of variables, such as patient demographics, clinical characteristics, and treatment regimens, to provide a detailed understanding of the factors influencing ARC in the pediatric population.

Ultimately, this research has the potential to enhance the quality of care provided to critically ill children and contribute to the advancement of pediatric critical care medicine.

## Significance of the Study

In critically ill patients attention is usually on decreased renal function which leads to unnecessary reduction of antimicrobial dosage. This is associated with treatment failure, increased length of hospital stay, increased rate of antimicrobial resistance, high cost and mortality. Understanding the prevalence and risk factors associated with augmented renal clearance(ARC) in PICU is essential for optimizing medication dosing, improving therapeutic outcomes, and improving patient care in PICU settings. This research aims to assess magnitude, associated factors of ARC and practice of antimicrobial prescription in our settings. As to the investigators knowledge this is the first study in Ethiopia and Africa.

## LITERATURE REVIEW

ARC is a phenomenon in critically ill patients which is associated with increased creatinine clearance and enhanced elimination of renally excreted drugs. Patients with severe neurologic injury, sepsis, trauma, burns, younger ages are consistently at higher risk of ARC. This condition is associated sub-optimal exposure to critical medications, including beta-lactams and vancomycin (4)

In a systematic review done in adult patients ARC(defined as CrCl >130mL/min/m²) is present in 20-65% of critically ill patients. Younger age, poly trauma, lower severity illness(indicating relatively stable renal status) have been identified,. ARC was consistently associated with sub therapeutic drug levels. The median age of patients with ARC is between 34 and 50 years, while in case of patients without ARC, over 60 years (5).

Febrile Neutropenia patients are at high risk of ARC. A retrospective chart review study conducted on 217 adult patients of whom 158(73%) had febrile neutropenia and 47.5% of patients had ARC. There was significant association between febrile neutropenia and ARC : $\chi^2(1, n=217)=8.60$, $P<0.05$. The proportion of co-existence of Febrile Neutropenia and ARC was 83.3%. The CrCl for febrile neutropenia patients with ARC was significantly higher than those without ARC(median of 8930 mL/min *vs* 155mL/min, $P<0.05$). The trough concentration of vancomycin among febrile neutropenia with ARC was significantly lower than for those without ARC($P<0.05$) with a median of 5.6µg/ml vs 9.646µg/ml. Patients with hypoalbuminemia also had lower trough level of vancomycin(adjusted OR=1.11, 95% CI 1.040-1.215, $P<0.05$) (7).

A retrospective observational study done in United Kingdom on ARC showed ARC prevalence of 47%. Younger age, male sex, lower APACHE II score, sepsis were associated with high risk of ARC. The median time to onset of ARC was 1 day, 64% of patients who developed the condition did so within 24 hours. Patients with ARC had a larger median body surface area compared with those not having(100m² vs 82m² $P<0.001$) (8).

A prospective observational study in adult ICU patients of 128 patients and 599 antimicrobial therapy days was done in Ghent University Hospital. ARC was present for atleast one antimicrobial therapy day in 51.6%. ARC patients had a median CrCl of 144mL/min/1.73 m². In ARC patients serum creatinine values were normal(0.7- 1.1 mg/dL) in 18% and low(<0.7mg/dL) in 76% of antimicrobial treatment days and 11.7% of patients experienced ARC permanently during antimicrobial treatment days. Younger age and male gender were associated with ARC, whereas severity of illness, was not (9).

Patients with neuro emergencies have increased risk of ARC. A prospective single-center study done on 20 adult patients with Sub Arachnoid Hemorrhage showed ARC of 100% in this group

of patients. GFR estimation was made by collecting 24-hr urine. In this group of patients implementation of hyperperfusion is associated with further increase in GFR and ARC (10).

A systematic review and meta-analysis done on prevalence and risk factors of ARC conducted on critically ill adults; pooled prevalence of ARC was 39%, neurotrauma or other trauma, young age, male sex were associated with high rate of ARC. The highest ARC occurrence was detected in neurocritical care patients(74% pooled prevalence), followed by other traumas(58%), 33% in septic patients. Younger age, male sex, trauma were significantly associated with ARC (11).

A prospective observational study done in Ghent University Hospital, Belgium on 105 children, the median age of the study population was 1.54 years and large proportion of patients were admitted after surgery(48.9%). Most of surgical cases were elective (86.7%). GFR values ranged from 63 to 236 mL/min/1.73 $m^2$ by Schwartz formula and ranged from 65 to 270 mL/min/1.73 $m^2$ by ClCr. ARC was present for atleast one day during the study period in 67.4% of patients. The proportion of ARC generally decreased over the study period, from 51.1% on $1^{st}$ day to 33.3% on the $4^{th}$ day. A Similar overall prevalence(66.3%) was observed when using revised shwartz formula for GFR estimation. Male sex, higher PRISM II score, treatment with antibiotics, mechanical ventilation were associated with higher ARC prevalence, while children who underwent cardiac surgery were less likely to develop. Male gender and treatment with antibiotics were independent risk factors for development of ARC (3).

A retrospective study done in Hokkaido University Hospital in Japan, including patients of age ≥ 18, ARC onset occurred within 3 days of admission in approximately half of the cases, and within one week in most of other cases. The median duration of ARC in Kaplan-Meier Curve was 5 days and ended within 3 weeks in many of those cases. Longer duration of ARC was associated with fewer ICU-free days. But onset of ARC was associated with a reduction in mortality indicating less severe nature of illness in this group of patients. Patients who are young and with lower SCr at admission, male sex, central nervous system disease, absence of comorbid illness, use of mechanical ventilation, vasopressor use are at highest risk of having ARC (12).

ARC is associated with sub-therapeutic drug levels of critical antibiotics including ß-lactams, vancomycin, and aminoglycosides. A PK/PD study done in China showed the need for high dose of vancomycin in critically ill patients, particularly those having ARC. It was a retrospective study done on PK/PD of vancomycin in critically ill adult patients. They analysed by dividing samples into ARC and non-ARC groups. Those patients in ARC group had lower trough serum concentrations of vancomycin than non-ARC. Sub-therapeutic vancomycin concentration(<10mg/L) were observed in 77.7% and 68.8% of ARC and non-ARC groups respectively($P<0.05$) and also there was lower AUC24 in ARC group(232.9 vs 316.2 μg.h/mL) (13)

A retrospective study on vancomycin population based PK and dosing recommendations in children with haematologic malignancy and ARC done in China. It included 53 patients with

106 samples. A one-compartment model with first order elimination was utilized. Monte carlo simulation results showed that when MIC was 0.5mg/dL or 1 mg/dL, the recommended doses to achieve target($AUC_{24hr}$/MIC ≥400 were 25-40 mg/kg/day and 50-75 mg/kg/day respectively. This shows that when MIC is higher, current standard recommended Vancomycin doses are insufficient and should be increased (14).

Population PK study of IV and oral acyclovir and oral valacyclovir in pediatric patients with Augmented renal clearance(ARC(defined as eGFR >250 mL/min/m²)) included 79 children and 212 concentration-time observation. Patient with ARC had higher elimination rate, therefore they need higher initial dose of acyclovir(15-20 mg/kg/6 hr) to achieve target maximal and trough concentrations( (15).

A retrospective observational cohort study done in France on adult HAP-VAP patients with ARC showed requirement of higher than licenced dosing regimens of ß-lactam antibiotics including cefazolin, amoxicillin or amoxicillin/clavulanic acid, ceftriaxone, cefotaxime. Piperacillin tazobactam which may be safe and effective in reducing rate of treatment failure and HAP-VAP recurrence in critically ill patients with ARC treated for a first episode of HAP-VAP (16).

A prospective open-label PK study conducted in Ghent university Hospital on critically ill children admitted to PICU showed that the standard dosing recommendations for amoxicillin-clavulanic acid can result in subtherapeutic treatment in this population. Hence patients with ARC needs increased dosing of amoxicillin-clavulanic acid (17).

In a prospective study done in portugal on 93 critically ill ventilated adult patients; serum vancomycin levels were measured during the first 3 days of treatment. ARC defined by CrCl >130 mL/min/1.73 m² occurred in 40% of patients. Patients with ARC were younger, less critical, trauma was the leading cause of admission. The serum vancomycin concentration in the study group was significantly lower than control group(9.7 vs 13.1 μmol/L on day1; 11.7 vs 16.6 μmol/L on day2; 13.8 vs 18.6 μmol/L on day3) (18).

In a retrospective PK study done on optimizing Aminoglycoside dosing in critically ill pediatric patients using cut off point for ARC as 130mL/min/1.73 m², 28% of patients were classified as having ARC. According to parametric model, Cmax0-24 and AUC0-24 were reduced on average by 38% and 34%, respectively in patients with ARC. Patients with ARC may benefit from increased aminoglycoside dosing, but caution should be applied particularly in children under 2 (19).

A study about a population PK of Cefazolin in children with MSSA infection, included 39 patients with a median age of 7. Continuous infusion with 100-150 mg/kg/day of cefazolin achieved the target of 100% $fT > 4 \times MIC$ in children with ARC and less than 10kg. In this group of patients normal standard dosing may be associated with subtherapeutic levels (20).

A prospective observational study performed in adult ICU with trauma and septic critically ill patients, receiving antibacterial therapy. Seventy one patients(sepsis n=43, multi-trauma n=28) were included and 57.7% of the cohorts experienced ARC. ARC was more prevalent in trauma patients(85.7% vs 39.5%, *P <0.001*)). Those having ARC were younger, male and lower APACHE II score and lower modified SOFA scores (21).

Another prospective observational PK study done in adult medical and surgical ICU patients involving 61 patients showed that almost half(48%) of patients had ARC . Multivariate regression analysis showed that high creatinine clearance was an independent predictor of not achieving targets. Patients who did not attain PK targets were also younger and had a higher weight. Patients without ARC achieved higher mean percentage of $f$T>MIC(94% vs 61%) than those with ARC and 76% of those having ARC did not reach predefined PK target (i.e. 100% $f$ T>MIC) (22).

Regarding the assessement of GFR a retrospective study done in South Korea on patients aged ≤18 years who underwent vancomycin therapeutic drug monitoring showed significant relationship between estimated GFR and vancomycin therapeutic level. An increased estimated GFR(eGFR) was a risk factor for a subtherapeutic vancomycin level. Estimated GFR is a reliable and efficient alternative to measured GFR for early identification of ARC and optimization of antimicrobial dosing in critically ill pediatric patients (23).

Novel antibiotics are also affected by ARC. A retrospective study of case series of critically ill patients who received Ceftaz/Avibactam 4 out of 40 patients had ARC. All patients were given Ceftaz/Avibactam 2.5g every 8 hours to be infused over 2 hours. Among four patients only one had an optimal PK/PD target and achieved microbiological eradication (24)

## Objectives of the Study

General objective

Assess magnitude and associated factors of augmented renal clearance in PICUs of TASH and ALERT Center in Addis Ababa

Specific objectives

To determine the magnitude of augmented renal clearance in PICUs

To identify clinical and demographic factors associated with the development of augmented renal clearance in pediatric intensive care units

To assess practice of antimicrobial prescription in patients with augmented renal clearance

## Materials and Methods

### Study Areas

The study was conducted in Addis Ababa, Ethiopia at Tikur Anbessa Specialized Hospital and ALERT Hospital, Department of Pediatrics and Child health. TASH was established in 1972. TASH is teaching hospital under Addis Ababa University. It is the largest tertiary hospital in Ethiopia with a total of 700 inpatient beds and had multiple Specialty and Subspecialty units. The hospital has dedicated 6 beds for pediatrics patients admitted to PICU.

All-Africa Leprosy, Tubeculosis and Rehabilitation Training Centre(ALERT Hospital), origionated as a leprosium established by the Sudan Interior Mission(SIM) in 1934. Origionally it was named princess Zenebework Memorial Hospital. Later in 1965 in response to escalating prevalence of leprosy in Africa the name was changed to ALERT i.e. leprosy training center. ALERT attained WHO collaborating center status for Leprosy training in 1988. It is the only medical research center regarding Leprosy for the past ninety years. It is the third largest hospital in the nation by flow and serves more than 450,000 patients annually. ALERT Hospital offers a comprehensive services including Emergency and Critical care, Trauma, Dermatology, Plastic and Reconstructive surgery, Opthalmology and others. Its Critical Care service includes PICUs which have six beds.

### Study Design and Period

Multi-center prospective Cross sectional study was done at TASH and ALERT Center; a tertiary hospitals in Addis Ababa, Ethiopia from july 2024 to december 2024.

## Source Population

All pediatric patients admitted to TASH and ALERT Center during the study period

## Study Population

All pediatric patients admitted to PICU during the study period

Sample Size Determination

$n=Z^2Pq/d^2 \rightarrow Z=1.96, P=0.5 \ q=0.5 \ d=0.05$

$=384$

Over the past six months there were 251 admissions at TASH(62%) and ALERT Center(38%) →**N=251**

Using infinite population formula $\frac{n}{1+n/N}$=152 considering 10% non-respondent rate

152+15→170 is sample size

## Sampling Method

All patients who fulfill the inclusion criteria were included in the study

## Inclusion and Exclusion Criteria

Inclusion Criteria

All patients admitted to PICU between 1 month and 15 years of age

Exclusion Criteria

1) Patients with chronic renal failure(Advanced CKD)
2) Patients with Severe AKI
3) Age < 1 month

## Variables

Independent variables

Sex, age, weight, height, body surface area, requirement of mechanical ventilation, C-reactive protein(CRP), diuretics and vasopressor agents, daily input, reason for admission, Phoenix Score

Dependent variables

Daily urine output, daily serum creatinine level, outcome at day 7, length of Pediatric ICU stay

## Data Collection Method

Consent form was prepared in English and translated in to the commonly spoken local language i.e. Amharic

Data was collected using a data abstraction tool, which is prepared by reviewing different studies. Written informed consent was obtained from parents/guardians.Patients who fulfill the inclusion criteria were included in the study. Finally data was analyzed using SPSS version 25.

A data collection sheet(questionnaire) was designed to include baseline and follow-up data for each patients admitted to PICU in TASH and ALERT Center. Baseline data include gender, age, weight, height, body surface area, admission diagnosis. A follow up data include serum creatinine, urine output, daily input, out come at day 7. The questionnaire was pretested at TASH PICU on 5% of sample size and was amended based on the findings. Blood sample of 2 mL for serum creatinin determination for pretest sample was tested at TASH laboratory. Day 1 and day 3 serum creatinine was taken from medical records of patients. Day 2 serum creatinine was analyzed by sending 2mL blood sample from patient the lab was tested by a machine called Cobas C11 and cost was covered by investigator. Pattern of antimicrobial prescription was taken from medical records of patient

Two general practioners one from each hospital were trained on how to collect data using a structured questionnaire and were monitored by principal investigator during study period.

### Data Quality Assurance

During data collection, weekly supervision was made for quality assurance and completeness by the primary investigator

### Data Analysis and Interpretation

After data cleaning and entry, analysis was be done using the Statistical Package for Social Sciences(SPSS) version 25. Descriptive and analytical statistics is used as applicable. Statistically significant association is taken for $P<0.05$. A mann-Whitney U test was used to compare two groups with continuous variables and chi square or Fisher's exact test was used for categorical variables. Logistic regression analysis was used to identify risk factors of ARC.

## Operational Definition

**Severe AKI** : defined when KDIGO stages 2 and 3 are present.

| Stage | Serum creatinin(SCr) | Urine output |
|---|---|---|
| 1 | ↑ to 1.5-1.9 times baseline, or<br>↑ of ≥0.3 mg/dL | <0.5mL/kg/hour for 6-12 hours |
| 2 | ↑ to 2-2.9 times baseline | <0.5 mL/kg/hr for ≥12 hours |
| 3 | ↑ to greater than 3 times baseline, or<br>SCr ≥4mg/dL or<br>Initiation of kidney replacement therapy, or<br>eGFR <35mL/min/1.73m$^2$(<18 years) | <0.3 mL/kg/hr for ≥24 hours, or<br>Anuria for ≥12 hours |
| Time frames for increase in SCr<br>• Increase of SCr ≥0.3mg/dL(≥26.5mcmol/L) within 48 hours<br>• Increase in SCr >1.5 times the baseline within the prior 7 days | | |

**Table 1.** KDIGO definition of AKI

**CKD:** Abnormalities of kidney structure or function , presenting for more than three months.

- GFR <60mL/min/1.73m$^2$ for greater than three months with implications for health regardless of wheather CKD makers present
- GFR >60mL/min/1.73m$^2$ that is accompanied by structural damage or other markers of functional kidney abnormalities

**Advanced CKD:** all patients with CKD stage 3, 4 and 5, i.e., GFR <60mL/min/1.73m² for ≥ 3 months (3).

**ARC**: Defined as eGFR greater than 20% of the upper limit of normal for age

**Table 2:** PlasmaCr-EDTA clearance in normal infants (25)

| Age(mo) | Mean GFR(mL/min/1.73 m²) ± SD | Cut-off to define ARC(mL/min/1.73 m²) |
|---|---|---|
| ≤1.2 | 52.0±9.0 | 73.3 |
| 1.2-3.6 | 61.7±14.3 | 91.2 |
| 3.6-7.9 | 71.7±13.9 | 102.72 |
| 7.9-12 | 82.6±17.3 | 119.88 |
| 12-18 | 91.5±17.8 | 131.16 |
| 18-24 | 94.5±18.1 | 135.12 |
| >24 | 104.4±19.9 | 149.16 |

**Modified Scwartz formula**:$\frac{K \times Ht}{Cr\ serum}$→K=0.413, Ht=height of patient in cm, Cr= serum creatinin in mg/dLof the patient

**Body Surface Area:** calculated by Mosteller equation→ $\sqrt{Ht(cm) \times Wt(kg)/3600}$

**Mean Arterial Pressure**:1/3 x Systolic blood pressure + 2/3 x diastolic blood pressure

**Critical illness**: a medical condition in which a patient, because of major surgery or severe illness, requires immediate intensive medical support of vital organs to survive (26).

**Standard dosing of Antibiotics**: in Pediatrics dosing depends on weight, renal status, severity of illness, site of infection. Higher doses are required for critically ill patients. Vancomycin loading dose should be given to all critically ill patients who have indication, irrespective of renal status. Subsequent dosing will be adjusted according to renal status of the patient

**Intermittent infusion**: administration of antibiotics over duration of less than two hours

**Extended infusion**: administration of antibiotics over 2-4 hours duration

**Continuous infusion**: administering antibiotics over the entire dosing interval(continuously over twenty four hours)

**Hypotension:** in children is defined as a systolic blood pressure (SBP) or mean arterial pressure (MAP) that is below the 5th percentile for their age, sex, and height.

**Hypertension**: in pediatrics is defined as a systolic blood pressure (SBP) or diastolic blood pressure (DBP) that is at or above the 95th percentile for the child's age, sex, and height (or age and sex for younger children).

| Antibiotics | Dosing per kilogram of body weight |
|---|---|
| Vancomycin | -loading dose → 20-25mg/kg IV to be infused over 3 hours<br>-maintenance dose →15-20mg/kg/dose IV every 8hr |
| Cefepime | 100-150mg/kg/day IV divided every 8-12hr |
| Ceftriaxone | 50-75mg/kg/day IV every 12-24 hr non meningitis, 100mg/kg/24 hr IV for meningitis |
| Cefotaxime | 150mg/kg/day IV divided every 6-8hr for non-meningitis infections, 200mg/kg/day IV divided every 6-8 hr in meningitis |
| Meropenem | 60mg/kg/day IV divided every 8 hour for non-meningitis, 120mg/kg/day IV for meningitis |
| Piperacillin-Tazobactam | 300-400mg/kg/day IV divided every 6-8hr |
| Ampicillin | 100-200mg/kg/day IV for non-meningitis, 200-400mg/kg/day IV divided every 4-6 hr for meningitis |
| Amikacin | 15-25mg/kg/day IV |
| Gentamicin | 5-7.5mg/kg/day once daily or 2.5mg/kg every 8-12hr |
| Fluconazole | 12mg/kg/day IV/PO once daily |
| Amphotericin B | Amphotericin B Deoxycholate: 0.5-1mg/kg/day IV<br>Lipid amphotericin B formulations: 3-5mg/kg/day IV |
| Acyclovir | - mucocutaneous or immunosuppression:10mg/kg/dose IV every 8hours<br>-Disseminated HSV or HSV encephalitis(3 months to <12 years): 15mg/kg/dose IV every 8hour; age ≥12 years:10mg/kg/dose every 8hr<br>- 0-3 month old 20mg/kg/dose IV every 8hr |

**Table 3 :** antimicrobial dosing in pediatric patients with normal renal function

## Ethical Clearance

Before beginning data , official letter was obtained from Addis Ababa University, College of Health Sciences, Pediatrics and Child Health Department's Research and Publications committee and ALERT hospitals research ethics committee. Then the copy of the letter was submitted to TASH and ALERT hospital's PICUs and the objective of the study explained for the concerned body. After getting consent from the families/guardians data was collected as per protocol. A code was given to each study subject and the patient's name or I-care number was never used by any means throughout the research

# Results

## Sociodemographic Data

During the study period, data were collected from 170 patients admitted to the Pediatric Intensive Care Units of TASH and ALERT hospitals. Of the 170 patients, 105 were male, while the remaining 65 were female. A total of 108 patients were admitted to TASH, and the remaining 62 were admitted to ALERT hospital. The mean age of the patients was 3.32 years, with a median age of 1.5 years, ranging from 0.1 to 14 years. The majority of the patients, 111, were admitted for medical conditions, and 54 were admitted after surgery. Most of patients were admitted for diagnosis of pneumonia. During the first three days of PICU stay, 66(38.8%) patients experienced at least one episode of augmented renal clearance, and 112 out of 438 serum creatinine measurements were within the ARC range. Thirty-eight out of 170 patients had two measurements, and 11 out of 170 had three measurements in the range ARC. Augmented renal clearance was predominantly occured in male(70.77% of ARC) patients. The proportion of ARC is higher in day1 than day2 and day3(i.e. 23.5%, 20.6% and 21.2% respectively).The proportion of ARC was higher on day 1 compared to days 2 and 3. The median duration of ARC was 2 days.

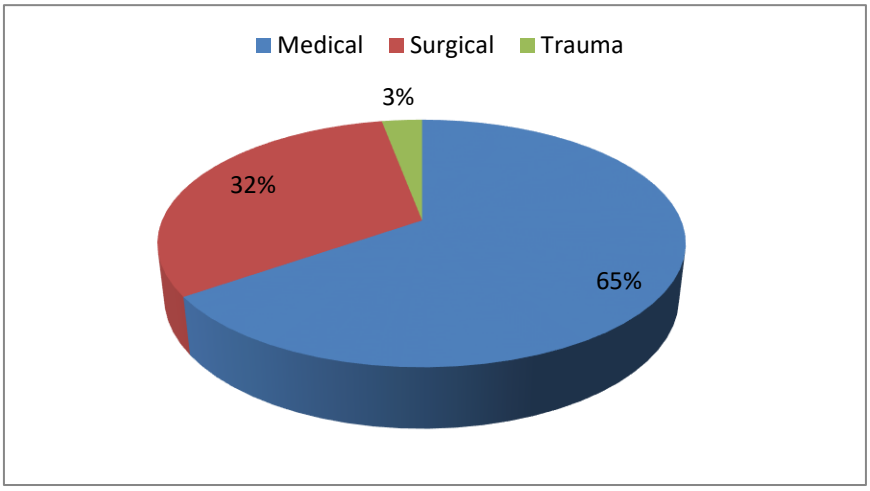


**Figure 1. Admission Category of patients**

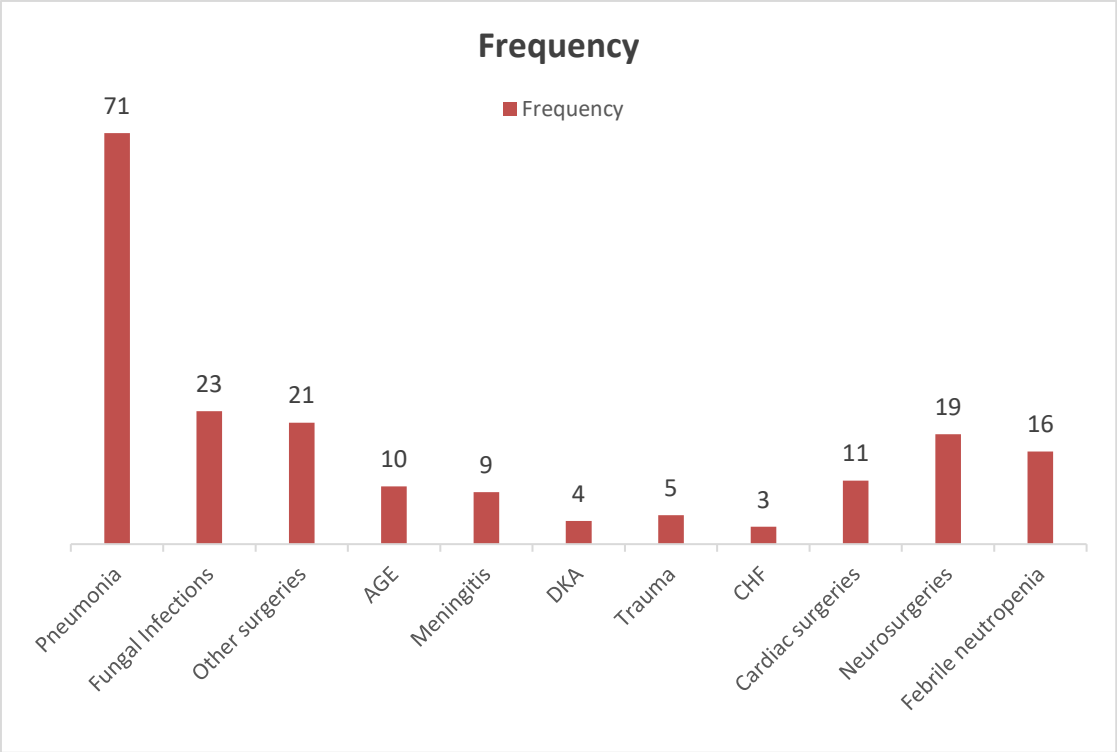


**Figure 2 Admission diagnosis**

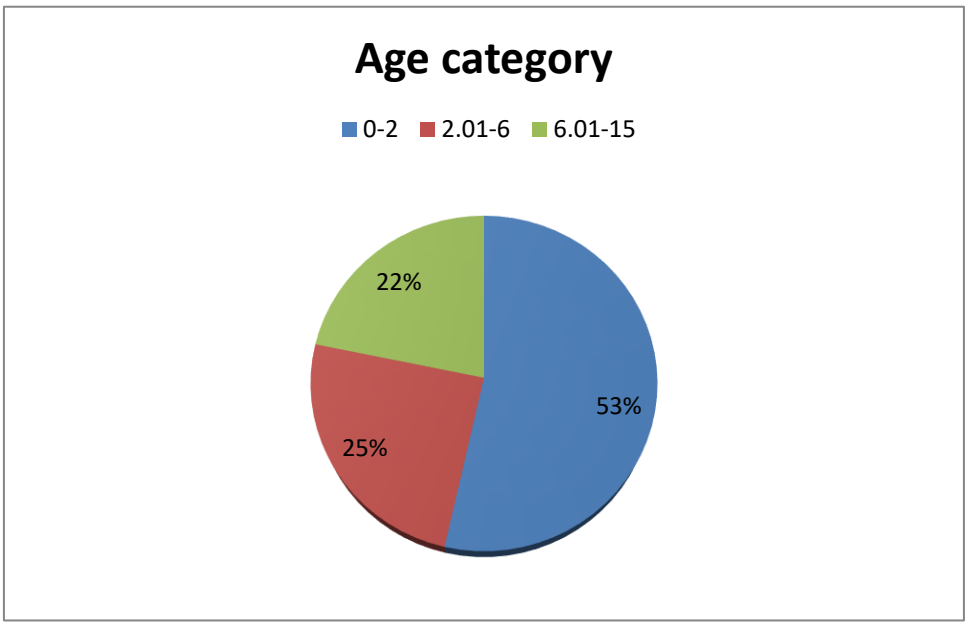


**Figure 3. Age categories of patients admitted to PICUs**

Majority of patients(137) have underlying chronic medical/surgical conditions.

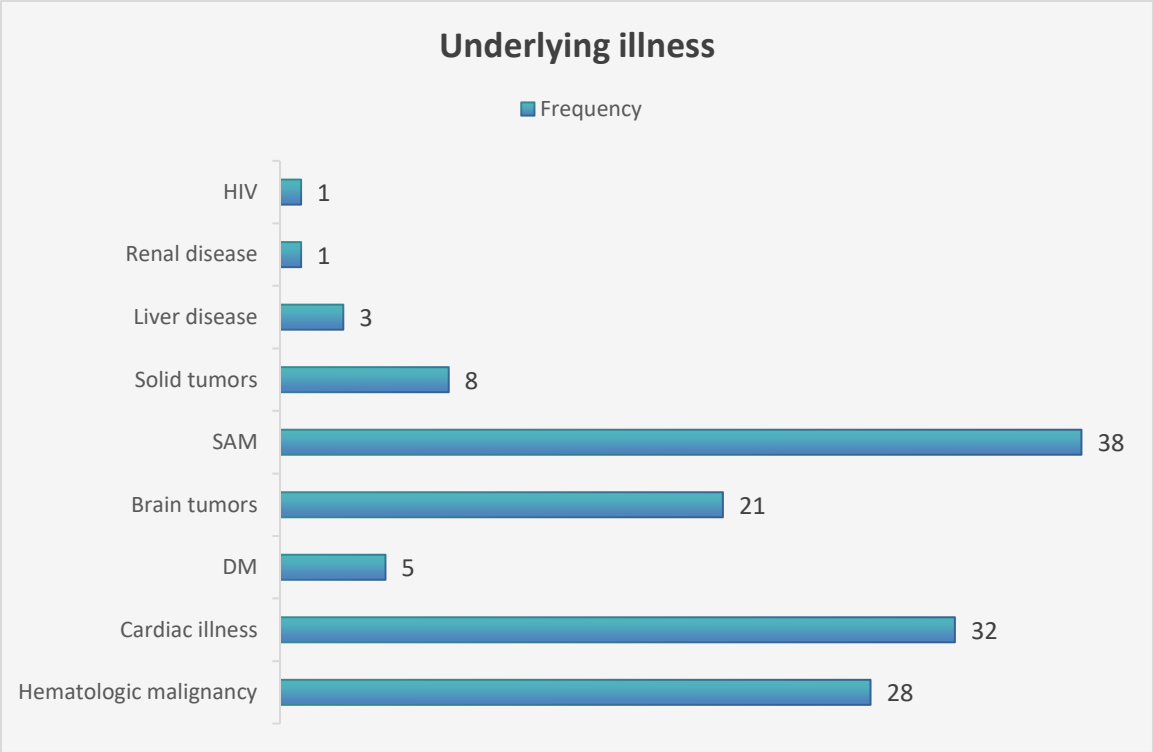


**Figure 4. Frequency of chronic underlying conditions**

The median time to onset of ARC is 1 day, and the majority of patients (63.07%) experienced ARC onset on the first day. Approximately one-quarter (24.6%) of patients had ARC onset on the second day, while 12.3% of patients experienced onset on the third day.

Patients admitted for febrile neutropenia and brain tumor demonstrate a high incidence of ARC, occurring in 68.75% and 71.4% of cases respectively, at least once during the three-day follow-up period.

Method of administration of antibiotics includes intermittent infusion in 92.8% and extended infusion in 6.6%

Antimicrobials were administered for 167/170(98.2%) patients. Beta-lactam antibiotics were most commonly prescribed antibiotics in PICU followed by vancomycin. Vancomycin was used in 9/16(56.5%) of febrile neutropenia patients. In our setting we are not monitoring serum vancomycin. But interms of medication dosing all patients with febrile neutropenia has got maximum approved dosing, though only 22.2%(2/9) patients have received extended infusion of vancomycin.

Most of patients(63.5%), received standard dosing, more than 1/3$^{rd}$ (35.3%) of patients have received maximum approved dosing. Most of(92.8%) of patients have received intermittent administration of antibiotics, while 11/167(6.5%) and 1(0.6%) patients received extended infusion and continuous infusion respectively.

Antimicrobial therapy was administered to 167 out of 170 patients. Beta-lactam antibiotics were the most commonly prescribed antibiotics in the PICU, followed by vancomycin. Antibiotics are administered via intermittent infusion in 92.8% of cases and extended infusion in 6.6% of cases.

Vancomycin was administered to 56.25% of febrile neutropenia patients. However, all patients with febrile neutropenia received the maximum approved dosage, although only 22.2% of patients underwent extended infusion of vancomycin. Among febrile neutropenia patients, 81.25% were treated with meropenem, and 85% received the maximum approved dosage. Additionally, three-quarters (77%) of patients received intermittent infusion.

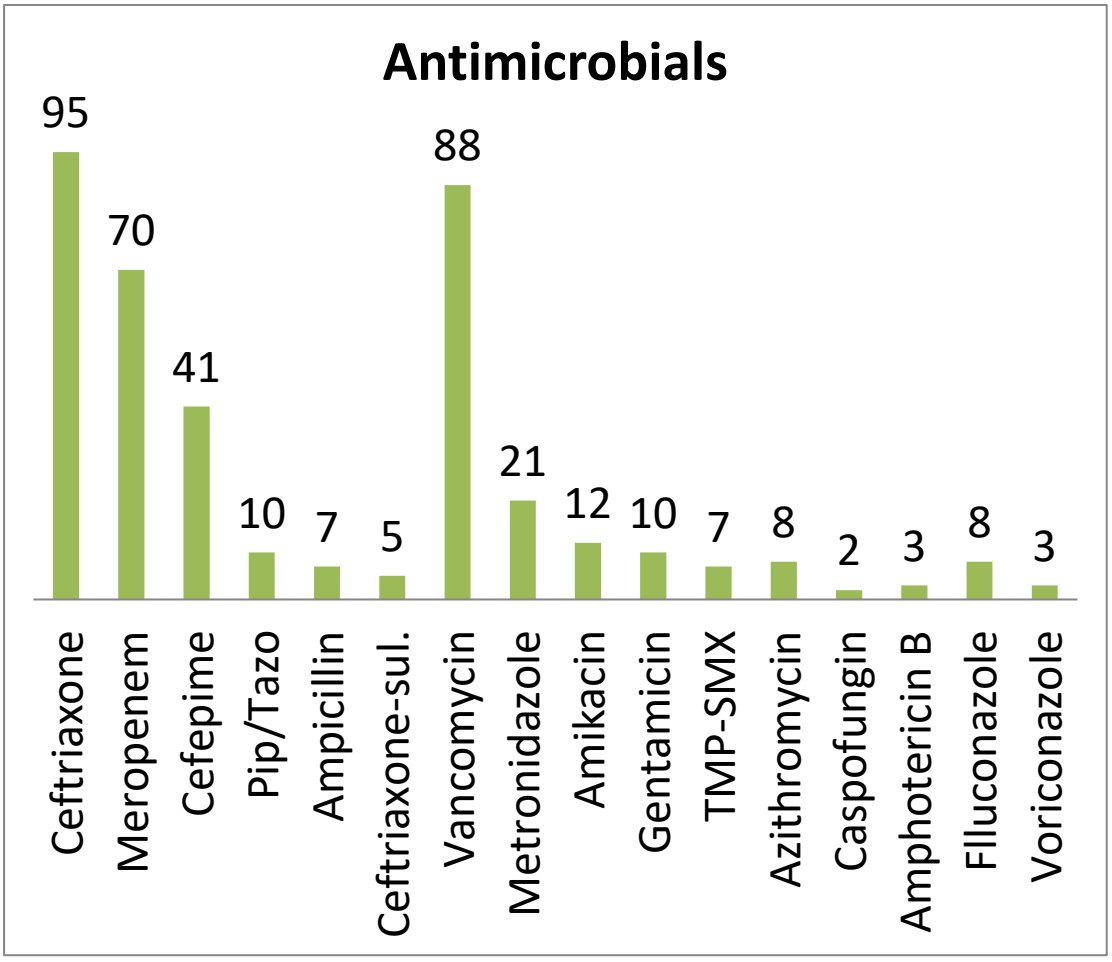


**Figure 5. Antimicrobials used in PICUs**

**Table1 Antimicrobials used in PICU patients**

| Antibiotics | N(%) | Antimicrobials | N(%) |
|---|---|---|---|
| Ceftriaxone | 95(56.9) | Amphotericin B | 3(1.8) |
| Meropenem | 70(41.9) | Caspofungin | 2(1.2) |
| Cefepime | 41(24.2) | Voriconazole | 3(1.8) |
| Piperacillin/Tazobactam | 10(5.9) | | |
| Ampicillin | 7(4.2) | | |
| Ceftriaxone-sulbactam | 5(3) | | |
| Vancomycin | 88(52.7) | | |
| Metronidazole | 21(12.6) | | |
| Amikacin | 12(7.2) | | |
| Gentamicin | 10(5.9) | | |
| Azithromycin | 8(4.8) | | |
| TMP-SMX | 7(4.2) | | |

**Table 2**

**Institutions at which patients were admitted**

| ARC | | No | Yes | Total |
|---|---|---|---|---|
| Institution | ALERT Center | 53 | 9 | 68 |
| | TASH | 52 | 56 | 102 |
| | | 105 | 65 | 170 |

Approximately one third(28.8%) of patients were hypotensive, 65.3% were normotensive at admission to PICU. The study reported a total of 45 deaths across the two participating Pediatric Intensive Care Units during the investigation period. Specifically, 17 deaths occurred at ALERT hospital, while 28 were recorded at TASH hospital.

**Table 3**

**Outcome of patients at Day 7 of PICU admission**

| | | Survived(%) | Death(%) | Total(%) |
|---|---|---|---|---|
| Institution | ALERT Center | 45(72.6) | 17(27.4) | 62 |
| | TASH | 80(74.1) | 28(25.9) | 108 |
| Total | | 125 | 45 | 170 |

**Table 4**

**Patient characteristics**

| | | ARC | No ARC | *P-value* |
|---|---|---|---|---|
| Age, years; medianQ1-Q3(0.5-5) | | 2.58(0.915-7.5) | 1(0.33-4) | *0.003* |
| Gender | Female | 19 | 45 | *0.076* |
| | Male | 46 | 60 | |
| Weight(kg),median(Q1-Q3) | | 12(8.4-17) | 8(5-14) | *0.001* |
| Height(cm), median(Q1-Q3) | | 90(71-112.5) | 74(56-99.5) | *0.001* |
| Body Surface area, median(Q1-Q3) | $m^2$ | 0.54(0.395-0.74) | 0.41(0.285-0.61) | *0.001* |
| Admission Category | Medical | 37 | 74 | |
| | Surgical | 28 | 26 | 0.023 |
| | Trauma | 0 | 5 | |
| Phoenix score, median(Q1-Q3) | | 3(2-4.5) | 2.86(1-4) | *0.827* |
| Length of PICU stay(day), median(Q1-Q3) | | 6(3-7) | 4(2-6.71) | 0.032 |
| Number of death(%) | | 19(42) | 26(57.8) | *<0.001* |
| Total input(mL), median(Q1-Q3) | | 2872(1818-4340)) | 2465(1624-3753)) | |
| Antibiotic therapy | | 65(38.9) | 102(61.1) | |
| Duration of Antimicrobial therapy(days), median(Q1-Q3) | | 10(6-14) | 10(6.75-14) | *<0.001* |
| Mechanical ventilation | | 30(42.2) | 41(57.8) | |
| eGFR, Median(Q1-Q3) | Day1 | 108.59(80.035-133.6) | 70.04(50-83.82) | *<0.001* |
| | Day2 | 115.8(90.517-171.175) | 69.1(51.80-88.75) | *<0.001* |
| | Day3 | 185.90(122.46-272.58) | 74.78(54.5-88.93) | *<0.001* |
| Patients treated with meropenem(%) | | 29(41.4) | 41(58.6) | |
| Patients treated with Vancomycin(%) | | 36(40.9) | 52(59.1) | |

## Factors Associated with ARC

By comparison, the male cohort (n=106) exhibited a higher eGFR of 91.33 (±3.14) on day 1. In order to investigate the hypothesis regarding the potential disparity in eGFR between males and females, an independent t-test was conducted after managing outliers by IQR method. The analysis revealed a statistically significant difference, with a t-value of -2.305, df=166, and p=0.022, indicating that males displayed notably higher eGFR levels compared to females.

**Table 5 comparison of eGFR based on gender**

| | F | Sign. | T | df | Sign.(2-tailed | Mean Difference | Std. Error Difference | 95%CI of the difference | |
|---|---|---|---|---|---|---|---|---|---|
| Day1eGFR | .002 | .967 | -2.305 | 166 | .022 | -11.98 | 5.20 | -22.25 | -1.72 |
| Day2eGFR | .248 | .620 | 2.037 | 148 | .043 | 13.20 | 6.48 | .393 | 26.00 |

The study used Pearson correlation coefficient analysis to examine the relationship between total fluid input and estimated glomerular filtration rate (eGFR) on days 1 and 2. The results showed a statistically significant positive correlation between eGFR and total fluid input on day 2(day1( r=0.275, p<0.001), day2(r=0.393, p<0.001).

Patients admitted for febrile neutropenia also had a significant association with augmented renal clearance. The Pearson correlation coefficient analysis revealed a statistically significant positive correlation with at least one, two, and three ARC measurements during the PICU stay.

**Table 6 correlation between Febrile neutropenia and ARC**

| | Pearson $\chi^2$ | Fisher's exact sig. | Likelihood ratio(exact 2 sided sig.) | Linear by linear association | Pearson correlation coefficient |
|---|---|---|---|---|---|
| Atleast one ARC | 8.673, *p=0.004* | *P=0.006* | 7.17, *p=0.007* | 8.622, *p=0.004* | r=0.226, *p=0.004* |
| Two ARC | 10.51, *p=0.003* | *P=0.003* | 8.895, *p=0.014* | 10.448, *p=0.003* | r=0.249, p=0.003 |
| Three ARC | 8.666, *p=0.017* | *P=0.017* | 5.862, *p=0.017* | 8.615, p=0.017 | r=0.226, p=0.017 |
| Day1 ARC | 8.491, *p=0.007* | *P=0.007* | 7.414 P=0.013 | 8.441, *p=0.007* | r=0.223, *p=0.007* |
| Day2 ARC | 2.530, p=.112 | *P=0.120* | 2.272 *P=0.132* | 2.513 *P=0.113* | R=0.13 P=0.094 |
| Day3 ARC | 10.363 *p=0.001* | *P=0.003* | 9.387 *P=0.002* | 10.276 *P=0.001* | r=0.295 *p=0.001* |

There was a significant positive association observed between patients admitted for brain tumors and the occurrence of ARC. The Pearson's chi-square analysis further confirmed this relationship as statistically significant ($\chi2 = 11.178$, $p = 0.001$). In contrast, no positive correlation was detected between SAM and ARC during the first three days of PICU stay.

Additionally, patients admitted following cardiac surgeries were less likely to develop ARC, as evidenced by the non-significant statistical results (OR = 0.599, $p = 0.439$, $r = -0.059$, $p = 0.442$).

Furthermore, the analysis revealed no significant correlation between ARC and the use of mechanical ventilation or antimicrobial treatment (mechanical ventilation: $\chi2 = 1.000$, $p = 0.317$; antimicrobial treatment: $\chi2 = 3.141$, $p = 0.076$).

### Comparative analysis of individuals with and without ARC

The study employed a Mann-Whitney U test to investigate differences in age, weight, height, and body surface area between the cohort with at least one instance of augmented renal clearance during the first three days and the cohort without any record of ARC during the same period. The results revealed statistically significant disparities across all four variables. Specifically, the cohort without a record of ARC in the initial three days exhibited significantly lower values for age, weight , height, and body surface area compared to the cohort that did have at least one instance of ARC in the first three days.

**Table 7 Mann-Whitney U test of age, weight, age, BSA**

| Variable | Mann-Whitney U | z | P |
|---|---|---|---|
| Age | 2475.00 | -3.009 | *.003* |
| Weight | 2403.50 | -3.237 | *.001* |
| Height | 2393.00 | -3.270 | *.001* |
| Body Surface Area | 2344.00 | -3.427 | *.001* |

One-way ANOVA test was conducted to examine the mean estimated glomerular filtration rate (eGFR) across the three admission categories. The results revealed statistically significant differences between the groups over three days: day1 ($F=5.11$, $p=0.007$), day2 ($F=7.94$, $p=0.001$), and day3 ($F=5.47$, $p=0.005$). Follow-up post-hoc tests using Tukey's HSD were performed. The findings indicated that the mean eGFR was significantly higher in the surgical group compared to the medical group during the three days of measurement.

**Table 8. One way ANOVA of admission categories**

| Day | Group Comparison | Mean Difference | *p Value* |
|---|---|---|---|
| 1 | Surgical vs Medical | 20.42 | *0.001* |
| 2 | Surgical vs Medical | 26.75 | *<0.001* |
| 3 | Surgical vs Medical | 54.38 | *0.011* |

## Predictors of ARC and Death

Binary logistic regression analysis was conducted to evaluate risk factors associated with ARC. After controlling for other variables, BSA demonstrated a significant positive correlation with ARC. For every 1 m2 increase in BSA, the risk of experiencing at least one ARC during the first three days of PICU stay increased by 4.66 times (p=0.023). Additionally, older age was also found to be associated with the development of ARC (AOR=1.119, 95% CI: 1.008-1.243, p=0.035**)**

Patients admitted following neurosurgical interventions and with febrile neutropenia exhibit an elevated risk of experiencing ARC at least once during the initial 3 days of their PICU stay. The analysis reveals that febrile neutropenia is associated with an adjusted odds ratio of 5.412 (95% CI: 1.724-16.992, p=0.004), while post-neurosurgery patients have an AOR of 4.132 (95% CI: 1.485-11.499, p=0.007).

Univariate logistic regression analysis males have significantly higher risk of ARC when compared to females on day 1 of admission to PICU(AOR=3.987; CI 1.17-13.586, *p=0.027)*

A logistic regression was performed with 'Age category' as a predictor variable. Compared with the reference age group(under 2), belonging to Age Category(6-15 year old) was associated with significantly higher odds of ARC (OR = 2.515, 95% CI [1.150, 5.501], *p = .021*).

**Table 9. Predictors of ARC**

| **Risk factors of ARC** | **OR** | ***P-value*(95% CI)** |
|---|---|---|
| BSA | 4.66 | *0.023*[1.241,17.52] |
| Age category (6-15) | 2.515, | *0.021* [1.150, 5.501] |
| Febrile neutropenia | 5.412 | 0.004[1.724, 16.992] |
| Neurosurgery | 4.132 | 0.007 [1.485, 11.499] |
| Hematologic malignancies | 2.72 | 0.019[1.18, 6.30] |
| Brain tumors | 5.90 | 0.001[2.12, 16.43] |

The Phoenix score was found to be an independent predictor of mortality at day 7 of PICU admission (adjusted odds ratio [AOR] = 2.137, 95% confidence interval [CI] 1.626-2.809, $p < 0.001$). Additionally, patients with febrile neutropenia were also at an increased risk of mortality at day 7 of PICU admission (AOR = 5.679, 95% CI 1.559-20.688, $p = 0.008$)

Multivariate binary logistic regression analysis also revealed a significantly elevated risk of mortality in hypotensive patients (Adjusted Odds Ratio [AOR] = 7.325, 95% Confidence Interval [CI] 3.388-15.836, $p < 0.001$). Additionally, there was a markedly increased risk of mortality on day 7 among those requiring vasopressor support (AOR = 8.091, 95% CI 3.740-17.520, $p < 0.001$).

In our study presence of ARC atleast once during first three days of PICU stay was associated with increased risk of death, but not statistically significant(AOR= 2.456; CI .740-8.145, *p=0.142*).

**Table 10. Predictors of death at day7**

| **Risk factors for death** | **OR** | **P –value, 95% CI( )** |
|---|---|---|
| Phoenix score | 2.137 | *<0.001*[1.626,2.809] |
| hypotension | 7.325 | *<0.001* [3.388,15.836] |
| Using vasopressor | 8.091 | *<0.001*[3.740,17.520] |
| Febrile neutropenia | 19.36 | 0.001[3.49, 107.43] |
| ARC | 2.45 | 0.142[.740,8.145] |

## Survival Analysis patients with ARC

Survival analysis was carried out to investigate the impact of experiencing at least one episode of ARC within the first three days of admission on patient survival. A series of statistical tests, including Log Rank were performed. It revealed a significant difference in survival distributions between the groups (Log Rank: $\chi^2 = 11.323$, $p = .001$; ), indicating that the presence of at least one ARC record during the initial three days of hospitalization is associated with patient survival outcomes. The median survival time was 3.70 for the ARC group compared to 2.75 for the non-ARC group.

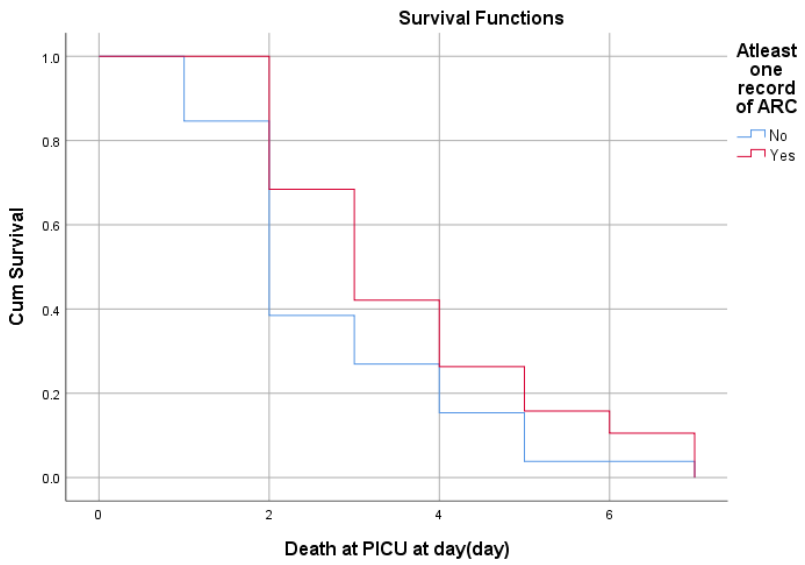


**Figure 6 survival Analysis of patients admitted at PICU**

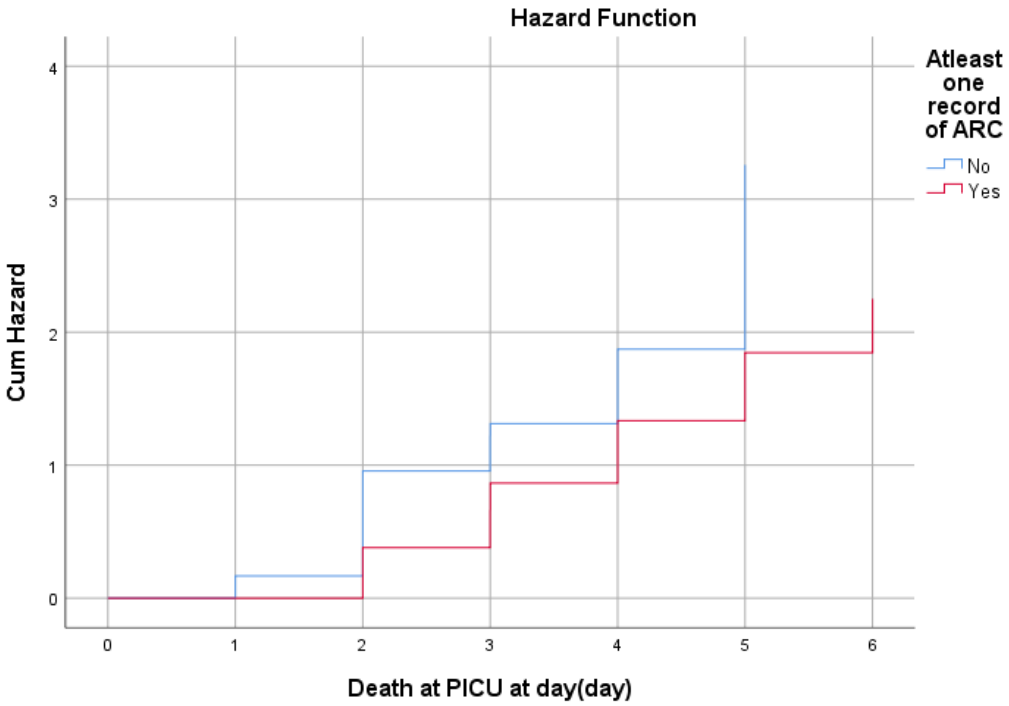


**Figure 7 Hazard ratio Analysis of patients admitted at PICU**

## ROC Curve of phoenix score as predictor of mortality

A Receiver Operating Characteristic (ROC) curve was generated to assess the performance of the Phoenix score. The ROC curve showed that the Phoenix score demonstrated good discriminatory ability. The Area Under the Curve (AUC) was 0.888 (95% CI [.838, .937]), which is significantly different from chance ($p < .001$) and small standard error (0.025) indicating good discrimination ability between the groups. This finding is supported by the visual observation that the ROC curve was clearly above the line of chance.

The trade-off between sensitivity and specificity at various threshold values for the Phoenix score is shown in **Table 9** The table demonstrates the sensitivity and 1 - specificity at each of the given threshold levels of the Phoenix score. The threshold value of 2.5 provided a sensitivity of 0.911, with a false positive rate of .256.

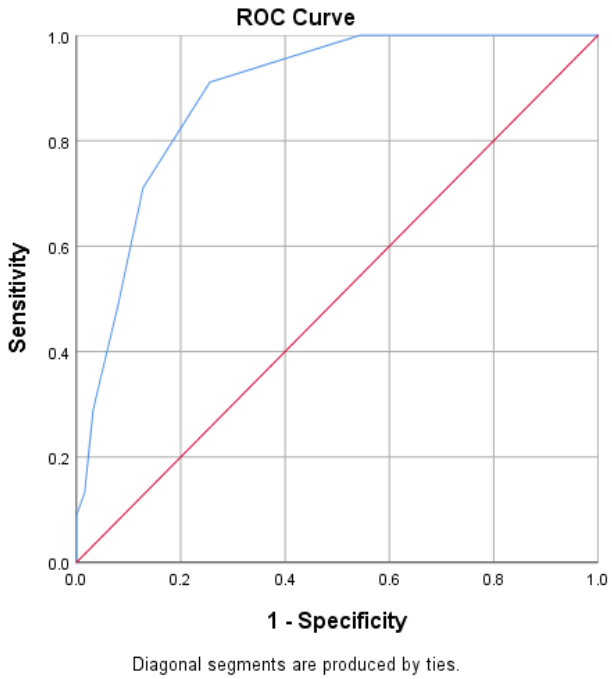


**Figure 7 ROC curve phoenix score as predictor of death at day 7**

**Table 11 Test Result: Phoenix score as predictor of death at day 7**

| Positive if ≥ | Sensitivity | 1-Specificity |
|---|---|---|
| -1.00 | 1.000 | 1.000 |
| .50 | 1.000 | .960 |
| 1.50 | 1.000 | .544 |
| **2.50** | **.911** | **.256** |
| 3.50 | .711 | .128 |
| 4.50 | .489 | .080 |
| 5.50 | .289 | .032 |
| 6.50 | .133 | |
| 7.50 | .089 | .000 |
| 9.00 | .000 | .000 |

## Discussion

This study sought to investigate the clinical and laboratory predictors associated with augmented renal clearance (ARC) and outcomes in a pediatric intensive care unit (PICU) settings. ARC is increasingly recognized as a phenomenon affecting critically ill patients, leading to suboptimal drug dosing and potential treatment failure. Despite its clinical importance, there remains a lack of consensus on its risk factors and consequences, particularly in pediatric populations.

The findings of this study provide valuable insights into the interplay between demographic, biochemical, and clinical variables in the occurrence of ARC. Significant associations were observed between ARC and variables such as age, sex, body surface area (BSA), and renal biomarkers, shedding light on potential predictors that may aid in early identification of at-risk patients.

In a systematic review done in Spain on adult patients (ARC was defined as CrCl >130mL/min/$m^2$) ARC was present in 20-65% of critically ill patients. Younger age, polytrauma, lower severity of illness have been identified as risk factors.ARC was consistently associated with sub-therapeutic drug levels. Our study aims at magnitude of ARC in children(under 15 year old) and the definition of ARC is different from this study. ARC is present atleast once during the first three days of PICU in 38.8% of patients which is in the range of the above study. Male sex, age between 6-15, patients admitted post surgical procedures were at risk of having ARC.

A retrospective chart review study done in Saudi Arabia on 217 adult patients of whom 73% had febrile neutropenia showed ARC prevalence of 47.5%. There was significant association between febrile neutropenia and ARC: $\chi^2(1, 270)=8.60$, $p<0.05$. The trough concentration of vancomycin among febrile neutropenia patients with ARC was significantly lower than for those without ARC. In our study patients with febrile neutropenia comprised of 9.4% of total sample

size, 68.8%(11/16) of febrile neutropenia have atleast one record of augmented renal clearance. There is statistically significant positive correlation between ARC and febrile neutropenia($\chi^2$1,170)=8.63, *p=0.003).* Vancomycin was used in 9/16(56.5%) of febrile neutropenia patients. In our setting we are not monitoring serum vancomycin. But interms of medication dosing all patients with febrile neutropenia has got maximum approved dosing, though only 22.2%(2/9) patients have received extended infusion of vancomycin.

A retrospective observational study conducted in the UK reported a 47% prevalence of ARC. Factors associated with an increased rate of ARC included younger age, male sex, lower APACHE II scores, and the presence of sepsis. The median time to ARC onset was 1 day, with 64% of affected patients developing the condition within 24 hours. Patients with ARC had a larger median body surface area compared to those without. The current study findings are consistent with the previous report, with a median ARC onset of 1 day and 63.07% of patients experiencing ARC onset during the first day. The difference in prevalence between the studies may be attributable to variations in patient age and ARC definitions.

A prospective study conducted on adult ICU patients at Ghent University Hospital revealed an ARC prevalence of 51.6% on at least one antimicrobial day. The study found ARC to be associated with younger age and male gender, but not with the severity of illness. Comparatively, the present study demonstrated a 25% lower ARC prevalence. Potential explanations include differences in patient demographics, ARC definition, and the duration of data collection, in the previous study. The current investigation also identified an association between male gender and ARC, but no correlation with the Phoenix score.

A prospective observational study on 20 adults with subarachnoid hemorrhage in the USA revealed a 100% incidence of augmented renal clearance. While our study did not include patients with subarachnoid hemorrhage, patients who underwent neurosurgical procedures exhibited an increased proportion of ARC(63.2%), with a significant positive correlation ($\chi^2$ = 5.626, p = 0.018, r = 0.182, p = 0.018). Additionally, nearly three-quarters (71.4%) of brain tumor patients exhibited ARC, and there was a significant positive association between admission for brain tumor and ARC ($\chi^2$ = 11.178, p = 0.001, r = 0.256, p = 0.001).

A comprehensive systematic review and meta-analysis conducted on critically ill adults in Canada revealed a pooled prevalence of ARC of 39%. The highest incidence was observed in neurocritically ill patients. Additionally, younger age, male sex, and trauma were identified as risk factors associated with increased susceptibility to ARC. Notably, the findings from our study corroborate these trends, with a comparable magnitude of ARC and the highest occurrence observed in the neurocritical patient population.

A prospective observational study was conducted on children admitted to Ghent University Hospital, with a median age of 1.54 years, and most patients were admitted after surgery. Acute

renal cortical changes were observed in 67.4% of patients for at least one day. The proportion of ARC decreased over the study period. Factors associated with an increased risk of ARC included mechanical ventilation, antibiotic treatment, and higher PRISM scores. Conversely, children who underwent cardiac surgery were less likely to develop ARC. The modified Schwartz formula was utilized to calculate estimated glomerular filtration rate (eGFR) in this study. In our study no association was found between mechanical ventilation and ARC, potentially due to patients who died without being on mechanical ventilation. The study population's median age was 1.5 years, similar to the previous report.

The retrospective study conducted on adult patients in Japan revealed that the onset of ARC occurred within three days in approximately half of the cases, and within one week in most cases. The prevalence of ARC was reported to be 33.4%, and the median duration of ARC, as indicated by the Kaplan-Meier curve, was 5 days. Interestingly, the onset of ARC was associated with a reduction in mortality. Additionally, the study found that younger age, vasopressor use, central nervous system diseases, and the presence of comorbid illnesses were associated with an increased risk of developing ARC. In our study, the median duration of ARC was 2 days, and they measured eGFR only during the first 3 days of the PICU stay. The univariate logistic regression analysis in our study revealed that older age was associated with a higher risk of ARC. Notably, our study found that ARC was neither associated with nor a risk factor for death. However, the true prevalence of ARC may have been underreported in our study due to the method of GFR estimation and inconsistencies in the definition of ARC.

## Conclusion

The research underscores the significant magnitude of augmented renal clearance in the given setting. Patients admitted following neurosurgical procedures,hematologic malignancy, brain tumor and febrile neutropenia were identified as being at heightened risk of developing ARC. The study highlighted meaningful associations between clinical variables and patient outcomes, providing valuable insights to optimize management strategies. Notably, the presence of ARC was linked to altered pharmacokinetics, emphasizing the need for individualized dosing approaches, particularly for antibiotics such as vancomycin, which warrant focused attention in this context. The findings suggest that early recognition of ARC and implementation of appropriate dosing adjustments could enhance therapeutic outcomes and mitigate the risk of suboptimal treatment in critically ill pediatric patients. Furthermore, the study demonstrated that factors including age, body surface area, and specific laboratory markers significantly influenced the likelihood of ARC development, further underscoring the importance of routine monitoring in high-risk populations. In conclusion, this research underscores the pivotal role of personalized medicine in PICU care and identifies areas for future investigation, such as prospective studies to validate dosing algorithms and further explore risk factors for ARC in pediatric patients.

Strengthening clinical guidelines based on these findings could lead to improved outcomes and enhanced quality of care for vulnerable patient populations.

## Limitations

This was a cross-sectional study conducted at two centers. The analysis was restricted to outcomes observed within the first 7 days of PICU admission, potentially overlooking long-term clinical sequelae or complications. Although the study explored dosing strategies and administration methods for vancomycin and other widely used antibiotics, the absence of direct serum drug level measurements constrained the comprehensive assessment of drug efficacy and toxicity. Due to critical status of the patients it was impossible to take height as per SOPs.Additionally, funding and time constraints impeded the inclusion of more advanced laboratory investigations.

## Recommendations

Based on the findings of this study on the prevalence and factors associated with Augmented Renal Clearance (ARC) among children admitted to TASH and ALERT Hospitals, the following recommendations are proposed:

1. Enhanced screening and identification:

We recommend implementing routine assessment of Glomerular Filtration Rate (GFR) in critically ill children upon admission to the PICUs

Utilize risk factor screening: Develop and implement a standardized screening tool or checklist based on the risk factors identified in this study.

2. Optimized medication dosing:
Pharmacokinetic Considerations: Clinicians should be aware of the potential for altered drug pharmacokinetics in children with ARC, particularly with medications that are primarily renally cleared. It's essential to adjust dosing regimens based on the child's GFR and the pharmacokinetic properties of prescribed medications.
Specific Drug Dosing Guidelines: Develop and implement specific dosing guidelines for commonly used medications, which takes into account the effects of ARC on drug clearance. Focus should be on medications such as beta-lactam antibiotics, vancomycin, and aminoglycosides, as these are often used and heavily affected by ARC.

3. Further Research and Data Collection: Prospective Studies: Conduct prospective studies to validate the risk factors identified in this study and to develop more accurate prediction models for ARC in children. This will allow for early interventions.

Longitudinal Follow-Up: Conduct longitudinal studies to determine the long-term implications of ARC in children

Multicenter Collaboration: We recommend establishing a multi-center collaborative network to facilitate data sharing and more robust research into ARC in pediatric populations. This will allow a larger and more diverse dataset to be used, providing a greater evidence base.

Develop Data Registry: Create a data registry to track the prevalence of ARC and the clinical outcomes in children, which will serve as a resource for future investigations and policy changes.

4. Clinical Practice and Policy Implications:

Develop Clinical Guidelines: Based on the evidence and best practices, develop evidence based clinical guidelines for the management of ARC in children in both TAH and ALERT hospitals.

Staff Education: Conduct regular educational programs for physicians, pharmacists, and nurses on the identification, assessment, and management of ARC in children. This will ensure that all staff involved are aware of this phenomenon.

Resource Allocation: Ensure adequate resource allocation to enable the implementation of the recommended screening, therapeutic drug monitoring, and data collection systems in the pediatric departments.

Implement Audit: Implement regular audits of medication practices to ensure compliance with ARC-informed dosing adjustments. This will ensure patient safety.

5. Special Considerations:

Address Specific Populations: Implement policies for special cases where ARC has more significant implications, such as in patients with sepsis, Hemotologic malignancy, burns, major surgery

Develop an ARC Protocol: Develop a specific protocol for managing pediatric patients with ARC within each of your hospital systems, that contains specific parameters for the identification, monitoring, and management of ARC

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## ANNEX 1

## Research Consent/Assent, Questionnaire and Data Collection list(English version)

### Assent form

Assent Form for Adolescents who Participate in  Research Program

Title of Study: MAGNITUDE AND FACTORS ASSOCIATED WITH AUGMENTED RENAL CLEARANCE AND PRACTICE OF ANTIMICROBIAL PRESCRIPTION IN PEDIATRIC INTENSIVE CARE UNITS AMONG CHILDREN ADMITTED TO TASH AND ALERT CENTER

Principal Investigator: Dr. Turegne Assefa Siyum

Advisors: Professor Workeabeba Abebe

Doctor Wondwossen Amogne

Doctor Bezaye Abebe

Introduction:

Hello,

We invite you to participate in a research program aimed at assessing renal status in critically ill children admitted to PICUs. Before you decide whether to take part, we want to provide you with more information about the study and what it involves.

Purpose and Procedures:

This is to inform and ask your assent that the research entitled “Magnitude And Factors Associated With Augmented Renal Clearance And Practice Of Antimicrobial Prescription In Pediatric Intensive Care Units Among Patients Admitted To TASH And ALERT Center, Ethiopia 2024” will be done by me and my advisors Professor Workeabeba Abebe, Dr. Wondwossen Amogne, Dr.Bezaye Abebe . The research tries to assess renal problem in critically ill children which is associated with excess loss of medications through urine. Knowing this will help us in optimizing dosing of antimicrobials in critically ill children. Your participation in this study is entirely voluntary.

- If you agree to participate, you will be asked to give sample of  2mL of blood on second day of PICU admission and the cost will be covered by the investigator. Other laboratory results will be taken from medical records

## Confidentiality:

- Your privacy and confidentiality are of utmost importance. Any information collected will be kept secure and anonymous. Your identity will be protected throughout the study. But for the sake of your health we will inform result of your renal status to treating physician(s)

Benefits and Risks:

- Every laboratory result will be communicated to treating physician to optimize antibiotic treatment and your participation will help us in optimizing antimicrobial dosing for critically ill children in the future.

- By participating in this study there is no short term or long term risks to you.

Your Rights:

- Your participation is entirely voluntary. You can choose to stop participating at any time without penalty.

- If you have any questions or concerns, feel free to contact the researcher

Researcher;- Dr. Turegne Assefa Siyum

Phone number:-+251978701279

Email:- turegnassefa@gmail.com

Assent Statement:

I have read and understood the information provided in this assent form. I agree to participate in the research program and confirm that I have my parent/guardian's permission to take part.

Participant's Name: _____

Participant's Signature: _____

Date: _____

Parental/Guardian Permission:

I, as the parent/guardian of the participant, hereby give my consent for my child to participate in the research program as described above.

Parent/Guardian Name: _____

Parent/Guardian Signature: _____

Date: _____

በጥናት ለመሳተፍ ከታዳጊ ጋር የሚደረግ የስምምነት ቅጽ

ጥናቱን የሚያከናውነው:- ዶ/ር ጡረኝ አሰፋ ሲዩም

አማካሪዎች:- ፕሮፌሰር ወርቅአበባ አበበ

-ዶ/ር ወንድወሰን አሞኘና

-ዶ/ር ቤዛዬ አበበ

መግቢያ

በፅኑ ሕሙማን ክፍል ውስጥ ተኝተው በሚታከሙ ሕፃናት ላይ የኩላሊታቸውን ሁኔታ አስመልክቶ በሚደረግ ጥናት ውስጥ እንድትሳተፍ/እንድትሳተፊ እጠይቃለሁ። በጥናቱ ለመሳተፍ ከመወሰንህ/ሽ በፊት ስለ ጥናቱ ተጨማሪ መረጃዎችን እሰጥሃለሁ/ሻለሁ

የጥናቱ ዓላማ

ዓላማው በፅኑ ሕሙማን ክፍል ውስጥ ተኝተው በሚታከሙ ሕፃናት ላይ የሚከሰትን የኩላሊት ችግር ለማጥናት ነው። ይህ ችግር የሚያጋጥማቸው ሕመምተኞች በሰውነታቸው ውስጥ ያለው የፀረ ባክቴሪያ መድኃኒቶች መጠን ከጤነኛ ሰዎች በበለጠ ሁኔታ በኩላሊታቸው አማካይነት ይወገዳል። ይህንን ሁኔታ ማወቅ በፅኑ ለታመሙ ልጆች የፀረ ባክቴሪያ መድኃኒቶችን የምንሰጥበትን መንገድ እንድናሻሽል ይረዳል።በጥናቱ ውስጥ የምትሳተፈው/ፊው በፈቃደኝነት ነው። ጥናቱ በሚሰራበት ጊዜ ፅኑ ህሙማን በገባህ/ሽ በሁለተኛው ቀን 2ሚሊ የደም ናሙና ተወስዶ የኩላሊት ምርመራ ይደረጋል። የቀረውን መረጃ ከህክምና ማህደር እንወስዳለን። ሌሎችን የጤና ሁኔታዎችም በተዘጋጀ መጠይቅ መሠረት ክትትል እናደርጋለን።

ሚስጥርን መጠበቅ

ያንተ/ያንቺ መረጃዎች ጥናቱን ከሚያከናውኑትና ለህክምና ሲያስፈልግ ማለትም የኩላሊትህ/ሽን ሁኔታ ለሚያክሙህ ባለሙያዎች ከማሳወቅ በስተቀር በማንኛውም መልኩ ለሌላ አካል ተላልፈው አይሰጡም።

የጥናቱ ጥቅምና ጉዳት

በዚህ ጥናት በመሳተፍህ የሚደርስብህ/ሽ ጉዳትም የለም።የላቦራቶሪ ውጤቱ እንደ ደረሰ ለቅርብ ሃኪም ይነገራል። ይህም ለህክምናው ውጤታማ መሆን ያግዛል። በጥናቱ በመሳተፍህ/ሽ ለወደፊቱ በፅኑ ለታመሙ ልጆች የፀረ ባክቴሪያ መድኃኒቶችን አሰጣጥ ለማሻሻል ይረዳል።

መብትን በተመለከተ

በዚህ ጥናት የምትሳተፈው/ፊው በፈቃደኝነት ነው። በማንኛውም ሰአት ጥናቱን የማቋረጥ መብት አለህ/ሽ።

ጥያቄ ካለህ/ሽ አሁንም በማንኛው ጊዜ መጠየቅ ትችላለህ/ሽ

ጥናት አድራጊ:- ዶ/ር ጡረኝ አሰፋ ሲዩም

ስልክ ቁጥር:-+251978701279

ኢሜይል:- turegnassefa@gmail.com

የስምምነት መግለጫ

በዚህ የስምምነት ቅፅ ላይ የተሰጡትን መረጃዎች ተረድቼያለሁ። በዚህ ጥናት ለመሳተፍ ፈቃደኛ ነኝ፣ የወላጆቼንም ፈቃድ አግንቻለሁ።

የተሳታፊው ስም_____

ፊርማ_____

ቀን_____

እኔ እንደ ወላጅ /አሳዳጊ ከላይ በተገለፀው መሠረት ልጄ በዚህ ጥናት እንዲሳተፍ ፈቅጃለሁ።

የወላጅ/የአሳዳጊ ስም_____

ፊርማ_____

ቀን_____

Informed Consent Form for Parents/Guardians to Allow Their Child to Participate in a Study(English version)

Title of Study: Magnitude And Factors Associated With Augmented Renal Clearance And Practice Of Antimicrobial Prescription In Pediatric Intensive Care Units Among Patients Admitted To Tash And Alert Center, Ethiopia 2024" will be done by me and my advisors

Principal Investigator: Dr. Turegne Assefa Siyum

Advisors: Professor Workeabeba Abebe and

Doctor Wondwossen Amogne

Doctor Bezaye Abebe

Introduction:

We seek your consent for your child to participate in a research study aimed at assessing renal status in critically ill children admitted to PICUs. Your child's involvement in this study is entirely voluntary. Before you make a decision, we want to provide you with detailed information about the study and what it entails.

Purpose of the Study:

- This is to inform and ask your consent that the research entitled "Magnitude and Factors Associated With Augmented Renal Clearance In Pediatric Intensive Care Unit Patients In TASH And ALERT Center, Ethiopia 2024" will be done by me and my advisors Professor Workeabeba Abebe and Dr. Wondwossen Amogne . The research tries to assess renal problem in critically ill children which is associated with excess loss of medications through urine. Knowing this will help us in optimizing dosing of antimicrobials in critically ill children. Your child's participation in this study is entirely voluntary.

If you agree to participate, your child will be asked to give sample of 2mL blood on second day of PICU admission. Other laboratory results will be taken from medical records

Confidentiality and Data Security:

- All information collected during the study will be kept confidential. Your child's identity will remain anonymous in any reports or publications resulting from the research. Any information collected will be kept secure and anonymous. But for the sake of your child's health we will inform result of his/her renal status to treating physician(s)

- Any personal information obtained will be stored securely and accessed only by authorized members of the research team.

Benefits and Risks:

- Every laboratory result will be communicated to treating physician to optimize antibiotic treatment and your child's participation will help us in optimizing antimicrobial dosing for critically ill children in the future.

- There is no immediate or long term risks associated with participation in this study.

Right to Withdraw:

- Your child's participation is entirely voluntary. You can choose to withdraw your child from the study at any time without consequences.

- If you have any questions or concerns, please contact the researcher

Primary Researcher: Dr. Turegne Assefa Siyum

Phone number: +251978701279

Email: turegnassefa@gmail.com

Consent Statement:

I have read and understood the information provided in this consent form. I agree to allow my child, _____(name), to participate in the research study.

Parent/Guardian Name: _____

Parent/Guardian Signature: _____

Date: _____

Additional Terms:

- By signing this consent form, you acknowledge that you have had the opportunity to ask questions and discuss the study with the research team.

- A copy of this consent form will be provided to you for your records.

ለወላጅ/አሳዳጊ ልጃቸው በጥናት እንዲሳተፍ ፍቃዳቸውን ለማግኘት የተዘጋጀ የስምምነት ቅጽ

ጥናቱን የሚያከናውነው:- ዶ/ር ጡረኝ አሰፋ ሲዩም

አማካሪዎች:- ፕሮፌሰር ወርቅአበባ አበበ

ዶ/ር ወንድወሰን አሞኘና

ዶ/ር ቤዛዬ አበበ

መግቢያ

በፅኑ ሕሙማን ክፍል ውስጥ ተኝተው በሚታከሙ ሕፃናት ላይ የኩላሊታቸውን ሁኔታ አስመልክቶ በሚደረግ ጥናት ውስጥ ልጅዎ እንዲሳተፍ/እንድትሳተፍ እጠይቃለሁ። ልጅዎ በጥናቱ ውስጥ የሚሳተፈው/የምትሳተፈው እርስዎ ፈቃደኛ ከሆኑ ነው። ይህንን ከመወሰንዎ በፊት ስለ ጥናቱ ሁኔታ መረጃዎችን እሰጥዎታለሁ።

የጥናቱ ዓላማ

ዓላማው በፅኑ ሕሙማን ክፍል ውስጥ ተኝተው በሚታከሙ ሕፃናት ላይ የሚከሰትን የኩላሊት ችግር ለማጥናት ነው። ይህ ችግር የሚያጋጥማቸው ሕመምተኞች በሰውነታቸው ውስጥ ያለው የፀረ ባክቴሪያ መድኃኒቶች መጠን ከጤነኛ ሰዎች በበለጠ ሁኔታ በኩላሊታቸው አማካይነት ይወገዳል። ይህንን ሁኔታ ማወቅ በፅኑ ለታመሙ ልጆች የፀረ ባክቴሪያ መድኃኒቶችን የምንሰጥበትን መንገድ እንድናሻሽል ይረዳል። ልጅዎ በጥናቱ ውስጥ የሚሳተፈው/የምትሳተፈው በእርስዎ ፈቃድ ነው። ጥናቱ በሚሰራበት ጊዜ ልጅዎ ፅኑ ህሙማን በገባ/ች በሁለተኛው ቀን 2ሚሊ የደም ናሙና ተወስዶ የኩላሊት ምርመራ ይደረጋል። የቀረውን መረጃ ከህክምና ማህደር እንወስዳለን። ሌሎችን የጤና ሁኔታዎችም በተዘጋጀ መጠይቅ መሠረት ክትትል እናደርጋለን።

ሚስጥርን መጠበቅ

የልጅዎ መረጃዎች ጥናቱን ከሚያከናውኑትና ለህክምና ሲያስፈልግ ማለትም የልጅዎን የኩላሊት ሁኔታ ለሚያክሙት/ሚት ባለሙያዎች ከማሳወቅ በስተቀር በማንኛውም መልኩ ለሌላ አካል ተላልፈው አይሰጡም።

የጥናቱ ጥቅምና ጉዳት

በዚህ ጥናት በመሳተፉ/ፏ የሚደርስበት/ባት ጉዳትም የለም።የላቦራቶሪ ውጤቱ እንደ ደረሰ ለቅርብ ሃኪም ይነገራል። ይህም ለህክምናው ውጤታማ መሆን ያግዛል። ልጅዎ በጥናቱ በመሳተፉ/ፏ ለወደፊቱ በፅኑ ለታመሙ ልጆች የፀረ ባክቴሪያ መድኃኒቶችን አሰጣጥ ለማሻሻል ይረዳል።

መብትን በተመለከተ

በዚህ ጥናት ልጅዎ የሚሰታፈው/የምትሳተፈው በእርስዎ ፈቃድ ሲሆን በማንኛውም ሰአት ጥናቱን ማቋረጥ ይችላሉ።

ጥያቄ ካልዎት አሁንም በማንኛውም ጊዜ መጠየቅ ይችላሉ።

ጥናት አድራጊ:- ዶ/ር ጡረኝ አሰፋ ሲዩም

ስልክ ቁጥር:-+251978701279

ኢሜይል:- turegnassefa@gmail.com

<u>የስምምነት መግለጫ</u>

በዚህ ስምምነት ቅጽ ላይ የተሰጡትን መረጃዎች ተገንዝቤያለሁ እንደ ወላጅ /አሳዳጊ ከላይ በተገለፀው መሠረት ልጄ በዚህ ጥናት እንዲሳተፍ ፈቅጃለሁ።

የስምምነት ቅጹ አንድ ኮፒ እንደሚሰጠኝም አውቄያለሁ።

የወላጅ/የአሳዳጊ ስም_____

ፊርማ_____

ቀን_____

## ANNEX 2

STANDARD OPERATING PROCEDURES(SOPs)

1. Baseline line and follow up patient data

A)Weight will be measured by calibrated weight scale by the same person & calibration will be done daily by using 1 Litre of Normal saline.

Procedure include:-

-Explain the procedure to the family

-Use weight scale(analogue) and place the scale on firm flooring and it should read zero when empty

-Remove shoes and heavy clothing

-Have the child or teen stand with both feet in the center of the scale

-Record weight to the nearest 0.1kg decimal

- For infants and children who cannot stand alone,diaper should be removed, the guardian will stand alone first and then stand hugging the baby on the weigh scale. The difference of the two is baby's weight.

B)Measuring height: for a child ≤2 year of age

- Explain the procedure to the family

-Take in recumbent position

-Needs assistant

-Child lies supine, flat and straight on a recumbent position on a board

-Assisstant put head to touch fixed head board

-Measuring person pulls the legs gently putting one hand on the thighs

-Move the feet-board until it touches the soles firmly

The measurement should be read to the nearest 0.1cm

For children who can stand, stadiometer will be used

- Explain the procedure to the family

- The child should stand with up straight, with buttocks, heels and shoulder blades, occiput touching the stadiometer

-The angles of the eyes should be parallel to the floor

-The feet should be together

-The upper plate should be moved down until it touches the head of the patient

- The measurement should be read to the nearest 0.1cm

C) Measuring mid upper arm circumference for patients between 6 -59month of age.

-Explain the procedure to the family

-Identify the mid point of the arm between the acromion and olecranon.

-The arm should be hanging freely by the side of the body, not flexed

-Measure MUAC by standard flexible measuring tape

-Record MUAC to the nearest 0.1cm

D)Urine output: will be measured

-catheterize using NG-tube or foley catheter

Appropriate size: 4 French for children younger than 6 months, 8 French for those between 6 months and adolescence age, 10 French for adolescence

-Explain the procedure to the family

-Restrain the child in the supine and frog leg position

-Clean anterior urethra thoroughly with antiseptic(e.g. povidone iodine solution)

-A sterile lubricant jelly should be applied to the end of appropriately sized catheter

<u>Boys</u>

-Gently retract foreskin of glans if uncircumscribed

-Straighten urethra by using nondominant hand and hold the penus perpendicular to the lower abdomen

-Insert the catheter using the dominant hand until the urine returns

-Be gentle and never force the catheter

- For uncircumcised males, once the catheter is inserted we should make sure that the foreskin returns back to its normal position to prevent paraphimosis

-Fix the catheter with adhesive tape(in those who are catheterized with nasogastric tube) to the inner thigh to prevent dislodging

Girls

-Swab the vulvar area from front to back by using epovidone-iodine solution

-An assistant retracts the labia majora

-Insert the catheter until urine returns

- Fix the catheter with adhesive tape(in those who are catheterized with nasogastric tube) to the inner thigh to prevent dislodging

-Urine output will be measured every twelve hourly and expressed as mL/kg/hr

2. Cut-off to define ARC

| Age(mo) | Mean GFR(mL/min/1.73 $m^2$) ± SD | Cut-off to define ARC(mL/min/1.73 $m^2$) |
|---|---|---|
| ≤1.2 | 52.0±9.0 | 73.3 |
| 1.2-3.6 | 61.7±14.3 | 91.2 |
| 3.6-7.9 | 71.7±13.9 | 102.72 |
| 7.9-12 | 82.6±17.3 | 119.88 |
| 12-18 | 91.5±17.8 | 131.16 |
| 18-24 | 94.5±18.1 | 135.12 |
| >24 | 104.4±19.9 | 149.16 |

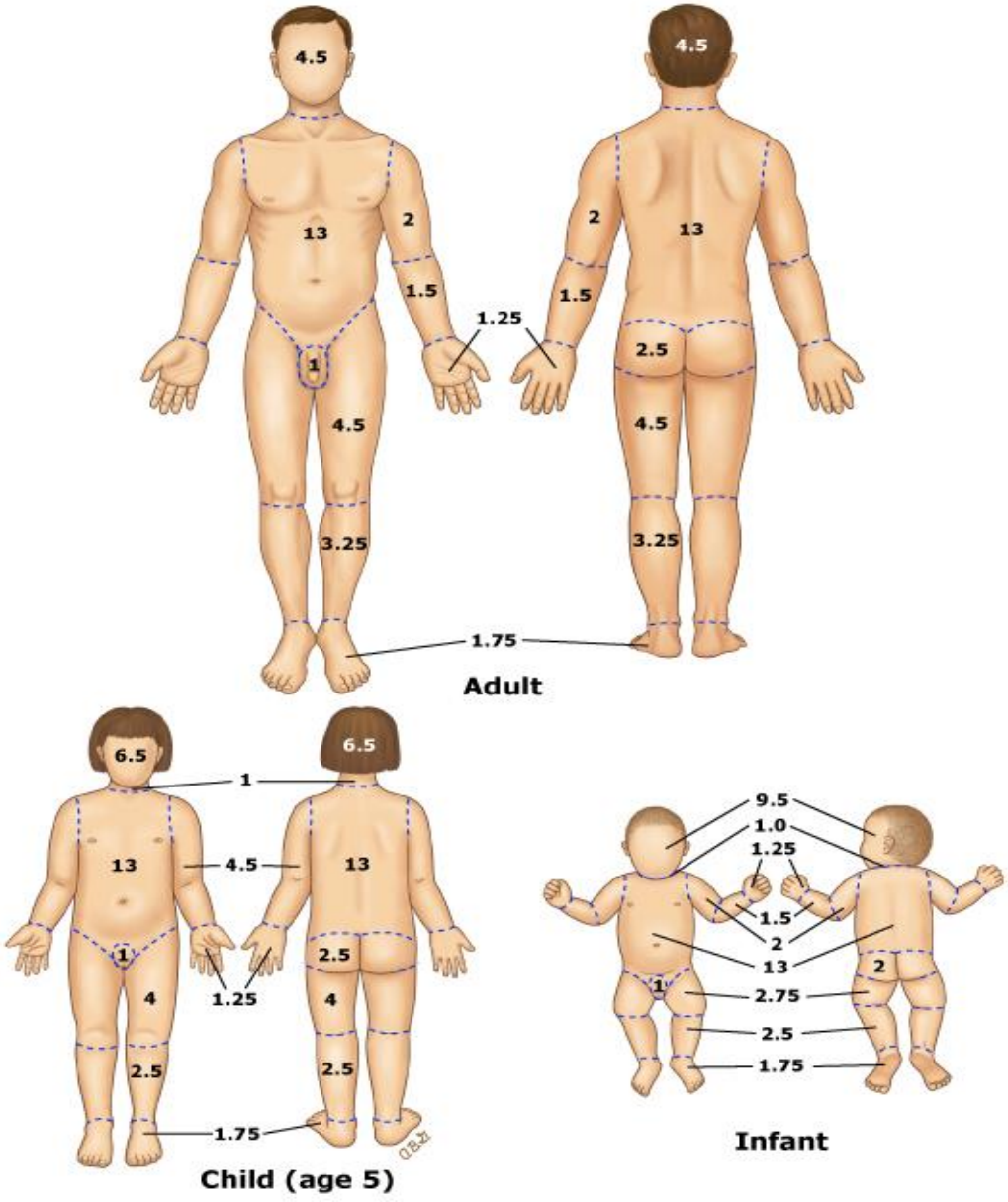
III)To assess renal function test 3mL of blood , to assess serum albumin level 2mL of blood, to assess C-RP level 2mL of blood will taken. Daily eGFR will be calculated based on serum creatinine level to assess whether the patient has Augmented renal clearance or not. The laboratories have their own daily quality control tests before starting routine Scr testing.

IV) standard dosing of antibiotics for patient with normal renal function

| Antibiotics | Dosing per kilogram of body weight |
|---|---|
| Vancomycin | -loading dose → 20-25mg/kg IV to be infused over 3 hours<br>-maintenance dose →15-20mg/kg/dose IV every 8hr |
| Cefepime | 100-150mg/kg/day IV divided every 8-12hr |
| Ceftriaxone | 50-75mg/kg/day IV every 12-24 hr non meningitis, 100mg/kg/24 hr IV for meningitis |
| Cefotaxime | 150mg/kg/day IV divided every 6-8hr for non-meningitis infections, 200mg/kg/day IV divided every 6-8 hr in meningitis |
| Meropenem | 60mg/kg/day IV divided every 8 hour for non-meningitis, 120mg/kg/day IV for meningitis |
| Piperacillin-Tazobactam | 300-400mg/kg/day IV divided every 6-8hr |
| Ampicillin | 100-200mg/kg/day IV for non-meningitis, 200-400mg/kg/day IV divided every 4-6 hr for meningitis |
| Amikacin | 15-25mg/kg/day IV |
| Gentamicin | 5-7.5mg/kg/day once daily or 2.5mg/kg every 8-12hr |
| Fluconazole | 12mg/kg/day IV/PO once daily |
| Amphotericin B | Amphotericin B Deoxycholate: 0.5-1mg/kg/day IV<br>Lipid amphotericin B formulations: 3-5mg/kg/day IV |
| Acyclovir | - mucocutaneous or immunosuppression:10mg/kg/dose IV every 8hours<br>-Disseminated HSV or HSV encephalitis(3 months to <12 years): 15mg/kg/dose IV every 8hour; age ≥12 years:10mg/kg/dose every 8hr<br>- 0-3 month old 20mg/kg/dose IV every 8hr |

3. Severity of Burn

Severity of burn will be assessed by using Modified Lund-Browder chart



**GCS**

| Sign | Glasgow Coma Scale | **Pediatric Glasgow Coma Scale** | Score |
|---|---|---|---|
| Eye opening | Spontaneous | Spontaneous | 4 |
| | To command | To sound | 3 |
| | To pain | To pain | 2 |
| | None | none | 1 |
| Verbal response | Oriented | Age-appropriate vocalization, smile, or orientation to sound; interacts (coos, babbles); follows objects | 5 |
| | Confused, disoriented | Cries, irritable | 4 |
| | Inappropriate words | Cries to pain | 3 |
| | Incomprehensible sounds | Moans to pain | 2 |
| | None | none | 1 |
| Motor response | Obeys commands | Spontaneous movements (obeys verbal command) | 6 |
| | Localizes pain | Withdraws to touch (localizes pain) | 5 |
| | Withdraws | Withdraws to pain | 4 |
| | Abnormal flexion to pain | Abnormal flexion to pain (decorticate posture) | 3 |
| | Abnormal extension to pain | Abnormal extension to pain (decerebrate posture) | 2 |
| | None | None | 1 |
| Best total score | | | 15 |

## ANNEX 3

QUESTIONNAIRE FOR PEDIATRIC PATIENTS ADMITTED TO PICUs OF TASH AND ALERT CENTER

**Part 1.** Socio-demographic characteristics and reason of admission for study participants

1. MRN_____ 2. ICN_____ 3. Age(yr/mo)_____ 4. Sex Male ☐ Female☐

5. Date of admission to PICU(E.C. date/month/year))_____ 6. Weight(kg)_____
7.MUAC_____ 8. Height(cm)_____ 9. BSA($m^2$)_____

10. Address of the family_____ 11. Admission category I. Surgery ☐ type_____

II. Medical ☐type_____

III. Trauma ☐type_____ IV. Burn ☐ Severity of Burn(percent of BSA)_____

**Part 2.** Phoenix score and comorbidity

12. Table of Phoenix score

| Variables | 0 point | 1 point | 2 points | 3 points |
|---|---|---|---|---|
| Respiratory(0-3) points | Pao2:FIo2≥400 or Spo2:FIo2≥292 | Pao2:FIo2<400 or Spo2:FIo2<292 on any respiratory support | Pao2:FIo2 100-200 or Spo2:FIo2 148-220 and IMV | Pao2:FIo2 <100 or Spo2:FIo2 <148 and IMV |
| Cardiovascular(0-6 points) | | | | |
| | | 1 point each(up to 3) | 2 points each(up to 6) | |
| | No vasoactive medications | 1 vasoactive medication | ≥2 vasoactive medications | |
| | Lactate <5mmol/L | Lactate 5-10.9 mmol/L | Lactate ≥11 mmol/L | |
| Age based | | | | |
| Mean arterial pressure(mm Hg) | | | | |
| <1 mo | >30 | 17-30 | <17 | |
| 1 to 11 mo | >38 | 25-38 | <25 | |
| 1to <2y | >43 | 31-43 | <31 | |
| 2 to <5 y | >44 | 32-44 | <32 | |
| 5 to <12 y | >48 | 36-48 | <36 | |
| 12 to 17 y | >51 | 38-51 | <38 | |
| Coagulation(0-2 points) | | | | |
| | | 1 point each(maximum 2) | | |
| | Platelets ≥$100x10^3$ /μL | Platelets <$100x10^3$ /μL | | |
| | INR≤ 1.3 | INR >1.3 | | |
| Neurological(0-2 points) | | | | |
| | GCS score >10; pupils reactive | GCS score ≤10 | Fixed pupils bilaterally | |
| Phoenix sepsis criteria | | | | |
| Sepsis: Suspected sepsis and phoenix Sepsis score ≥2 points | | | | |
| Septic Shock: Sepsis with ≥1 cardiovascular point(s) | | | | |

13 Is there comorbid condition? Yes ☐ No ☐

14. If answer to the above question is "Yes" which of the comorbid conditions does the patient have? Choose among the following

Diabetes mellitus☐ Diabetic ketoacidosis ☐ Cancer☐ type_____ HIV☐ CKD☐ Liver failure☐ SAM ☐

Congestive heart failure☐ other☐_____

**Part 3**

Laboratory workup

15. What was white blood cell count at admission?_____

16. What was proportion of neutrophils in percent?_____

17. Serum C-RP level(mg/dL)day1_____, Serum Albumin day1_____

18. Serum Cr(mg/dL); day1_____, day2_____, day3_____

19. eGFR(mL/min/1.73 $m^2$); day1_____, day2_____, day3_____

**Part 4**

Therapeutic interventions at PICU

20. Is the patient getting antimicrobials? Yes ☐No ☐

21. If the answer for the above question is "Yes" which type of antibiotics is the patient getting?

Vancomycin☐ Ceftriaxone☐ Cefotaxime☐ Cefepime☐ Meropenem☐

Piperacillin/Tazobactam☐ Ampicillin ☐ Amikacin☐ Gentamicin☐

22. Antifungals: Fluconazole☐ Amphotericin B☐

23. Antiviral: Acyclovir ☐ other_____

24.Route of adminstration of antimicrobials

IV ☐ Oral ☐

25. How was dosing of Antimicrobials? Sub-standard ☐ Standard ☐ maximum approved dosing ☐ If > antimicrobials:

Antibiotic 1(_____): Sub-standard ☐ Standard ☐ maximum approved dosing ☐

Antibiotic 2(_____): Sub-standard ☐ Standard ☐ maximum approved dosing ☐

Antibiotic 3(_____): Sub-standard ☐ Standard ☐ maximum approved dosing ☐

26. How was medication administration? Intermittent Bolus ☐ extended infusion ☐ continuous infusion ☐

27. what is the duration of antimicrobials in day(s)?_____

28.Was antimicrobial switched to alternative regimen which is not largely renally eliminated?

Yes ☐ No ☐

29. If 'Yes' to what antibiotics?_____

30.Were blood cultures sent? Yes ☐ No ☐

31.Was there growth? Yes ☐ No ☐

32.What was growth?_____

33. Was there samples of cultures from other sites? Yes ☐ No ☐

34. If "Yes" what sample?_____, _____, _____ Was their growth? Yes ☐ No ☐

35. What was growth? _____

36. What was fluid status of patient? Normotensive ☐ Hypotensive ☐ Hypertensive ☐

37. Does the patient need Vasopressors? Yes ☐ No☐

38. If answer for the above question is "yes" how many vasopressors does the patient need?

One ☐ Two☐ Three☐

39. Does the patient need diuretics? Yes☐ No☐

40. Does the patient need Mechanical Ventilation? Yes☐No☐

41. Does the patient need IV fluid boluses? Yes No☐

42.If answer to the above question is "Yes", how many boluses does the patient get at PICU?

Day1 One☐ Two☐ Three☐ ≥4☐

Day2 One☐ Two☐ Three☐ ≥4☐

Day3 One☐ Two☐ Three☐ ≥4☐

43.Was patient given blood products? Yes☐ No☐

44. If “Yes” what kind products?day1_____,day2_____, day3_____

45. How much blood products given?

On Day1_____(mL)

Day2_____(mL)

Day3_____(mL)

46. What is daily input of fluid in mL? day1 _____, day2_____, day3_____

47. What is daily urine output(mL/kg/hr)? day1_____, day2_____, day3_____

48. What is length of hospital stay (days)?_____

49. What is length of stay in Pediatric ICU (days)?_____

50. Outcome at day 7: death☐Improved☐ Deteriorate ☐ transferred ☐ the same ☐

51. Death at day_____ of PICU admission