

# The prevalence of Adverse Drug Events in septic patients after Rapid Response Team Activation

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## Research article

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## Abstract

**Background:** Antibiotics are commonly prescribed in hospitals, some use are unnecessary or inappropriate, which may increase Adverse Drug Events (ADEs) rate. ADEs can be a leading cause of morbidity and mortality, despite this; it is receiving little attention. A meta-analysis done by Lazarou. J and colleagues, estimated that more than 2 million (6.7%) of hospitalized patients have a serious adverse drug reaction (ADR) with a mortality rate of 0.32%, means ADR causing over 100,000 deaths annually. This study was conducted to evaluate the prevalence of antibiotics ADEs in Critical Care Response Team (CCRT) activated patients.

**Methods** Single-center, randomized, prospective observational cohort study took place at an academic tertiary hospital in Riyadh, Saudi Arabia. All adult patients who received antibiotics were included in the study. ADE was defined as any recognized / possible injury associated with antimicrobials use and were evaluated post CCRT (RRT) activation. Results A total of 315 patients with a mean age of 61.1±20.4 who received antibiotics mainly for pneumonia included in the study. 29.5% experienced at least one ADE through the study period. The most frequently common ADE were renal in 12.4%, followed by the hematological adverse events in 11.4% of the patients.

**Conclusion** We found that antibiotics –associated ADEs were common in CCRT patients, minimizing the unnecessary use of antibiotics, following hospital antibiotic guideline and applying other necessary measures can decrease ADEs morbidity rate.

## Introduction

CCRT is a multidisciplinary team consists of physician, nurse and respiratory therapist that bring high care service within an average of 15 minutes to the deteriorated patient on bedside in non-intensive care wards, evaluating and assessing patient's condition, making recommendations and interventions, and if required transferring the patient to the ICU, which saves hospital about \$3500 for each CCRT call. Some recommendations include adding and modifying medications which carries the risk of ADE. Risk factors associated with ADE in CCRT patients include admission to ICUs, older age, renal and hepatic impairment, length of hospital stay, polypharmacy and patient movement among wards.<sup>1,2,3</sup>

1,2,3

ADEs are a noticeable concern that can increase morbidity and mortality rate associated with medications use.<sup>24</sup> They can lead to increase length of hospital stay, intensive care units (ICUs) admissions, ordering additional medications, and labs, which in turn increase healthcare costs.<sup>1,9</sup> A study from Saudi Arabia showed an ADE incidence rate of 16% in four hospitals, about one third of these incidence events were preventable, of the preventable events, 11.9% were life-threatening and 1.2% was fatal.<sup>2</sup> They reported a total 245 ADE cases, of which 51 cases related to antibiotics use.<sup>2</sup> Antibiotics accounted as one of the most common medication classes associated with ADEs during hospital stay. Per JADE study, the overall mortality of antibiotics related ADE was ten out of 14 patients.<sup>3</sup>

Antibiotics are a commonly prescribed in hospitals, up to 50% of all prescribed antibiotics in US acute care hospitals are inappropriate per the Centers for Disease Control and Prevention (CDC).<sup>26-27</sup> In 2007, to improve antimicrobial therapy and to optimize the use of antibiotics, the Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) published guidelines for developing an antimicrobial stewardship programs (AMS) program.<sup>28</sup> AMS regulations have been updated and approved in January, 2017 by the Joint Commission.<sup>25</sup> Clostridium difficile infection and resistant rate are indicators for AMS outcomes.<sup>25</sup> In our hospital, the resistant rate is dramatically increasing, which may indicates inappropriate use of antibiotics. The U.S. malpractice lawsuits in 2016, mostly showed claims related to antibiotics.<sup>25</sup> For this and because the needing of well-established ADE studies, we are aiming to examine the CCRT-ordered antimicrobial ADEs prevalence and to develop a plan to minimize those events.

## Methods

**Setting.** This study took place at one of the largest hospitals in the area, King Abdulaziz Medical City (KAMC), an academic tertiary hospital with a bed capacity of 1501 in Riyadh, Saudi Arabia. The study was approved from King Abdullah International Medical Research Centre (KAIMRC) Institutional Review Board, with a waiver of informed consent from patients as there was no intervention and no more than minimal risk involved.

**Population.** All patients 15 years and older admitted to KAMC from FEB 2018 to JAN 2019, with CCRT activation who received antibiotics. Exclusion criteria included antimicrobials agents other than antibiotics or antifungal (e.g. antiviral), antibiotics with an indication other than infection (e.g. erythromycin for gastroparesis), and routes other than oral and intravenous.

**Study design and Data collection.** Single-center, prospective observational cohort study design used. Data were collected using a monitoring form, following characteristics were assessed: demographic data (table.1), date of CCRT activation, hospital admission/discharge dates, vital signs,

antibiotics used, microbial culture, ADE (anaphylaxis, skin, hematological, renal, liver and others). CCRT team send a list of the patients have been visited in the prior week, CCRT coordinator will randomly include patients in the study. An infectious disease specialist physician and a clinical pharmacist meet weekly to determine the appropriateness of antibiotic use and the ADE incidence.

### Outcome definition

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Appropriateness of antimicrobial use: The use of an agent/s following MNGHA antimicrobial guidelines which maximizes clinical therapeutic effect while minimizing drug-related toxicity and the development antimicrobial resistance<sup>13</sup>

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ADEs: any recognized injury/ potential injury associated with antimicrobials use and were evaluated post CCRT activation.

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Acute kidney injury: Per KDIGO an increase in SCr by  $\geq 0.3$  mg/dl ( $\geq 26.5$   $\mu$ mol/l) within 48 hours; or increase in SCr to  $\geq 1.5$  times baseline, which is presumed to have occurred within the prior 7 days; or urine volume  $\leq 0.5$  ml/kg/h for at least 6 hours<sup>14</sup>

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Hepatic impairment: marked elevation in aminotransferase levels more than 10 times the upper reference limit, or moderate elevation with 5–10 times the upper reference limit<sup>15</sup>

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Hematological ADE: platelet count drop by 50% from the baseline or below a count of 150,000 $\mu$ l.

### Statistical methods

Descriptive statistics were utilized to analyze the data. Continuous variables were summarized using mean  $\pm$  standard deviation

### Patients

A total of 315 CCRT patients received antibiotics treatment were included in this cohort study. The most common indication for antibiotics was pneumonia. The mean age of the patients was 61.1 $\pm$ 20.4, and 54.6% participants were male. The most common admission diagnosis were cancer (52 [16.5%]), renal related conditions (37 [11.7%]), hepatobiliary and pneumonia of (34 [10.8%]) and infection (32 [10.2%]). The median length of hospital stay was 15 days (IQR, 10-30 days). The baseline characteristics are shown in Table 1.

**Table 1.** The baseline characteristics.

Characteristics	Mean (%)
Age	61.1±20.4
Gender:	
Male	172 (54.6%)
Female	143 (45.4%)
BMI	
< 30 kg/m <sup>2</sup>	210 (66.7%)
≥30 kg/m <sup>2</sup>	105 (33.3%)
Service	
Medical	177 (56.2%)
Surgical	68 (21.6%)
Oncology	44 (14.0%)
Others	26 (8.2%)
Admission diagnosis	
Cancer/tumor	52 (16.5%)
Renal	37 (11.7%)
Hepatobiliary	34 (10.8%)
Pneumonia	34 (10.8%)
Infection/sepsis	32 (10.2%)
Trauma/orthopedic	28 (8.9%)
Cardiac	23 (7.3%)
Other lung disease	18 (5.7%)
Surgical/post-surgical	18 (5.7%)
Stroke	17 (5.4%)
Others	51 (16.2%)
Length of stay (days)	15 (10-30)

### Antibiotics Used

Through this study, we evaluated the antibiotics use before, during and after CCRT activation. Broad spectrum beta lactams and vancomycin were the most commonly used antibiotics (Table2). At any phase during the study, meropenem was the most frequent used antibiotics with a rate of 51.4%, followed by vancomycin 41.3%, and Piperacillin and tazobactam 28.6%.

**Table 2.** Antibiotics.

	Before CCRT	By CCRT team	After CCRT	At any phase
Meropenem	25%	38%	37%	51.4%
Vancomycin	14%	30%	20%	41.3%
Piperacillin and tazobactam	18%	15%	16%	28.6%
Ceftriaxone	10%	4%	2%	12.1%
Linezolid	3%	5%	6%	8.6%
Colistin	4%	4%	4%	7.3%
Caspofungin	1%	3%	4%	6.7%
Anidulafungin	2%	2%	4%	5.7%
Tigecycline	3%	3%	3%	5.4%
Ciprofloxacin	4%	3%	3%	5.4%
Imipenem	3%	3%	2%	4.4%
Others	41%	37%	28%	70.5%

### Adverse Drug Event

Total of 93 patients (29.5%) experienced at least one adverse event. The most common organ affected by antibiotics used was the renal 39 (12.4%), followed by the hematological adverse events in 36 patients (11.4%), gastrointestinal tract in 24 (7.6%), and hepatic with 14 (4.4%) (Table.3).

**Table 3.**

	Total
Antimicrobial AE	
None	222 (70.5%)
One or more	93 (29.5%)
One	72 (22.9%)
Two or more	21 (6.7%)
Antimicrobial AE	
Renal	39 (12.4%)
Hematologic	36 (11.4%)
GIT	24 (7.6%)
Hepatic	14 (4.4%)
Skin	4 (1.3%)
Anaphylaxis	1 (0.3%)

**Table 4.** Other Outcomes.

<b>Outcome</b>	<b>Total patients (315)</b>
Stay at floor	171 (54.3%)
Admission to ICU	114 (36.2%)
Mortality	9 (2.9%)
Discharge Home	2 (0.6%)
Others	2 (0.6%)

## Discussion

World Health Organization (WHO) identified ADE as “Medical occurrence temporally associated with the use of a medicinal product, but not necessarily causally related”, unlike the Adverse Drug Reaction (ADR) which has a causal relationship with pharmaceutical product use that may require discontinuing or changing therapy.<sup>1,4,5</sup> U.S. Food and Drug Administration (FDA) defined ADE as “any undesirable experience associated with the use of a medical product in a patient”.<sup>11</sup> In a prospective cohort study, Bates and colleagues described ADE as a medical intervention injuries caused by a drug.<sup>12</sup> For this study, the ADE was defined as any recognized or possible injury associated with antimicrobials use from the day of CCRT activation.

ADEs can occur because of multiple medication use, in particular the use of four or more medications.<sup>33</sup> Jacubeit T and colleagues found a positive correlation between the ADRs incidence and the number of prescription per patient, with no effect of age.<sup>32</sup> Drug interaction can occur in several mechanisms, is another factor that contributes for up to 5% of the total ADEs.<sup>33</sup> Here in Ministry of National Guard – Health Affairs (MNGHA), we use a systemic reporting system (SRS) for reporting ADEs. In 2006, a medication safety program was launched to improve patient safety. An Antimicrobial Stewardship Program was established to ensure proper antimicrobial use. At a national level, SFDA (Saudi FDA) encourages health care professionals to report ADRs through SFDA-National Pharmacovigilance and Drug Safety Center reporting system. In one month, only one ADR was reported from our institution to the SFDA reporting system which indicates a poor reporting practice, and it is expected to have a greater number.

The next crucial step of this study is developing strategies to implement ADEs prevention criteria. Proposed ways to reduce ADEs rates and improve safety may include, emphasizing the importance of using appropriate antimicrobial agents and avoiding unnecessary usage to healthcare providers by ensuring to achieve the “4 D’s of optimal antimicrobial therapy” suggested by Joseph J and Rodvold KA that include; right Drug, Dose, De-escalation to pathogen, and Duration of therapy<sup>31</sup>. Utilizing information technology, Bates<sup>19</sup> suggested computerized adverse drug event detection, as self-reporting was only 5% of ADEs. Preventing excessive and unnecessary alerts of drug interactions, to minimize the high overridden practice that may happen to an important and high priority drug interaction.<sup>33</sup> Actively involving clinical pharmacists in rounds showed to reduce medication errors, duplicate therapies, unnecessary ordering and optimize drug therapy plans.<sup>1,17,18,20</sup> In addition, the involvement of a trained pharmacist in the rapid response team / CCRT has shown to improve medication accessibility, help optimize medication recommendations, dosing, medication-related causes of deterioration within 15 minutes for each call.<sup>29,30</sup> Implementing an effective medication reconciliation process which is recognized by Joint Commission, January 2018 as an essential goal for patient safety.<sup>21,22</sup> Encourage collaboration between ASP and Medication Safety Program to assess the insinuation of ADEs as an outcome measurement to achieve their mission.

## Abbreviations

ADR  
Adverse Drug Reaction, ADE = Adverse Drug Event, CCRT = Critical Care Response Team, RRT = Rapid Response Team

## Declarations

Not applicable

Abbreviations:

ADR= Adverse Drug Reaction, ADE= Adverse Drug Event, CCRT= Critical Care Response Team, RRT= Rapid Response Team

Ethics approval and consent to participate:

Not applicable

Consent for publication:

Yes

Availability of data and material:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

None

Funding :

None

Authors' contributions:

SA contributed to the study design and writing. SA and KA contributed to the study design and critical review. KA contributed to data collection and analysis. Both authors read and approved the final manuscript.

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