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The Effective Participation of a Clinical Pharmacist in Detecting Medication Errors in the COVID-19 Intensive Care Unit

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Abstract

With the emergence of the COVID-19 pandemic, a large number of patients required hospitalization and intensive care unit admissions. Patients with pre-existing medical conditions were associated with a higher chance of severe disease. On the other hand, medication errors in part resulting from polypharmacy are commonly observed in hospitalized patients. At the time of the Delta variant peak and the high influx of COVID-19 patients to the hospitals, clinical pharmacy ICU ward rounds were implemented to detect, and prevent medication errors to improve patient safety and care. Patients with known COVID-19 infection that were admitted to the ICU for a duration of 4 months were included in this prospective study. Every day (Saturday to Thursday) ICU patient rounds was performed by the clinical pharmacist. Medication reconciliation was done for all patients to detect probable drug omission or duplication during admission. Pharmaceutical Care Network Europe Foundation (PCNE) classification was used for classifying drug-related problems. A total of 86 patients were evaluated for medication errors during ICU admission. A total of 398 drug-related comments were given and 90% of the interventions were accepted by the attending physician. The most common medication error was attributed to overdosage of medications, mostly glucocorticoid therapy. The survival rate amongst patients was 56.1%. Clinical pharmacy interventions and medication reconciliation at times of pandemics can help towards improvement of clinical practice, patient safety, and saving of medication resources. Early detection of medication errors by clinical pharmacists can prevent further patient complications and death.

Keywords: Clinical Pharmacy, COVID-19, Medication Reconciliation, Medication Errors

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1. Background

With the outbreak of COVID-19 and the increase in the number of hospitalized patients, almost all healthcare facilities and hospitals had to re-arrange their settings to be able to give proper care to patients requiring hospitalization. The emergence of the B.1.617.2 variant introduced as the Delta variant, lead to massive involvement with greater clinical severity, requiring not only hospital admission but intensive care unit (ICU) admissions and extra supportive measures (1, 2). The high mortality rates of the deadly COVID-19 pandemic have affected lives in every aspect (3, 4) and the damage is expected to be ongoing (5). The role of multidisciplinary critical care teams with multi potential specialties has shown to be efficacious in providing better care for the patients (6), specifically at the emergence of a pandemic with high loads of patients with critical conditions (4).

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Medication-related errors, adverse events, and interactions are common among patients specifically the ones admitted to the ICU. Drug-related problems or medication errors are conditions resulting from medication therapy that can actually or potentially influence a patient's medical outcome (7). These errors can be preventable if properly detected. By the early detection of medication errors, and clinical management, a patient's length of hospital stay, and overall mortality can be affected (6, 8). It has been reported that nearly one medication error may occur for every patient for every day of hospital admission (9). Although some errors in the ICU setting are inevitable, due to the critical condition of the patients in this setting, it is mandatory that errors be prevented to avoid further damage. The role of a clinical pharmacist's participation in optimizing pharmacotherapy has been valued in different settings (10-12) including the ICU requiring maximum care for the patient (4, 13). Medication reconciliation has been introduced as a means to prevent medication errors. It can be performed after admission as a mainstay of clinical pharmacist's services and can reduce duplication, omission, or probable interactions of a patient's past medications with the medications initiated upon admission (14). Also clinical recommendations regarding application of the correct therapeutic approach for the patient can be the responsibility of the clinical pharmacist in charge of conveying improved patient outcomes (15). In 2017, the World Health Organization (WHO) urged an important action to be taken toward patient safety, introducing the importance of reducing medication harm by 50% globally during 5 years (16). Recommendations of a clinical pharmacy specialist during daily ward rounds and detecting probable interactions and medication errors can all be efforts to minimize the level of harm associated with medications that has been highlighted in previous reports at the time of COVID-19 pandemic (17, 18).

The unexpected clinical deterioration of the patients, the level of care required in the ICU, and also the high turnover of COVID-19 patients at the time of the Delta variant peak at our institution, mandated the presence of a multipotential clinical team to manage patients to minimize medication faults. In this study, we aimed to detect medication errors that occurred in the COVID ICU setting at the time of the Delta variant peak.

2. Materials and methods

In this prospective study, a total of 86 patients during a period of 4 months from April to July 2021 were investigated for medication errors at the time of ICU admission at the COVID Intensive care unit (ICU) of Shahid Faghihi Hospital, a major referral hospital for COVID-19 patients at the time of the pandemic. Ethical principles for medical research involving human subjects were performed according to the Declaration of Helsinki.

Patients were evaluated for previous medication history upon admission to the ICU by the clinical pharmacist. Patients' past medical and medication histories were documented in the medication reconciliation form. Dosage form, dose, and frequency of patient's previous medications were recorded. In case of missed medications and change in dosing of medications after admission, the clinical pharmacist notified the attending physician. The medication reconciliation form was also attached to the patient's medical records. If no clinical contraindication existed considering patients' clinical status at the time of ICU admission, missed medications were added to the patient's medication list. Specific medications for the management of COVID-19 were evaluated for correct dosing and duration of consumption according to the latest global and local guidelines for the management of COVID-19 (19). Patients' medication lists were evaluated for the probability of overdosage, under dosage, drug interaction, missed medications with indication, administration of medications without indication, appropriateness of duration of treatment, accordance with guidelines and dual medication prescription according to Pharmaceutical Care Network Europe Foundation (PCNE) classification for drug-related problems (DRP) V9.1. DRPs are categorized according to the domains of DRPs including causes of the problems, probable planned interventions and level of acceptance of the error that was detected and reported to the healthcare physician in charge of the patient. Clinical significance of the medication errors are also evaluated based on Stan-

dards of Practice for Clinical Pharmacy Services provided by the Society of Hospital Pharmacy of Australia (SHPA) (20, 21). Results of the study are presented as percentages for non-continuous data and as mean ± SD for continuous data. The rate of occurrence of errors is presented as frequency (%).

3. Results

From a total of 86 patients, with severe COVID-19 infection that were admitted to the ICU, the mean age of the study population was 53.91±15.4, ranging from a minimum of 19 years to a maximum of 88 years of age. A predominance of female to male was evident, with female and male patients accounting 47 and 39 of the total population respectively. Seventy-nine percent of the patients had at least one previous medical condition or comorbid disease. The highest rate of comorbid disease was attributed to hypertension as demonstrated in Table 1. Considering that the majority of patients had a past medical condition before admission to the ICU, almost all patients had a history of receiving at least two medications at the time of admission. The average number of past medications for the study population was 4.91±2.96. The length of hospital stay was 9.82±7.31 days. A minimum of one to a maximum of 15 (mean± SD: 4.91±2.96) clinical pharmacy interventions in terms of correcting the dose, selecting the correct medication, using alternative medications in case of drug interactions, dose adjustments required for renal or hepatic impairment, implying the correct monitoring required for prevention of drug adverse events, were documented for each patient during the course of ICU admission. Overall, 398 clinical pharmacist's drug-related comments and interventions were documented during the 4 months of study by daily ICU patient rounds taking place by the clinical pharmacist in charge. Almost ninety percent (89.7%) of the comments were approved by the attending physician. Survival rate amongst patients was 56.1%.

Patients' baseline data are elaborated in table 1.

Table 1. Patients' demographic and baseline data on admission to the COVID ICU (n=86).

Factor (n=86)	**Frequency**
Age (Mean ± SD)	53.9 ±15.4
Gender (%)	
Female	55%
Male	45%
Length of ICU admission (days, Mean ± SD)	9.82±7.31
Past medical history (%)	
Hypertension	37 %
Diabetes	18.6 %
Ischemic heart disease	15.1 %
Thyroid dysfunction	10.4 %
Respiratory disease	7 %
Kidney dysfunction	7 %
Autoimmune disease	5.8 %
Seizure	5.8 %
Malignancy	3.4 %
Psychiatric disorders	<3 %
Number of past medications (Mean ± SD)	4.91±2.96
Glomerular filtration rate ml/min (Mean ± SD)	77.4±44.94
COVID-19 medications	
Remdesivir	91.8 %
Corticosteroids	88.8 %
Tocilizumab	33.7 %

Table 2. Medication errors detected in patients during clinical pharmacy daily ICU rounds.

Medication Error	Frequency
Inappropriate dose of previous medication after admission	67.4 %
Inappropriate dosing of medication prescribed during admission	62.8 %
Omission of medication after admission	9.3 %
Past medication not indicated after admission	65.1 %
Same class (dual) medication	11.6 %
Overdosage	76.7 %
Underdosage	17.4 %
Non-confirmatory to guidelines	52.3 %
No-indication	29.1 %
Source of interaction	25.6 %
Source of adverse events	51.6 %
With indication without drug therapy	30.2 %
Inappropriate duration of therapy	25.6 %

Detailed descriptions of the medication errors that were detected by the clinical pharmacist during ICU patient visits are elaborated in Table 2.

According to Table 3. That demonstrates drug-related problems according to PCNE classifications, treatment effectiveness is evaluated based on inefficacy or sub-optimal efficacy of a treatment despite the correct use of a medication. Also, untreated symptoms that may have had indication for treatment are classified in this category. The category "other" accounts for unnecessary drug treatments. Drug selection refers to inappropriate drug selection, no indication for treatment, duplication of therapeutic group, incomplete treatment, too many drug prescriptions for one indication. Dosing errors relate to wrong dosing of the medication, frequency or its timing for administration. Patient-related medication errors do not comply with this study's study population since patients were ICU admitted and medications are routinely given to the patient by the healthcare staff in charge. Patient transfer related problems refer to

Table 3. Drug-related problems (DRPs) classified according to PCNE classification.

Category of Medication Error	Frequency
Type of problem	
Problem associated with treatment effectiveness	30.2 %
Problem associated with adverse drug event	51.6%
Other	29.1 %
Cause of Problem	
Drug selection	93.0 %
Dose selection	94.1 %
Treatment duration	25.6 %
Patient transfer-related	76.7 %
Planned Intervention	
No Intervention	0 %
At prescriber level	100 %
At drug level	100 %
Intervention Acceptance	
Intervention accepted	89.7 %
Intervention not accepted	9.3 %

medication reconciliation that was done for the patients. Interventions were all at prescriber level at our institution in this study, since patients were ICU-admitted and did not have self-use of medications. All (100 %) detected errors were reported to the prescribing physician in charge of the patients. Interventions at drug level include change in drug selection, dosage, instruction of use, stopping or starting a medication.

Considering that all interventions weredru-related and done by the clinical pharmacist, all (100 %) of the interventions that were reported and the ones that were accepted were at the drug level. The most frequent error attributed to dose of medications before admission was for antihypertensive medications and also underdosing of corticosteroids. Considering patients' severe respiratory involvement, corticosteroid therapy was administered for the majority of the study population (88.8 %) along with biologic anti-inflammatory therapy including tocilizumab that was administered for 33.7% of the study population. Majority of patients (91.8 %) had received remdesivir either before admission to the ICU, or at the time of ICU admission. The highest rate of dosing error during ICU admission was observed in corticosteroid dosing for which dosages above the recommended dose in global guidelines were given (19). Also, overdosage of medications related to suppressing gastric acid secretion including pantoprazole and famotidine, were second in dosing errors. The error of missed medications was low compared to other errors (9.3%) almost all attributed to poor history taking. Missed medications were detected through the process of medication reconciliation. A large number of patients' past medications did not have clinical indication after ICU admission of COVID-19 patients. Dual prescription of medication from the same drug class was seen mostly in antibacterial medications with the same spectrum of activity, beta agonists and anticholinergic inhalers and beta blockers. Overdosage of medications was seen in 76.7% of patients, of which 43% was associated with corticosteroids. Underdosing of medication was detected in 17.4% of patients. The highest rate of underdosing was seen in antibiotic therapy most commonly in piperacillin-tazobactam dosage. In 52.3% of cases, dosing of medications was either higher or longer than respectively the dosing and duration stated in the guidelines for the treatment of COVID-19. This error was more frequently seen in corticosteroid treatment (75 %). Some medications in patients' medication list were not clinically indicated at the time of admission. This error was associated to 29.1 % of patients. Combination of medications that were identified as a source of drug-drug interaction were seen in 25.6 % of cases. The highest rate of interaction was documented in the co-administration of CNS depressant agents (55 %). In 51.6% of patients drug therapy led to at least one adverse effect. Rise in serum creatinine following the administration of two or more nephrotoxic medications including remdesivir, piperacillin-tazobactam and vancomycin was the most common adverse event observed. Excessive hypotension observed with the combination of sedative-hypnotics and other antihypertensive medications was the second most common adverse event. Some medications were not ordered by the physician and their need for administration was informed by the clinical pharmacist. Potassium chloride and magnesium sulfate supplementation for electrolyte imbalances, empiric gram-positive antibacterial coverage for patients at risk of Staphylococcus Aureus infections, bronchodilator inhalers and mucolytic medications such as bromhexine and N-acetyl cysteine were of the most common medications that were added after the clinical pharmacist's intervention. Longer durations of treatment compared to clinical guidelines were mostly seen in corticosteroid (45.4%) and antimicrobial (27.7%) medications.

The frequency of medication errors attributed to each class of medications has been shown in Table 4.

Clinical severity and significance of medication errors that were detected have been evaluated according to SHPA guidelines and have been presented in Table 5. As presented, none of the medications errors led to serious complications resulting in death. However, Major permanent injury was observed in 8% of the patients. The major injury was mostly permanent renal complications following use of combination of nephrotoxic medications that led to longer hospitalization of the patients and eventual discharge with temporary or

Table 4. Frequency of medication errors in each class of medication.

Medication Class	Number of errors (Total n = 461)	Overall frequency of error (%)
Glucocorticoid	57	12.4 %
Antibacterial	46	10 %
Medications for acid related disorders	44	9.5 %
Anticoagulant	32	6.9 %
Medications for obstructive airway disease	31	6.7 %
Analgesics	29	6.3 %
Sedatives	25	5.4 %
Beta-blocker	21	4.5 %
Supplements (Vitamins and minerals)	19	4.1 %
Angiotensin Converting Enzyme Inhibitors/ Angiotensin Receptor Blockers	18	3.9 %
Antidiabetic	18	3.9 %
Others	18	3.9 %
Antiviral	17	3.7 %
Antihistamine	15	3.2 %
Thyroid agents	12	2.6 %
Antiseizure medication	12	2.6 %
Lipid modifying agents	11	2.4 %
Antipsychotics	9	1.9 %
Antiplatelets	9	1.9 %
Diuretics	7	1.5 %
Calcium channel blockers	4	0.9 %
Liver supplements	4	0.9 %
Antidepressants	3	0.6 %

permanent need for hemodialysis.

4. Discussion

In this single-center study on ICU-admitted COVID-19-infected patients, the role of a clinical pharmacist in the detection and prevention of medication errors has been demonstrated. Detection of medication errors during patients' hospital

Table 5. Severity and clinical significance of medication errors detected by the clinical pharmacist (n=398).

Severity and significance of medication error	**Description**	**n (%)**
Insignificant	No harm or injuries	168 (42.2 %)
Minor	Minor injuries, minor treatment required, no increased length of stay or re-admission	87 (21.8 %)
Moderate	Major temporary injury, increased length of stay or re-admission, cancelation or delay in planned treatment/procedure	111 (27.9 %)
Major	Major permanent injury, increased length of stay or re-admission, morbidity at discharge	32 (8.1 %)
Catastrophic	Death or large financial cost	0 (0 %)

admission can prevent serious harm, and can lead to patient safety, efficacy of treatment and economic benefit for the healthcare system (14, 22). As medication errors can be a viable source of harm to the patient, the WHO intended to reduce avoidable and severe medication harm associated with patients by 50% in a period of 5 years (16). Implementation of this initiative requires exact knowledge of the medication errors and their extent of occurrence in the health care system. Rate of medication errors varies in different studies due to differing definitions and settings but has been estimated to occur in 10-20% of prescriptions (23-25). Timing of administration of medications has been pointed out as the leading medication error in most studies, however in our study, timing of medications was not recorded. The second most common medication errors were omission and wrong dosage of medication. As seen in our results, the rate of omission was not high (9%) compared to other errors detected. The rate of mis dosing of medications was high and mostly attributed to overdosing of medications (76.7%) accounting for the highest rate of error. Considering that the study population was COVID-19 patients with severity of disease, most patients were admitted to the ICU with severe respiratory conditions and on admission to the ICU, higher than approved doses of corticosteroids were administered for the patients to reduce the inflammatory response. Corticosteroids showed survival benefit in the management of COVID-19 infection however at the time of the study controversies on the effective dose of medications for the treatment of COVID-19-associated ARDS existed and the benefit of high dose vs low dose therapy could not been demonstrated (26). Duration of treatment with corticosteroids and antimicrobials was considered as a source of error and was carefully overlooked by the clinical pharmacist to prevent excessive corticosteroid or antibiotic use. Continuation of corticosteroids can put the patient at further risk of developing glucose intolerance, hypertension and adrenal insufficiency. Long duration of high dose corticosteroid therapy may have attributed to medication errors with moderate severity increasing risk of systemic infections and sepsis, increasing patient's length of ICU stay and complicating patient's clinical condition. However, no such error led to catastrophic complications such as death. Also, inappropriate continuation of antimicrobials not only can induce side effects, but it can also increase the risk of resistance patterns. This error was detected in 25.6% of patients and intervention to stop excessive treatment was done. Aside from the risks threatening the patient, limitation of resources at the time of the pandemic and the cost burden of overuse of medications was a concern that was prevented by performing this intervention (27). Mortality rate of the Delta variant has been reported to be the highest amongst all other variants, accounting for 39.8% from another regional report with more or less the same facilities as our setting (28). The higher mortality rate of this study although performing medication related interventions, may be attributed to the poorer condition of patients, the severity of disease and also patient comorbidities. Considering that a high majority of the study population had at least one comorbid condition and on average each patient was admitted with a medication history of 4-5 drugs, the importance of performing medication reconciliation is highlighted in this study, especially in the ICU setting with patients requiring more precise care. As previously reported, medication reconciliation can reduce medication transfer errors and offer a cost-benefit approach toward ICU patients' optimum care (29). Medication reconciliation was done for all patients in this study taking an average time of 40 minutes per patient, comparable to other studies (14) and helped towards identifying probable missed medications and also preventing dual therapy of the same class of medications. Also, upon history taking from the patient or his caregiver, history of antibiotic use and risk of resistance was identified and helped towards further selection of antibiotic therapy. Upon performing medication reconciliation, a thorough evaluation of the patients' prior and current clinical and medication status is performed. This performance has led to minimizing drug discrepancies in the ICU setting in the most recent reports (30, 31). Also, the length of hospital stay can affect patients' number of medications and can lead to polypharmacy and at last increase rates of medication errors. In this study the average length of ICU stay was almost 10 days, in-

creasing the chance of medication-related interactions and adverse events respectively seen in 25.6 % and 51.6 % of the study population. Early detection of probable interactions and drug-related adverse events can prevent further harm and decrease mortality rate and therefore none of the interactions or adverse events led to patient's death in this study. As the most common adverse event reported in this study, acute kidney injury (AKI) was a common complication in severe forms of COVID-19, resulting from both the invasion of the virus and also the antiviral and immunosuppressant medications used as COVID-19 treatment (32). AKI was considered as the major complication of patients with severe medication errors reported. However, considering the pathophysiology of the viral infection itself, it is noteworthy that AKI and renal impairment following use of nephrotoxic medications may not be solely attributed to drug combinations and the nature of the disease may have also attributed to this major event. Ontime dose adjustments of medications at the time of AKI by the clinical pharmacist in charge, is of great importance and could prevent further drug toxicity. However, we must insist that the necessity for drug therapy in severe forms of COVID-19, may outweigh the risk associated with adverse events or mild to moderate interactions, and in such clinical cases treatment is inevitable. The emergence of new re-purposed drugs at the time of the COVID-19 outbreak also necessitated the need for evaluation of their probable adverse events and also interactions with other routinely practiced medications by a clinical pharmacist having the expert knowledge of applied therapeutics. Also lack of appropriate knowledge of this severely fatal virus at the time of the Delta variant peak, highlighted the need for a multidisciplinary clinical practice involving dedicated clinical pharmacists helping the medical team towards better decision-making (33). A high number of patients in this study did not require their past medications according to their clinical condition at the time of ICU admission. Clinical situations such as hypotension following the use of sedative-hypnotics after the need for mechanical ventilation in a previously hypertensive patient, the substitution of intravenous gastrointestinal (GI) stress ulcer prophylaxis with previously peroral (PO) forms after insertion of NG tube feeding, lack of requirement of alpha1 antagonists in a patient with benign prosthetic hyperplasia (BPH) that now has internal urinary foley, or PO anxiolytic medication in a mechanically ventilated patient on intravenous sedative-hypnotics and muscle relaxing agents are of the many medications that were discontinued upon admission based on patients condition at the time. Overuse of stress ulcer prophylaxis was evident at the time of the pandemic and therefore excessive use was detected and dosages of acid suppressant medications were controlled. Excessive and long-term GI ulcer prophylaxis can itself increase the risk of eradication of GI normal flora and induce the risk of further infections. Severity of medication errors detected were comparable with a similar study indicating 8% major harm associated with patients following occurrence of medication errors, however the study setting was slightly different and evaluated medication errors after discharge of the patients from the hospital (34). The acceptance rate of clinical pharmacist's comment has been reported to be as high as the results of our study (acceptance rate of 89.7%). Reports of as high as 89.5 % to 95.5 % have been published (33, 35).

5. Conclusion

At last, we can conclude that at the time of the pandemic, with a large influx of patients with severe clinical conditions, limitation of medical and medication resources, and lack of sufficient facilities and medical experts, the intervention and attendance of a dedicated clinical pharmacist in the clinical settings can benefit the patient and health care system by preventing inevitable medication errors and helping towards patient safety, the efficacy of treatment and saving resources. Knowing sources of error and the most common medications that are error-prone can help towards prevention of further medication overuse at the time of crisis with limited resources and also prevent errors that can harm patients, cause death

Limitations

This study has some limitations. Being a single-center study without a control group limits

the ability to compare the effectiveness of clinical pharmacist's participation. Also, larger study sample may have helped in better identification of drug-related problems in this setting.

Conflict of Interest

The authors declare no conflict of interest.

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