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# Drug-related problems identified during pharmaceutical care interventions in an intensive care unit at a tertiary university hospital

**Vichapat Tharanon[1], Krongtong Putthipokin[1] and Phantipa Sakthong[2]**

## Abstract

**Introduction:** Drug-related problems could potentially worsen the clinical outcomes in critically ill patients. Critically ill patients are generally considered more vulnerable to harm from drug-related problems due to frequent medication-related events and complicated clinical courses. However, drug-related problems identified by on-ward clinical pharmacists in medical intensive care units in Thailand are not well reported. This study reports clinically relevant data with the description of identified problems, common causes of drug-related problems, and pharmacists' interventions performed in real world, so that it may serve as an educational material for pharmacists who implement a pharmaceutical care and participate in medical intensive care units.

**Methods:** A retrospective descriptive study was conducted at a tertiary university hospital in Bangkok, Thailand, from January 2015 to December 2020. The drug-related problems were categorized according to Cipolle et al.'s classification. The severity of drug-related problems in this study was rated by modifying the definition of The National Coordinating Council for Medication Error Reporting and Prevention Taxonomy of Medication Error to report harm from drug-related problem-related patient outcomes.

**Results:** A total of 698 drug-related problems were detected in 374 critically ill patients. The prevalence of drug-related problems occurring in critically ill patients admitted to the medical intensive care unit was 73.9%. The most frequent drug-related problems were dosage too high (27.7%), ineffective drug (17.2%), need for additional drug therapy (15.3%), unnecessary drug therapy (14.6%), dosage too low (14.3%), adverse drug reaction (9.7%), and non-adherence (1.2%). The severity of drug-related problems in the medical intensive care unit was assessed as a drug-related problem with no harm (78.2%). Pharmacists' interventions were advised according to drug-related problem identification to provide personalized pharmacotherapy optimization in critically ill patients.

**Conclusion:** The most frequent drug-related problem identified during pharmaceutical care interventions in the medical intensive care unit at tertiary university hospital is dosage too high. The severity of drug-related problems is mostly determined as drug-related problems with no harm.

## Keywords

Drug-related problems, pharmaceutical care, intervention, medical intensive care unit

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## Introduction

Drug-related problems (DRPs) are circumstances that interfere with and potentially worsen optimal clinical outcomes.[1,2] A previous study reported that the prevalence of DRP-related hospital admission was 1.3%–41.3%, and most of the DRPs found in hospitalized patients could be preventable.[2] Critically ill patients receive twice the number of medications that

[1]Clinical Pharmacy Section, Pharmacy Division, Ramathibodi Hospital, Bangkok, Thailand
[2]Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand

**Corresponding author:**
Vichapat Tharanon, Clinical Pharmacy Section, Pharmacy Division, Ramathibodi Hospital, 270, Bangkok 10400, Thailand.
Email: vichapat.t@gmail.com

non-critically ill hospitalized patients receive, hence a higher probability of adverse drug events.[3] Intensive care unit (ICU) patients are more likely to experience drug–drug interactions (DDIs), drug accumulation due to multiple organ dysfunction, and sensitivity to drug responses resulting from their labile status.[4,5] The factors that influence the complexity of the patient's drug regimens include the alteration of pharmacokinetic and pharmacodynamic properties of drugs, severity stages of illness, multiple chronic diseases, drug interaction, polypharmacy, and ICU environment.[6,7] Critically ill patients are at higher risk of harm from DRPs due to frequent and more severe medication-related events. Thus, medication safety and efficacy must be considered in patients with critical illness.

A systematic review and meta-analysis revealed that pharmacist participation in a multidisciplinary treatment team could improve patient outcomes by reducing the mortality rate length of ICU stay and preventing adverse drug events.[8] According to a previous study, clinical pharmacists on ICU teams could improve the efficacy and safety of medication.[9] The clinical pharmacists' interventions that are provided for patients in the ICU consist of optimizing drug dosage; identifying and preventing adverse drug effects, drug interactions and unintentional drug discrepancies; and performing therapeutic drug monitoring (TDM) of the narrow therapeutic index drugs.[10] In addition, clinical pharmacists could curtail escalating drug costs from non-optimized medication therapy by selecting the most appropriate sedative agents, promoting antibiotic stewardship, and preventing adverse drug effects in accordance with a pharmacoeconomic study in the ICU.[11]

Patient safety is a priority and iatrogenic injuries must therefore be avoided. DRPs in critical care settings are frequent, serious, and predictable. Thus, knowing and understanding the nature of common DRPs and pragmatic management can assist on-ward clinical pharmacists in detecting, resolving, and preventing DRPs, as well as enable optimal personalized interventions for patient safety and efficacious drug therapy. This study identifies the types and severity of common DRPs and reports clinical pharmacists' interventions for DRP resolution in a medical intensive care unit (MICU) at a tertiary university hospital. It aims to help healthcare providers in a similar setting devise effective strategies to reduce DRP occurrences during the inadequate implementation of clinical pharmacists in ICUs in Thailand.

## Methods

### *Study design and setting*

This is a retrospective descriptive study in critically ill patients admitted to the MICU at Ramathibodi Hospital, a tertiary university hospital in Bangkok, Thailand. In practice, when MICU clinical pharmacists could identify DRPs, DRPs and subsequent pharmacists' interventions for DRP resolution were readily advised to physicians and documented in the medical records. Then, the responses of physician or nurse acceptance were followed up. Consequently, DRP information, patient characteristics, and relevant clinical information could be retrospectively reviewed from paper and electronic medical records for data collection and analysis. DRPs and pharmacist interventions that were documented in the medical records were carefully reviewed for data collection from January 2015 to December 2020. The patients who met the following criteria were eligible for the study: (1) 18 years of age and older, (2) admitted to the MICU, and (3) medication reconciliation and medical records were reviewed and verified by MICU pharmacists. The exclusion criteria were patients who were transferred to other units or died within 24 h prior to completing the data collection. A diagram of the inclusion and exclusion criteria process of the study is shown in Figure 1.

### *Clinical pharmacists' interventions*

Pharmacist interventions were performed directly toward DRPs for DRP resolution and to prevent undesired outcomes. A modified Schumock and Thornton[12] criteria were also applied in the MICU pharmacist's responsibility as follows for patients' safety, drug efficacy, and prevention of predictable adverse drug reactions (ADRs):

1. A history of drug allergies and ADRs in medical records and electronic databases was routinely reviewed and verified to avoid prescribing inappropriate drugs to the patients.
2. Medication review and medication reconciliation were evaluated daily and followed up by MICU pharmacists to optimize the dosage regimen, avoid DDIs, and assess medication adherence.
3. TDM was performed by MICU pharmacists to minimize toxicity and enhance therapeutic responses of the narrow therapeutic index drugs such as vancomycin, aminoglycosides, and valproic acid.
4. Laboratory parameters for ICU medication were monitored for any potential ADRs of the drugs prescribed.
5. Medication dosage was adjusted through dose, frequency, strength, treatment duration, and schedule for the most appropriate dosage regimen.
6. The pharmaceutical care interventions included change of dosage form, different routes of administration, and starting or stopping medication.
7. Moreover, patients were educated to enhance their adherence to and promote positive behavioral change toward the use of pharmacotherapy.

The average participation time of clinical MICU pharmacists was 7 h a day from Monday to Friday. Two clinical pharmacists with a master's degree in Clinical Pharmacy attended the multidisciplinary team round.

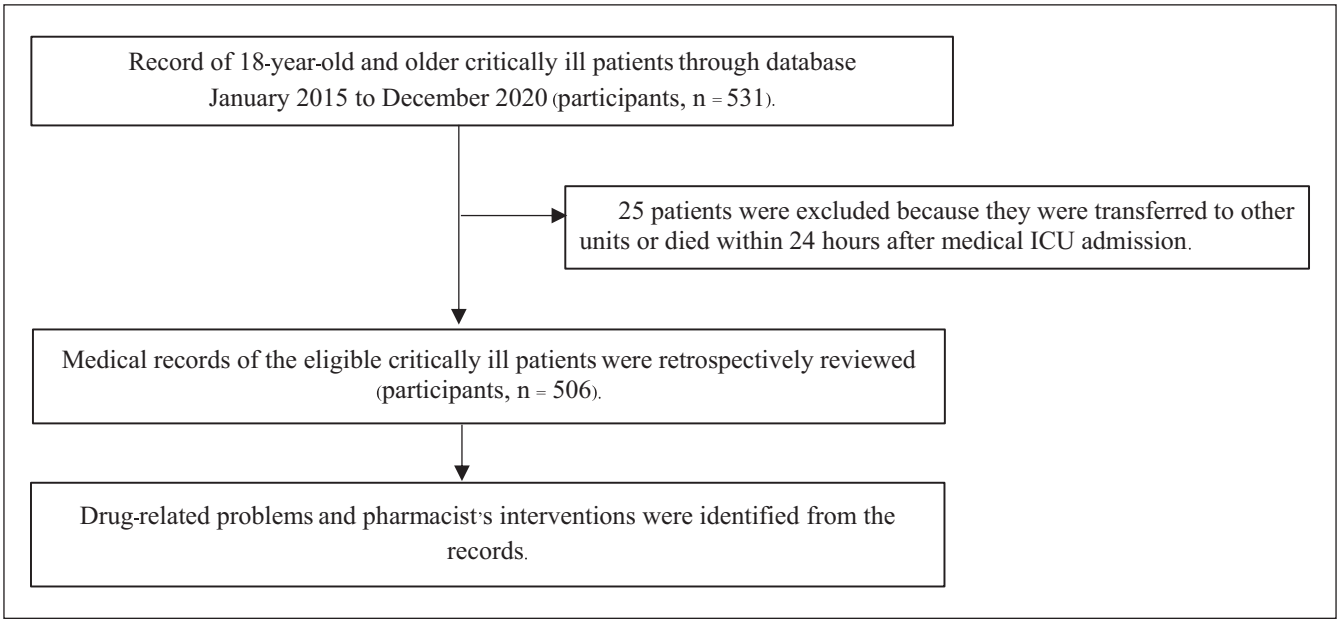



**Figure 1.** Diagram of the inclusion and exclusion criteria process of the study.

### *Tools for defining drug-related problems and severity of drug-related problems*

In this study, DRPs were defined and categorized according to Cipolle et al.[13] as shown in Table 1. Pharmacist performed clinical interventions to optimize pharmacotherapy and resolve the DRPs.

The severity classification of DRPs in this study was identified as the level of patient harm by adapting and modifying the medication error index adopted by The National Coordinating Council for Medication Error Reporting and Prevention Taxonomy of Medication Error (NCC-MERP)[14] to report the severity of DRP-related patient outcomes, as shown in Table 2. The severity category of the result was classified as DRP with no harm, DRP with potential harm, DRP with harm, and DRP with death. The severity was assessed by two MICU clinical pharmacists to report the outcomes of DRP-affected patients.

### *Statistical analysis*

The sample size was calculated using an $\alpha$ (alpha/significance level) of 0.05 and the assumed incidence of DRPs in ICU was 76%.[15] The prevalence of patients who had DRPs in the MICU was calculated from all critically ill patients who had DRPs during MICU admissions divided by the total number of critically ill patients who were admitted to the MICU over 6 years. Descriptive analyses were performed with Statistical Package for the Social Sciences (SPSS) Version 18 for Windows.

## Results

The DRPs in MICU were detected in 374 critically ill patients from total of 506 patients in this study. Most patients were male with an average age of 61.8 years old. Sepsis or septic shock was the most frequent indication for MICU admission. The Acute Physiology and Chronic Health Evaluation (APACHE II) scoring system was used for predicting patient mortality while patients were admitted. The mean APACHE II score was 22 and the mean length of ICU stay was 15.5 days. Table 3 presents the characteristics of MICU patients included in this study. The medication order and pharmacist notes documented were retrospectively reviewed and analyzed to summarize the DRPs' and the interventions by MICU pharmacists over a total of 6 years.

The prevalence of DRPs occurring in critically ill patients in the MICU at a tertiary university hospital in Thailand was 73.9%. A total of 698 DRPs were identified in this study, as shown in Figure 2. Dosage too high was the most frequent DRP (27.7%) that MICU clinical pharmacists could detect and resolve. The optimal dosage adjustment was advised to prevent the risk of undesired adverse effects. Dosage too low was 14.3%. In addition, 17.2% of DRPs were ineffective drugs resulting from inappropriate drug choice or dosage form selection, while the most effective drug was available for patients. The other types of DRPs in the MICU were described as percentages as follows: the need for additional drug therapy, unnecessary drug therapy, ADRs, and non-adherence were 15.3%, 14.6%, 9.7%, and 1.2%, respectively.

**Table 1.** Categories and common causes of drug-related problems defined by Cipolle et al.[13]

| Drug-related problem category | Common causes of drug-related problems |
|---|---|
| 1. Unnecessary drug therapy | ♦ There is no valid medical indication requiring drug therapy (no medical indication).<br>♦ Multiple drug products are used for a condition that requires single drug therapy (duplicate therapy).<br>♦ The medical condition can be more appropriately treated with non-drug therapy (non-drug therapy more appropriate).<br>♦ Drug therapy is taken to treat and avoid adverse reaction associated with another medication.<br>♦ Drug abuse, alcohol use, or smoking causes the problem. |
| 2. Need additional drug therapy | ♦ Preventive drug therapy is required to reduce the risk of developing a new condition (preventive therapy).<br>♦ A medical condition requires the initiation of drug therapy (untreated condition).<br>♦ A medical condition requires additional pharmacotherapy to attain synergistic or additive effects (synergistic therapy). |
| 3. Ineffective drug | ♦ The drug is not the most effective for the medical condition and a different drug is needed (more effective drug available).<br>♦ The medical condition is refractory to the drug product and a different drug is needed.<br>♦ The dosage form of the drug product is inappropriate.<br>♦ The drug product is contraindicated in the patient.<br>♦ The drug product is not an effective product for the indication being treated. |
| 4. Dosage too low | ♦ The dose is too low to produce the desired response.<br>♦ The dosage interval is too infrequent to produce the desired response.<br>♦ A drug interaction reduces the amount of active drug available.<br>♦ The duration of drug therapy is too short to produce the desired response. |
| 5. Adverse drug reaction | ♦ The drug product causes an undesirable reaction that is not dose-related.<br>♦ A safer drug product is required due to risk factor.<br>♦ A drug interaction causes an undesirable reaction that is not dose-related.<br>♦ The dosage regimen is administered or changed too rapidly.<br>♦ The drug product causes an allergic reaction.<br>♦ The drug product is contraindicated due to risk factors. |
| 6. Dosage too high | ♦ The dosage is too high, resulting in toxicity.<br>♦ The dosage interval is too short.<br>♦ A drug interaction reduces the amount of active drug available.<br>♦ A drug interaction occurs resulting in a toxic reaction to the drug product.<br>♦ The dose of the drug was administered too rapidly. |
| 7. Non-adherence | ♦ The patient does not understand instructions.<br>♦ The patient prefers not to take the medication.<br>♦ The patient forgets to take the medication.<br>♦ The drug product is too expensive for the patient.<br>♦ The patient cannot swallow or self-administer the drug product appropriately.<br>♦ The drug product is not available for the patient. |

**Table 2.** The classification of severity of drug-related problems defined by modified The National Coordinating Council for Medication Error Reporting and Prevention Taxonomy of Medication Error (NCC-MERP)[14] definition.

| Major division | Category | Description |
|---|---|---|
| No drug-related problem | A | Circumstances or events that have the capacity to cause error. |
| Drug-related problem, no harm | B | The drug-related problem occurred but the error did not reach the patient. |
| | C | The drug-related problem occurred that reached the patient, but did not cause patient harm. |
| Drug-related problem, potential harm | D | The drug-related problem occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm. |
| Drug-related problem, harm | E | The drug-related problem occurred that may have contributed to or resulted in temporary harm to the patient and required intervention. |
| | F | The drug-related problem occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization. |
| | G | The drug-related problem occurred that may have contributed to or resulted in permanent patient harm. |
| | H | The drug-related problem occurred that required intervention necessary to sustain life. |
| Drug-related problem, death | I | The drug-related problem occurred that may have contributed to or resulted in the patient's death. |

"Dosage too high," the most frequent DRPs from the study, is commonly found in the antibiotic group. The top five antibiotics of which dosage was most frequently suggested by pharmacists to adjust based on creatinine clearance were trimethoprim and sulfamethoxazole, meropenem, levofloxacin, fluconazole, and colistin. Meanwhile, extended-release delivering medications might cause "ineffective drug," the second-most common DRPs, if they are crushed or broken for nasogastric tube administration. Patients might suffer from potentially high toxicity and an inability to control symptoms from inappropriate dosage form administration.

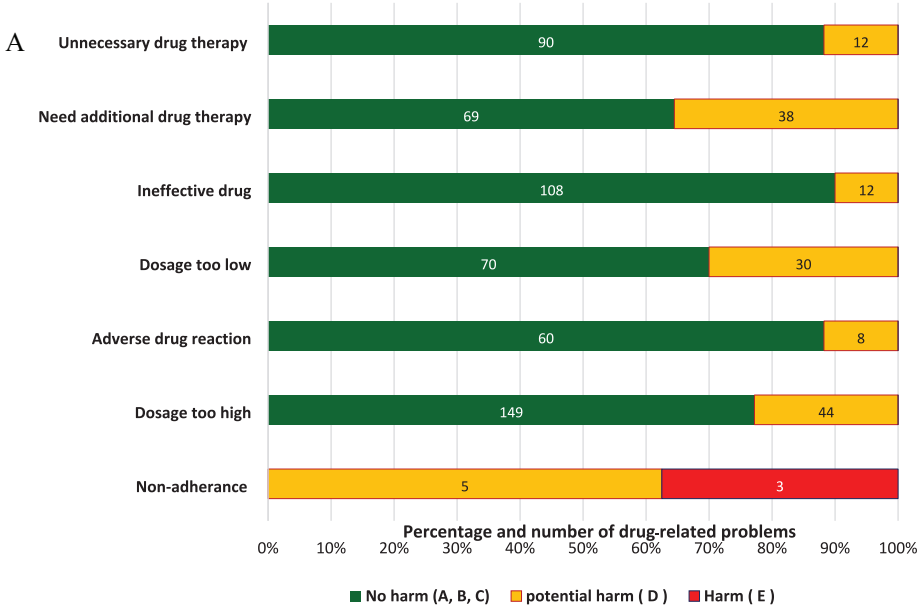
The most common drugs that were found to require additional drug therapy ("need additional drug therapy") based on the study were ophthalmic lubricants, proton-pump inhibitors (PPIs), and laxatives. These medications were recommended for ICU patients to prevent unpleasant events in critically ill patients, for instance, corneal ulceration from loss of blinking reflex during prolonged paralysis, upper

**Table 3.** Characteristics of medical intensive care unit patients.

| Characteristics (total n = 374) | Value |
|---|---|
| Male, n (%) | 200 (53.6) |
| Female, n (%) | 174 (46.5) |
| Age, years (mean ± SD) | 61.8 ± 19.1 |
| Causes of medical intensive care unit admission, n (%) | |
| Sepsis or septic shock | 216 (57.8) |
| Hemodynamic unstable | 87 (23.3) |
| Hemorrhagic or hypovolemic shock | 32 (8.6) |
| Postcardiac arrest | 18 (4.8) |
| Status epilepticus | 17 (4.5) |
| Drug overdose | 4 (1.0) |
| APACHE II score, (mean ± SD) | 22 ± 9.8 |
| Length of medical intensive care unit stay, days (mean ± SD) | 15.5 ± 10.8 |
| Number of drugs per patient, median (min, max) | 10 (5, 15) |

SD: standard deviation; APACHE II: Acute Physiology and Chronic Health Evaluation.

A




B

| Drug-related problems | Unnecessary Drug therapy | Need additional drug therapy | Ineffective drug | Dosage too low | Adverse drug reaction | Dosage too high | Non-adherence | Total |
|---|---|---|---|---|---|---|---|---|
| No harm (A,B,C) | 90 | 69 | 108 | 70 | 60 | 149 | 0 | 546 (78.2%) |
| Potential harm (D) | 12 | 38 | 12 | 30 | 8 | 44 | 5 | 149 (21.3%) |
| Harm (E) | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 (0.5%) |
| Total | 112 (14.6%) | 107 (15.3%) | 120 (17.2%) | 100 (14.3%) | 68 (9.7%) | 193 (27.7%) | 8 (1.2%) | **698 (100%)** |

**Figure 2.** Number and percentage of drug-related problems (DRPs) in medical intensive care unit classified by DRP categories and severity.

**Table 4.** Description of common problem-related drugs frequently detected in medical intensive care unit and pharmacists' interventions.

| Problem-related drugs | Description of drug-related problems | Pharmacist's interventions |
|---|---|---|
| 1. Unnecessary drug therapy | | |
| Acyclovir | Oral acyclovir for herpes simplex prophylaxis was unintentionally continued concomitant with intravenous ganciclovir when patient was suspiciously infected with cytomegalovirus. | Discontinuing the oral acyclovir. |
| Thiamine | Intravenous thiamine administration in septic shock patients could improve lactate clearance and mortality. Duration of thiamine is 3–4 days. In practice, thiamine was continued with no indication after patient was out of septic shock. | Discontinuing intravenous thiamine or switching to oral thiamine, vitamin B1-6-12. |
| Proton-pump inhibitors (PPIs) | PPIs could prevent stress ulcer induced gastrointestinal bleeding in critically ill patients with mechanical ventilation over 48 h. Nevertheless, PPIs should be discontinued in non-critically ill hospitalized patients. For instance, extubated patients or patients who had no evidence of upper gastrointestinal bleeding. | Discontinuing PPIs when no indication. |
| 2. Need additional drug therapy | | |
| Ophthalmic lubricants | Patients who were heavily sedated and paralyzed with neuromuscular blocking agents generally lost blinking reflex. The ophthalmic lubricant needed to be prescribed to prevent serious corneal complication such as corneal ulceration, infection, and visual loss. | Ophthalmic lubricants were prescribed for paralyzed patients. |
| Proton-pump inhibitors (PPIs) | Patients who had high risk of gastrointestinal bleeding during critically ill period should be prescribed acid suppression prophylaxis. | PPIs prophylaxis was always advised to be prescribed in mechanically ventilated patients. |
| Laxatives | Laxatives should be prescribed in patients who had sedative agents especially opioid drugs to prevent chronic constipation. Constipation might cause abdominal distension and discomfort, poor tolerance of enteral feeding, confusion, and intestinal obstruction with vomiting and risk of pulmonary aspiration. It may also be associated with raised intra-abdominal pressure which can impact on respiratory function. | Constipation should be closely observed in MICU patients. Laxatives or stool softener should be prophylactically prescribed in sedated patients. |
| Prokinetics | Patients who had gastroparesis or residual gastric content after enteral feeding should be considered to initiate the prokinetics. | Metoclopramide, erythromycin itopride, or domperidone are effective prokinetics that could improve gastrointestinal motility. |
| 3. Ineffective drug | | |
| Meropenem | Patients with suspected sepsis or septic shock were generally prescribed meropenem as an empirical broad-spectrum antibiotic. However, antibiotics de-escalation should be adjusted when the bacterial culture and sensitivity was reported. | Meropenem was suggested to be discontinued and switched to the specific or narrow spectrum antibiotics. |
| Extended-release delivering medications | Crushing medications for a nasogastric tube administration was a general practice. However, crushing method of extended-release dosage form was not appropriate due to a potential risk of toxic peak and insufficient drug concentration. | The alternative dosage form or alternative drugs which were suitable for a nasogastric tube administration were suggested. |
| 4. Dosage too low | | |
| 1. Meropenem<br>2. Piperacillin and tazobactam<br>3. Ganciclovir<br>4. Ceftazidime<br>5. Imipenem and cilastatin sodium | The top five problem-related antimicrobial agents were detected for dosage too low in critically ill patients when renal function improved but proper dosage adjustment was not prescribed. | Increasing drug dosage based on calculated creatinine clearance was advised. |

*(Continued)*

**Table 4.** (Continued)

| Problem-related drugs | Description of drug-related problems | Pharmacist's interventions |
|---|---|---|
| Valproic acid | Combining of valproate acid with carbapenem antibiotics was associated with a potential drug interaction that decreased serum concentration of valproaic acid and might expose the patient to uncontrolled seizure risk from subtherapeutic valproic acid concentrations. | Valproic acid level was monitored and the alternative anticonvulsants were considered. |
| Propofol-cisatracurium | Patient-ventilator dyssynchrony was detected while patient was already sedated and paralyzed. When MICU pharmacist monitored patient bedside, it was found that propofol and cisatracurium were administered together at the same intravenous route. This couple of drugs was incompatible via Y-site intravenous administration. | Y-site intravenous compatibility of the drugs should be usually checked by MICU pharmacists. |
| 5. Adverse drug reaction | | |
| Phenytoin intravenous | Patient had hypotension with bradycardia while she was administered intravenous phenytoin with a rapid infusion rate (25 mg/min). | Careful cardiac monitoring was advised. Phenytoin intravenous infusion was decreased to prevent cardiac adverse effects. |
| Amiodarone | The treatment-emergent adverse effects of amiodarone were hypotension and bradycardia. In addition, interstitial pneumonitis was likely the most common presentation of amiodarone-induced pulmonary disease, especially in patients who had amiodarone dose in excess of 400 mg per day. | Amiodarone ADR was closely monitored in vulnerable patients. |
| Vancomycin | Vancomycin-associated nephrotoxicity was found in critically ill patients. A number of factors which contributed to acute kidney injury are organ failure and multiple co-administrated nephrotoxic drugs. | Vancomycin level was monitored to minimize toxicity and maximize efficacy. |
| Midazolam | Hypotension commonly occurred when intravenous midazolam was rapidly administered in patients with unstable hemodynamic. | Midazolam administration was recommended to be slowly intravenous injected to patient. |
| Voriconazole-levofloxacin | Voriconazole and levofloxacin were member of drug-induced QTc prolongation antibiotics. Higher risk of QTc prolongation might occur when multiple drug-induced was concomitantly prescribed. | QTc monitoring was required to ensure safety |
| 6. Dosage too high | | |
| 1. Trimethoprim and sulfamethoxazole<br>2. Meropenem<br>3. Levofloxacin<br>4. Fluconazole<br>5. Colistin | The top five problem-related antimicrobial agents were detected for dosage too high in critically ill patients when renal function declined but no proper dosage adjustment. | Decreasing drug dosage based on calculated creatinine clearance was advised. |
| Tacrolimus and posaconazole | Elevated tacrolimus level was detected due to potential drug interaction from strong CYP3A4 inhibitor (posaconazole). | Tacrolimus was monitored to minimize toxicity and maximize efficacy. |
| Cyclosporin and voriconazole | Elevated cyclosporin level was detected due to potential drug interaction from strong CYP3A4 inhibitor (voriconazole). | The therapeutic drug monitoring of cyclosporin and voriconazole was performed to minimize toxicity and maximize efficacy. |
| Ergotamine tartrate | Two cases of HIV patients who developed peripheral vascular insufficiency required being admitted to MICU due to ergotism from drug interaction between antiviral protease inhibitor (lopinavir/ritonavir) and ergotamine tartrate/caffeine. | Patient education and drug interaction in computerized-based data were offered to prevent serious adverse drug reactions. |

MICU: medical intensive care unit; ADR: adverse drug reaction.

gastrointestinal bleeding, and bowel obstruction or impaired respiratory function from chronic constipation. Furthermore, hypotension commonly occurred as an ADR that was possibly related to intravenous phenytoin, amiodarone, propofol, and midazolam. Nephrotoxicity occurred in patients who were prescribed vancomycin together with other nephrotoxic drugs such as acyclovir, ganciclovir, amikacin, and colistin. To contribute the clinical knowledge of experienced MICU pharmacists in detecting and resolving DRPs, the descriptions of common problem-related drugs frequently detected are described in Table 4.

The severity of DRPs most commonly found in the MICU was DRP with no harm categorized as severity A, B, and C at 78.2%. The DRP with potential harm and DRP with harm were 21.3% and 0.5%, respectively. In practice, once DRPs were detected, the clinical pharmacists' interventions were performed and discussed with a multidisciplinary team to resolve the cause of the drug problems and achieve higher efficacy and safety of drug therapy. Interventions were designed individually for each critically ill patient to resolve DRPs, including the full spectrum of modification in drug dosage regimens, TDM, and ADR monitoring. These included initiating new drug therapy, changing the drug product, altering the dose and/or the dosing interval, discontinuing drug therapy, and providing personalized patient instruction or dosage regimen. The interventions of MICU clinical pharmacists are described in Table 4.

## Discussion

This is the first study of DRPs in the MICU at a tertiary university hospital in Thailand and the clinical pharmacists' interventions for DRP resolution. The objective of the study is to report common types of DRPs and pharmacists' clinical interventions in MICU, in order to guide clinical pharmacists who work in critical care settings, especially because there is an inadequate opportunity for Thai pharmacists today to gain specialized experience in pharmacy practice and in the real implementation of clinical pharmacists in ICUs.

The prevalence of DRPs occurring in adult patients hospitalized in the MICU over 6 years was 73.9%. The 698 DRPs were evaluated in 374 critically ill patients using Cipolle et al.'s[13] definition. The most frequent DRP in this study was a dosage that was too high (27.7%), which is aligned with several previous studies.[6,16,17] The cause of the dosage being too high in this study might result from renal impairment related to sepsis or septic shock. The majority of drug classes that were detected at dosage that was too high in this study were antimicrobial agents, which is in accordance with a previous study.[6,16,18,19] The top five antimicrobial agents which were frequently intervened for dosage adjustment according to a calculated creatinine clearance using the Cockcroft and Gault formula were trimethoprim and sulfamethoxazole, meropenem, levofloxacin, fluconazole, and colistin. In addition, polypharmacy could cause DDIs and lead to dosages that were too high because the drug concentration of the target drug was increased due to inhibition of the CYP-mediated metabolic pathway.[20] CYP3A4 was the most clinically significant isoenzyme and was implicated in the majority of drug interactions.[21] Several ICU medications were eliminated via the CYP3A4 metabolism pathway. In this study, it was reported that tacrolimus or cyclosporin levels were highly increased in kidney transplant patients from DDIs because they were prescribed concomitantly with strong CYP3A4 inhibitors such as posaconazole and voriconazole for invasive fungal infections. It should be noted that immunosuppressive levels that are too high might result in adverse effects, including renal impairment and immune suppression-related severe infection.[22] To minimize the adverse effects and maximize drug efficacy, TDM is one of the essential interventions of pharmacists to optimize individual drug dosages, especially narrow therapeutic index drugs.[23] Dosage too low was also detected with 14.3% of the total DRPs. Subtherapeutic dosage was found in patients who had renal recovery after acute kidney injury, but dosage adjustment of renally cleared drugs was not considered. Thus, the main type of clinical pharmacist interventions in the MICU was dosage adjustment to ensure the appropriate dose and frequency. Optimal drug dosage in critically ill patients is a considerable challenge because patients have unstable clinical conditions related to renal or liver failure and sometimes these patients receive extracorporeal life support or renal replacement therapy. Therefore, dosage may require frequent adjustments during such serious illness.[24]

Ineffective drug was reported to be 17.2% of the total DRPs. The cause of the ineffective drug was an inappropriate dosage form for nasogastric tube administration, which required other suitable dosage forms. This result accords with previous studies.[17,25,26] The common ineffective medication was PPIs which were used for stress ulcer prophylaxis in mechanically ventilated patients.[27] Some PPIs could not be crushed for nasogastric tube administration because they were made with enteric coated pellets to protect them from acid in the stomach which could compromise the drug effect. Alternatively, PPIs that could be dispersed and stable in water, such as lansoprazole, would be the drug of choice for MICU patients with nasogastric tube feeding.[25] Moreover, the need for additional drug therapy constituted 15.3% of the total DRPs. The most common condition that required additional drug therapy was found in paralyzed patients with acute respiratory distress syndrome (ARDS) who needed ophthalmic lubricants to prevent corneal abrasion.[28,29] Constipation was the following condition that should always be observed and needed to be prevented in sedated patients, especially in those who received opioid drugs; therefore, laxatives were essential for preventing bowel obstruction or pulmonary aspiration.[30] To promote bowel mobility during deep sedation, prokinetic drugs should be prescribed to stimulate bowel movement to decrease gastric residual content.[31] The hospital admissions associated with medication nonadherence had also been previously investigated. In this

study, metformin, insulin products, and beta blocker were related to hospital admissions due to patients' medication non-adherence. ADR usually occurred in an ICU because of medical complexity including high-alert medication. In this study, the ADR was 9.7% of the total DRPS.

According to the modified NCC-MERP definition in this study, the percentage of potentially harmful DRP (severity category D) was 21.3%, which is in agreement with a previous study.[32] The incidence of DRPs with no harm (severity category A, B, and C) was 78.2%. It also implied that MICU clinical pharmacists could detect and alleviate DRPs before they aggravated the conditions of critically ill patients. The outcome of this study was congruent with Lee et al.,[8] who reported that critical care and interventions from pharmacists on multidisciplinary teams could enhance the quality of ICU care, medication safety, and pharmacotherapy.

Pharmacotherapy can treat and prevent not only the diseases but the possible DRPs. Critically ill patients in the MICU had a higher risk of DRPs. Nevertheless, pharmacist who had experience and knew of common DRPs in critically ill patients could foresee and prevent harmful outcomes from those DRPs. The implication of these findings is that pharmaceutical care by clinical pharmacists in the MICU could resolve various types of DRPs in critically ill patients using Cipolle et al.'s[13] definition to identify the causes of DRPs. In addition, many common DRPs can be prevented and managed prior to occurrence and harm to patients. This study has some limitations as follows. First, this study is a retrospective descriptive study in which there were no intervention studies or randomized controlled trials of pharmacists' interventions. Second, this study was conducted in only one MICU at a tertiary care unit in a university hospital. The results might not be generalized to other ICU settings and other countries. Thus, future studies can be performed with other study designs and populations.

## Conclusion

The most frequent DRP identified during pharmaceutical care interventions in an MICU at a tertiary university hospital is a dosage too high of antimicrobial agents. The severity of DRPs detected in this study was mostly DRP with no harm. Pharmacists' interventions were performed to resolve DRPs and optimize pharmacotherapy in critically ill patients.

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### Author contributions

V.T.: informed consent, collected, analyzed and interpreted data, and wrote and revised manuscript; K.P.: analyzed and interpreted data, and wrote manuscript; P.S.: analyzed and interpreted data, and wrote and revised manuscript.

### Availability of supporting data

The data used and/or analyzed during this study are available from the corresponding author on reasonable request.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Ethical approval

The study protocol was approved by the Institutional Review Boards of Mahidol University (MURA2021/482). The date of approval is 4 June 2021. The study followed the Helsinki Declaration, The Belmont Report, CIOMS Guideline, and the International Conference on Harmonization in Good Clinical Practice (ICH-GCP).

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### Informed consent

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### ORCID iD

Vichapat Tharanon https://orcid.org/0000-0003-2830-9248

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