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Pharmacists in Critical Care

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Abstract
The beginnings of caring for critically ill patients date back to Florence Nightingale's work during the Crimean War in 1854, but the subspecialty of critical care medicine is relatively young. The first US multidisciplinary intensive care unit (ICU) was established in 1958, and the American Board of Medical Subspecialties first recognized the subspecialty of critical care medicine in 1986. Critical care pharmacy services began around the 1970s, growing in the intervening 40 years to become one of the largest practice areas for clinical pharmacists, with its own section in the SCCM, the largest international professional organization in the field. During the next decade, pharmacy services expanded to various ICU settings (both adult and pediatric), the operating room, and the emergency department. In these settings, pharmacists established clinical practices consisting of therapeutic drug monitoring, nutrition support, and participation in patient care rounds. Pharmacists also developed efficient and safe drug delivery systems with the evolution of critical care pharmacy satellites and other innovative programs. In the 1980s, critical care pharmacists designed specialized training programs and increased participation in critical care organizations. The number of critical care residencies and fellowships doubled between the early 1980s and the late 1990s. Standards for critical care residency were developed, and directories of residencies and fellowships were published. In 1989, the Clinical Pharmacy and Pharmacology Section was formed within the Society of Critical Care Medicine, the largest international, multidisciplinary, multispecialty critical care organization. This recognition acknowledged that pharmacists are necessary and valuable members of the physician-led multidisciplinary team. The Society of Critical Care Medicine Guidelines for Critical Care Services and Personnel deem that pharmacists are essential for the delivery of quality care to critically ill patients. These guidelines recommend that a pharmacist monitor drug regimen for dosing, adverse reactions, drug-drug interactions, and cost optimization for all hospitals providing critical care services. The guidelines also advocate that a specialized, decentralized pharmacist provide expertise in nutrition support, cardiorespiratory resuscitation, and clinical research in academic medical centers providing comprehensive critical care.

Keywords: Pharmacists; Caregivers; Teamwork; Medication; Error; Patient

Abbreviations: Society of Critical Care Medicine (SCCM); The Canadian Journal of Hospital Pharmacy (CJHP); Healthcare Establishment (HCE); Pharmacist interventions or Recommendations (PhRs); Acute Renal Failure (ARF); Chronic obstructive pulmonary disease (COPD); Simplified Acute Physiology Score (SAPS); Adult Respiratory Distress Syndrome (ARDS); Mechanical Ventilation (MV); Intra-Aortic Balloon Pump (IABP); Medication Administration Errors (MAEs); Intravenous Fat Emulsions (IVFEs); Pediatric Intensive Care Units (PICU); Antibiotic Stewardship Program (ASP); Days Of Therapy (DOT); Cost Of Therapy (COT); Neonatal Intensive Care Unit (NICU); Propensity Score (PS); Fatal Adverse drug events (FADE); Coronary Care Unit (CCU);

Introduction

The value of critical care pharmacists has been well documented. Various studies have shown that critical care pharmacists reduce medication errors, improve patient outcomes, reduce costs and waste, and decrease mortality rates among patients with thromboembolic diseases or infections. It would therefore appear that critical care pharmacists should be a basic requirement for any ICU, because they are involved in diverse aspects of care and scholarly activities related to critically ill patients, because they are well accepted by their peers, and because their work is associated with improved clinical, economic, and humanistic outcomes. The reasons why critical care pharmacists are not present all the time in any type of HCE are multifactorial and may include lack of financial resources, lack of adequately trained personnel, inconsistent documentation of pharmacists' activities in medical records, lack of a shared practice model, and perhaps (however counterintuitive) the belief of both hospital and pharmacy administrators that critical care pharmacists are not really essential. However, critical care is a rapidly expanding pharmacy specialty, and today's pharmacy students have more opportunities than ever to become successful critical care pharmacists if they demonstrate their expertise and their commitment to the lives of their patients. Working as pharmacists in the intensive care unit begins with our ability to be engaged and meticulous in identifying key patient interventions. Pharmacists must be able to assess the

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status of each organ and determine the patient's problem list. Addressing the patient's neurological status, checking vitals for hemodynamic stability, managing pain, and knowing when prophylaxis is indicated are all factors in providing a care plan for the patient. Along with the roles aforementioned, the pharmacist aids in evaluating the need for fluids, diuretics, or stool-inducing medications, while taking into consideration the patient's input/output, nutritional status, and comorbidities. Additionally, pharmacists must remember to address liver function, as well as any drug monitoring parameters. Ensuring that patients are on their home medications, identifying possible intravenous to enteral agents, and verifying proper medications are also important in performing an intervention. Antibiotic stewardship is a core part of critical care, and many times, the physician will rely on the pharmacist's recommendations and expertise. Critical care pharmacists are also recognized as essential by those outside the pharmacy profession, including the SCCM. In fact, several SCCM guidelines describe the scope of pharmacy practice and pharmacists' role within best practice models for ICU staffing. A CJHP study highlights the potential role of critical care pharmacists in quality improvement, detection of errors, and production of scholarly work. Although less than 10% of hospitalized patients are admitted to the ICU, over 30% of hospital costs are allocated for patients needing acute care. It seems that patients admitted to ICUs are prone to a higher risk of medication-related problems because of the higher numbers of prescribed medications, intensity of the work environment, presence of critical illness, and increased use of high-risk medications.

1.1. Scope of Pharmacists in critical care

A survey of pharmacist services included only 382 of the 3,238 hospitals (11.8%) with an ICU at the time of the survey. The exact number of pharmacists practicing in the critical care environment is not known. There are approximately 1,500 pharmacist members of the SCCM Clinical Pharmacy and Pharmacology Section and about 3,000 critical care pharmacist members as part of the American College of Clinical Pharmacy and the American Society of Health System Pharmacists. This has led to a conservative estimate of 6,000 practicing critical care pharmacists. The time that these pharmacists dedicate to ICU services is unknown. It is projected that the demand for critical care pharmacists will remain stable or grow in the future [1].

1.2. Role as a Team Member

Clinical pharmacists in the ICU (and in other practice areas) are part of an interprofessional team working toward the common goal of improving patient outcomes. Teams in the ICU often include physicians, pharmacists, nurses, respiratory therapists, dieticians, physical therapists, social workers, and others. Each of these caregivers has a specific role in patient care, and each can contribute positively to patient outcomes. Because interprofessional critical care teams have been shown to benefit patients and their families, integrated team-based care is expressly included in the SCCM-envisioned future statement and guiding principles for the organization and members. The performance of teams is studied in many ways, including team processes. In the ICU, utilization of daily patient-centered goals checklists and commencement of daily multidisciplinary patient care rounds are associated with positive patient outcomes. Improving team interactions has been associated with positive patient outcomes, and poor team interactions have been associated with ICU adverse events. Pharmacists can play a role in ensuring that all patient goals are addressed by the team, clarifying tasks, developing care plans, and communicating plans among caregivers. In light of the positive impact of pharmacist participation on ICU interprofessional teams, each hospital should have a clinical pharmacist rounding and participating in other aspects of team-based patient care in the ICU [1-3].

2. Pharmacists' role in critical care

The use of medication by seriously ill patients represents an example of the complex nature of the care provided in the ICU. The reason for this complexity is that patients are usually subjected to poly-medication, which makes pharmacological treatment a significant risk factor for the occurrence of adverse events that might negatively interfere with the clinical progression of patients [4]. Pharmacists have been incorporated into ICU multi-professional staff to improve the care provided to patients, particularly by monitoring the drugs administered and assessing their efficacy, thus contributing to improving patient safety. The participation of clinical pharmacists in routine ICU care mainly includes active involvement in daily rounds, where they provide relevant information to the medical and nursing staff, analysis and monitoring of the efficacy of pharmacological treatments, implementation of medication reconciliation, and prevention, identification, and reporting of adverse reactions [5-7]. The actions performed by clinical pharmacists relative to the monitoring of pharmacological treatment are referred to as PhRs. Such professional interventions presuppose actions targeting pharmacological treatment to correct or prevent negative clinical outcomes derived from the use of medications. These are planned and documented actions performed with users and healthcare professionals, as they are a part of the process of monitoring/follow-up of pharmacological treatments [8].

2.1. Challenges encountered in the ICU

Critical care areas present a particular challenge with regard to medication errors. They are a dynamic environment with critically ill patients who often require rapid adaptation of on-going management. ICUs can be error-prone settings, where even otherwise minor adverse events can lead to serious disability. The frequency of medication errors in adult ICUs can be as high as 947 per 1,000 patient-days, with a median of 105.9 per 1,000 patient-days. Medication errors are estimated to account for 78% of all medical errors in ICUs, with an average of 1.75 medication errors per patient per day. Not only are medication errors more frequent in ICU settings than in non-

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ICU settings, they are also more likely to be severe and cause harm [9].

2.2. Factors associated with morbidity in ICU

Many factors are hypothesized to contribute to the relatively high incidence and associated morbidity of medication errors in the ICU. The patients themselves are the most complex and critically ill in the hospital setting. By virtue of being sicker, older, and having more comorbidities, these patients are less resilient to errors.

- Because they require a higher intensity of care provision and may receive more medications, they may be at greater risk of iatrogenic harm. Pharmacokinetics of medications can also be altered in critically ill patients, principally through changes in volume of distribution and drug clearance. Large volume resuscitations, positive pressure ventilation, surgical procedures, systemic inflammatory response, and changes in protein binding, all common in ICU patients, affect the pharmacokinetics of many drugs.
- In addition, these patients are usually unable to help facilitate their own care, a problem aggravated by the volume of transfers to and from ICUs. Medication safety in ICUs might also be compromised because of the risks associated with the use of multiple medications per patient and the use of high-risk drugs associated with potentially severe adverse events. Drugs used in the ICU are more likely to be potent, require dose calculations, have medication interactions, and be continuous infusions (which have a greater potential for error). Many medications may be used for off-label indications in the ICU setting, similar to the non-ICU inpatient and outpatient settings. The combination of these elements makes patients in critical care areas particularly vulnerable to medication errors and their potentially dire consequences.
- Patients admitted to ICU with COPD often have multiple comorbidities and present with acute respiratory failure as a result of an infective exacerbation or at the end stage of their disease.
- Atrial fibrillation (AF) is the most common arrhythmia encountered in the ICU. Preexisting AF is highly prevalent among older patients with chronic conditions who are at risk for critical illness, whereas new-onset AF can be triggered by accelerated atrial remodeling and arrhythmogenic triggers encountered during critical illness. The acute loss of atrial systole and onset of rapid ventricular rates that characterize new-onset AF often lead to decreased cardiac output and hemodynamic compromise. Thus, new-onset AF is both a marker of disease severity as well as a likely contributor to poor outcomes, similar to other manifestations of organ dysfunction during critical illness. Evaluating immediate hemodynamic effects of new-onset AF during critical illness is an important component of rapid clinical assessment aimed at identifying patients in need of urgent direct current cardioversion, treatment of reversible inciting factors, and identification of patients who may benefit from pharmacologic rate or rhythm control. In addition to acute hemodynamic effects, new-onset AF during critical illness is associated with both short- and long-term increases in the risk of stroke, heart failure, and death, with AF recurrence rates of approximately 50% within 1 year following hospital discharge. In general ICU patients, incidence of new-onset AF was more than 11% with a high impact on morbidity and mortality, particularly associated with the presence of ARF.
- Variables that have been commonly linked to an increased risk for in-hospital mortality in mechanically ventilated patients include age, comorbidities, SAPS III, severe ARDS, deep sedation, duration of MV, and ICU complications. However, there is a wide variation in the prognostic variables between studies, which may be related to differences in the characteristics of patient cohorts, clinical variables recorded, and the geographical setting of different studies.
- Patients in ICU are usually at high risk of mortality not only from their critical illness but also from secondary complication such as nosocomial infection. Nosocomial pneumonia, a common ICU infection, affects 27% of all critically ill patients, where 86% of it is associated with mechanical ventilation. The mortality rate for VAP (hospital-acquired/nosocomial pneumonia hat develops more than 48–72 h after endotracheal intubation) ranges between 27% to 76%. Pseudomonas or Acinetobacter pneumonia is associated with higher mortality rates than those associated with other organisms.
- Delirium is a multifactorial entity, and its understanding continues to evolve. Delirium has been associated with increased morbidity, mortality, length of stay, and cost for hospitalized patients, especially for patients in the ICU. Recent literature on delirium focuses on specific pharmacologic risk factors and pharmacologic interventions to minimize course and severity of delirium. While medication management clearly plays a role in delirium management, there are a variety of nonpharmacologic interventions, pharmacologic minimization strategies, and protocols that have been recently described.
- There has been an increase in the number of patients undergoing open heart operation with the prolongation of life expectancy and medical advances. It has been reported that approximately 19%–45% of the cases may go through prolonged intensive care after open heart operation. In some studies, advanced age, female gender, reduced left ventricular function, arrhythmia, inotropic agent support and IABP requirements have been identified as risk factors for prolonged intensive care. Cardiac arrest following neurosurgery (craniotomy and spine surgery) is a devastating complication associated with significant postoperative morbidity and mortality [9-18].

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Exhibit 1. Definition of Potential errors in ICU [22]	
Medical error	The failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim.
Medication error	Any error in the medication process, whether there are adverse consequences or not.
ADE	Any injury related to the use of a drug. Not all adverse drug events are caused by medical error, nor do all medication errors result in an adverse drug event.
Preventable adverse events	Harm that could be avoided through reasonable planning or proper execution of an action.
Near miss	The occurrence of an error that did not result in harm.
Slip	A failure to execute an action due to a routine behavior being misdirected.
Lapse	A failure to execute an action due to lapse in memory and a routine behavior being omitted.
Mistake	A knowledge-based error due to an incorrect thought process or analysis.
Error of omission	Failure to perform an appropriate action.
Error of commission	Performing an inappropriate action.

2.3. Medication Errors in ICU

Medication errors are the most common type of medical error critical care patients experience. In the ICUs, on average, patients exposed to 1.7 errors per day and medication errors account for nearly 80% of serious medical errors. Patients in the ICUs receive more drugs than patients in the other wards. Critically ill patients are prescribed twice as many medications as patients outside of the ICU and nearly all will suffer a potentially life-threatening error at some point during their stay. They are vulnerable to ADEs because of changing organ function leading to alterations in the pharmacokinetics of drugs, complex drug regimens, and fast-paced decision-making. Also, the severity, length of stay, and costs associated with ADEs are greater in the ICU compared to general care units. Because of drowsiness or unconsciousness, ICU patients are not able to monitor and report the ADEs: thus, medication errors occur more often and have serious consequences. Intensities of medication errors are minor, severe, and life-threatening leading to death. Medication errors lead to an increase in the duration of hospitalization and disability and death in up to 6.5% of hospital admissions. Critical care medication errors occur most frequently in the administration phase. Administration errors include errors associated with infusion rates, incorrect or omitted doses, administration time, and physicochemical incompatibility of parenterally administered products. Most medications in the ICU are administered as weight-based infusions. These infusions require mathematical calculations and frequently are based on estimated weights increasing the risk of error. Potassium chloride, heparin, magnesium sulphate, vasoactive drugs, sedatives, and analgesics as the medications with the greatest risk of error in ICU. Antibiotics frequently are empirically prescribed in the ICU and errors have potential implications both for individual patients and populations. Cardiovascular drugs, antibiotics, sedatives/analgesics, and electrolytes were the drug categories most associated with errors. Patients are prescribed these medications in an environment that is stressful, complex, changing, under the stewardship of multiple providers, and frequently managing patients in crisis. Moreover, they are reliant on sophisticated technologies and equipment to deliver essential care and yet relatively little is known about medical equipment failures and the associated safety risks. Critical care pharmacist group consensus on the most important medication error reduction resources was established. Pharmacists working on high-resourced units made more clinically significant medicines optimizations [9], [19-23].

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Exhibit 2. Risk factors for medication errors in the intensive care unit [22]

Factors	Specific risk factors
Patient	**Severity of illness** Strongest predictor of ADE ICU patients more likely to experience ADE than patients in other units **Extreme of ages** Increased susceptibility to ADEs **Prolonged hospitalization** Increased exposure and susceptibility to ADEs **Sedation** Patients unable to participate in care and defend themselves against errors
Medications	**Types of medications** Frequent use of boluses and infusions Weight-based infusions derived from estimated weights or unreliable determinations Mathematical calculations required for medication dosages Programming of infusion pumps **Number of medications** Twice as many medications prescribed as for patients in other units Increased probability of medication error and medication interactions **Number of interventions** Increased risk of complications
ICU environment	**Complex environment** Difficult working conditions make errors more probable High stress High turnover of patients and providers **Emergency admissions** Risk of an adverse event increases by approximately 6% per day **Multiple care providers** Challenges the integration of different care plans

2.4. Working with Patients and Their Families

Having a loved one in an ICU can impair family integrity, making some changes in family roles and responsibilities. Four themes emerged as important to families: information, clinician skills, ICU environment, and discharge from the ICU. Relatives often lack important information about intensive care unit patients. High-quality information is crucial to help relatives overcome the often-considerable situational stress and to acquire the ability to participate in the decision-making process, most notably regarding the appropriate level of care. Fear of death or permanent disability, uncertainty about the patient's condition and prognosis, emotional conflicts, financial concerns, role changes, and unfamiliarity of the intensive care environment, especially during the first 72 h after ICU admission, can trigger feelings of shock, anger, guilt, denial, despair, and depression within the family. 50% of U.S. hospital deaths occur during or after a stay in an ICU, and nearly 70% of ICU deaths involve an active decision to limit treatment. Because most ICU patients are not able to make decisions for themselves, family members must make these difficult decisions on behalf of their loved ones. When doing so, they may worry that their loved one has suffered or that they have given up too soon, and they frequently harbor lingering feelings of doubt, regret, and guilt. During this vulnerable time family members rely on healthcare professionals to guide them through the decision-making process. Patients and their families are being encouraged to participate in the patient's care. Communication with patients and their families in the ICU will continue to increase as families are being engaged in activities such as ICU team rounds. Families participating in patient care rounds for pediatric patients frequently initiated discussions of medications. Also, family participation in delirium prevention to avoid pharmacologic treatment is undergoing current consideration. Enhancing patient and family communication will result in greater satisfaction with care and a mitigation of ADR frequency and severity [1], [24-27].

2.5. ICU Pharmacy Service Description

Critical care pharmacy activities are associated with perceptions of beneficial clinical and financial outcomes. Fundamental services are viewed more favorably than desirable or optimal services, possibly because they occurred more frequently or were required for safe patient care.

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Substantial inefficiencies may occur if pharmacy services disappeared. Considerable support existed for funding and reimbursement of critical care pharmacy services. The self-description of pharmacy practice in the ICU is variable and poorly defined, with clinicians often describing their practice as being dependent on specific patient requirements. Clinical coverage models, patient load, and pharmacist training levels also differ. Documentation of drug therapy decisions largely relies on physicians' progress notes, and the majority of pharmacist documentation occurs outside the legal record. However, clinical pharmacists are commonly expected to document their interventions, and doing so has been shown to have benefits in terms of cost avoidance. Work, research, and programming to decrease barriers to pharmacist documentation are ongoing. However, the critical care pharmacist should be responsible for comprehensive medication management that includes:

- Participation in interprofessional rounding, patient care meetings, and code arrests.
- Performance of patient admission medication histories, medication reconciliation, and patient profile reviews. This proposal will allow us to move from 45% to 100% coverage of this key metric in surgical ICU patients.
- Involvement in transfer/discharge medication consultation. The critical care pharmacist will focus on moving to oral meds from IV and on reducing medications that result in longer term ICU stays, such as sedatives and pain medications, to minimize ICU length of stay.
- Involvement in medication use review (as appropriate).
- Service as a mentor/educator to trainees (pharmacy, nursing, and medicine).
- Support of quality improvement and research initiatives.
- Service as an educator and medication information resource that is easily accessible to ICU clinicians.
- Performance of medication order review for cost effectiveness and appropriateness.
- Implementation and demonstration of cost-savings initiatives related to medications.
- Service as a leader for critical care pharmacy services [28-30].

3. ICU Medication management

In addition to processing medication orders and coordinating the arrival of medications, pharmacists can also assist with therapeutic drug monitoring (vancomycin, aminoglycosides, and warfarin), medication dosing, renal dosing, and responding to medical emergencies (stroke, code blue, therapeutic hypothermia, rapid sequence intubation, etc).

3.1. Medication labeling

Medication vials, liquid medication cups, intravenous (IV) medication bags, and packaging that have similar labeling font, font size, and color scheme trigger misperception and mix-ups at every stage of the medication use process. These look-alike medications contribute to medication errors and are of utmost concern at the time of dispensing and administration. Containers within or across a product line should not be similar in appearance. Different strengths and product or vial sizes should be distinguishable by size, color, shape, or some other mechanism [31].

3.2. Route-specific problems related to drug formulation design

Absorption is another commonly cited issue with enteral administration of a medication in critical care. Medications administered via a naso-jejunal or jejunostomy tube bypass the duodenum, the principle absorption site for most medications, leading to variable effects on absorption and first-pass metabolism. The absorption of some medications can be affected by concomitant administration with enteral nutrition (eg, warfarin, phenytoin, levothyroxine), and so special care must be taken to appropriately interrupt enteral nutrition around the timing of drug administration. Even if a medication is able to be administered to the stomach or duodenum, small bowel resection, gastroparesis, ileus, and decreased splanchnic flow all have the potential to affect absorption and efficacy. However, clinicians may also overestimate the absorptive problem and decline to use an enteral formulation in a patient who could actually benefit from it. Additional research into how these problems affect medication absorption in critically ill patients would help guide decision-making in this population [32-34].

A. **Enteral route of administration:** Access issues related to enterally administered medications are encountered frequently in critical care. Medications that are only available in an enteral formulation pose a problem for patients with a strict nothing by mouth (NPO) order. Carbidopa/levodopa, which is only available as an enteral formulation, is one example. Related to this challenge is the problem of medication administration via small-bore feeding tubes. Because of the small lumen, these tubes are prone to becoming clogged and, as many are placed in the duodenum or jejunum, they are also difficult to replace. For these reasons, clinicians often decide against administering crushed medications via small bore feeding tubes. Some medications are available as manufactured suspensions for enteral administration, but most are not. Pharmacies can prepare suspensions of some medications when they are not commercially available, but not all drugs can be adapted to a suspension, and stability information is often limited. Another issue related to enteral access is immediate-release (IR) versus extended-release (ER) formulations of medications. These different formulations are often confusing for clinicians, and the differences between the formulations vary from drug to drug. For a patient who receives medications via a nasogastric tube, it would be appropriate to crush a metoprolol tartrate tablet (the IR formulation), but crushing a metoprolol succinate tablet (the ER formulation) could lead to a more rapidly profound, yet un-sustained, effect than is desired. The problem of tablet crushing is not unique to drugs with an

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IR and ER formulation. A number of medications should not be crushed for a variety of reasons, ranging from onset of effect to cytotoxic potential [35,36].

B. Subcutaneous (SC) route of administration: Accuracy of administration, specifically the depth of injection, is a concern with medications administered subcutaneously. Variable absorption is also a concern with subcutaneously-administered medications in critically ill patients. It has been suggested that hemodynamic instability, vasoactive medications, and fluid shifts may alter the absorption of medications such as subcutaneous insulin and heparin, but the data are conflicting. Additionally, the prescribing information would include details about pharmacokinetics and pharmacodynamics specifically in critically ill patients [37,38].

C. Intramuscular (IM) route of administration: Intramuscular medications are subject to the same problem of administration accuracy as subcutaneous medications. Inadvertent administration of these medications to tissue other than muscle could lead to differences in absorption and effect. Additionally, many critically ill patients experience muscle wasting, which further complicates this route of administration. Intramuscular administration of medications poses a risk of hematoma in any patient. In the critically ill population, where many patients are anticoagulated or coagulopathic, the concern for hematoma is even greater. Although data suggest intramuscular injection may be safe in anticoagulated patients, it is generally avoided whenever possible. “IM better than SC” involves epinephrine. “SC better than IM” involves interferon-beta-1a, methotrexate, human chorionic gonadotropin, hepatitis B immunoglobulin, hydrocortisone, and morphine. [39,40].

D. Intravenous (IV) route of administration: Intravenous fluid therapy is one of the most common interventions in acutely ill patients. Each day, over 20% of patients in intensive care units (ICU) receive intravenous fluid resuscitation, and more than 30% receive fluid resuscitation during their first day in the ICU. Virtually all hospitalized patients receive intravenous fluid to maintain hydration and as diluents for drug administration. Because medications delivered via the IV route pharmacokinetically bypass an absorption phase, they cause systemic effects within seconds of administration, making this route especially important for critically ill patients. These same characteristics also leave patients vulnerable to harm from IV-associated medication errors. Incorrect dosing and rates, including unintentional bolus administration, are common errors encountered with IV medication administration. IV medications that require further dilution before safe administration should never be packaged in a manner that suggests or could allow for direct administration (eg, prefilled syringes). Additionally, medications that require mixing before use or administration should be avoided, and when absolutely necessary, should be labeled as such. A number of medications in the ICU are provided via continuous infusion. As a result, large fluid volumes might be administered to patients who are already volume overloaded or have one or more electrolyte abnormality. The requirement for a carrier fluid may complicate this challenge even further in critically ill patients. The use of a high carrier rate allows the drug to reach the patient quickly and minimizes the time to a systemic effect after a change in rate, especially with vasoactive medications. However, use of a high carrier rate increases the risk of infusing an unintentional medication bolus when changes are made to either the carrier rate or drug infusion rate. Ideally the medications delivered to ICU patients should be easily titratable, meaning they have a rapid onset; have a short half-life; are supplied in standard-concentration, inexpensive, ready-to-use bags; and are not extremely concentrated (requiring a carrier fluid) or diluted (minimizing the volume required to deliver the drug). Smart infusion pumps with integrated decision support represent a targeted approach to minimize IV-associated medication errors. However, the presence of smart infusion pumps alone does not decrease serious medication errors. Smart infusion pumps were designed to promote safety and simplify medication administration. These pumps can store large drug libraries with information about weight-based dosing, standard infusion rates, and maximum infusion rates. They can also enforce these parameters to prevent inappropriate infusion rates and errors. Kopp et al. reported lack of drug knowledge was the cause of 10% of errors and slips and memory lapses were responsible for 40% of errors at the administration stage. Some pumps can be accessed wirelessly, allowing an entire fleet of pumps to be updated simultaneously. “SC better than IV” involves trastuzumab, rituximab, antitumor necrosis factor medications, bortezomib, amifostine, recombinant human granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor, recombinant interleukin-2, immunoglobulin, epoetin alfa, heparin, and opioids. “IV better than SC” involves ketamine, vitamin K1, and abatacept. With respect to insulin and ketamine, whether IV has advantages over SC is determined by specific clinical circumstances. “IM better than IV” involves epinephrine, hepatitis B immunoglobulin, peg-aspargase, and some antibiotics. “IV better than IM” involves ketamine, morphine, and antivenom [31], [40-44].

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Exhibit 3. Specific Error Problem Areas of IV Administration

- Pumps programmed incorrectly
- Drug injected too fast
- Drug injected through wrong type of access, oral medication injected
- Similar labeling
- Stressful situation
- Wrong drug taken from drug dispensing machine
- Wrong amount of fluid aspirated from drug vial containing more drug than ordered
- Obtained drug from drug dispensing machine in advance, then order was changed but nurse not aware
- Mixed up hanging IV bags changing dose rate on wrong drug

In the US, 60% of serious and life-threatening medication errors that occur in patients involved IV drugs; in the UK approximately 56% of the errors administered with IV drugs. Although only a few medications are administered IV in the hospital setting, the IV drugs account for the majority of medication errors. A high incidence of medication errors related to IV therapy was found in Germany, where 23% of the total medication errors occur during IV administration. However, there are also a lot of possible direct and negative side effects such as pulmonary complications, thrombophlebitis, and infection with the possibility of sepsis. There have been reports of death and harm following medication errors such as wrong dose drug diluents and cross contamination errors. Thus, the primary focus should be to identify IV therapy associated drug-related problems (DRPs). Nurses often cited lack of experience with the patient population, drug dosage, administration route (i.e. intrathecal), or a stressful and busy environment for the occurrence of error. Safety, efficacy, patient preference, and pharmacoeconomics are four principles governing the choice of injection route. Safety and efficacy must be the preferred principles to be considered (eg, epinephrine should be given intramuscularly during an episode of systemic anaphylaxis). If the safety and efficacy of two injection routes are equivalent, clinicians should consider more about patient preference and pharmacoeconomics because patient preference will ensure optimal treatment adherence and ultimately improve patient experience or satisfaction, while pharmacoeconomic concern will help alleviate nurse shortages and reduce overall health care costs. Besides the principles, the following detailed factors might affect the decision: patient characteristics-related factors (body mass index, age, sex, medical status [eg, renal impairment, comorbidities], personal attitudes toward safety and convenience, past experience, perception of current disease status, health literacy, and socioeconomic status), medication administration-related factors (anatomical site of injection, dose, frequency, formulation characteristics, administration time, indication, flexibility in the route of administration), and health care staff/institution-related factors (knowledge, human resources) [40,41], [45].

E. **Transdermal route of administration**: A number of safety concerns surround use of the transdermal route in critically ill patients. Transdermal drug delivery is erratic in critically ill patients. Because perfusion to epidermal and subcutaneous tissue is often lower than normal, it can cause unpredictable and often less-than-optimal absorption. On the other hand, elevated core temperature and febrile states, which are not uncommon in critically ill patients, increase absorption and the risk of excessive drug release. Many patches include aluminum backing, making them unsafe for wear in a magnetic resonance imaging machine. It is for these reasons that medication delivery via the transdermal route should largely be avoided in critically ill patients. If patients are admitted to the ICU wearing a transdermal medication patch, it should be discontinued as soon as possible, and other more reliable routes should be utilized. The transdermal route should not be a target for novel drug delivery in the critically ill patient population [46]

F. **Epidural route of administration:** Epidural analgesia (EA) is one of the most widely utilized neural deafferentation techniques. It is used for analgesia during the perioperative period, but also for obstetrics labor and trauma as well as in the treatment of acute, chronic and cancer-related pain. Its objective is not only to block noxious afferent stimuli, but also to induce bilateral selective thoracic sympathetic blockade. In addition to analgesia itself, the modulatory effects of thoracic EA could improve organ perfusion with reduced complications in the perioperative period, thus possibly decreasing postoperative complications, shortening hospital stay and improving survival. Local anesthetics (eg, bupivacaine, ropivacaine) must be used with caution in the ICU. Anesthesiologists must first verify that epidural catheters are indeed in the epidural space. Even when infused appropriately, local anesthetics administered via the epidural route can cause systemic vasodilation and hypotension. In critically ill patients, the risks and benefits should be weighed carefully. It may be most appropriate to use separate infusions for local

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anesthetics and systemic opioids because the clinician can titrate each individually to minimize adverse effects. However, inadvertent systemic administration of local anesthetics can cause significant cardiotoxicity that could lead to arrhythmias, disturbances in contractility, or even cardiac arrest. A number of safety measures must be in place to prevent such mistakes. If not available commercially, infusions should be compounded in the pharmacy and not in the operating room or ICU. Medication bags and syringes should be labeled clearly with information regarding the route of administration if other than IV (eg, wording such as "epidural use only"). Independent double-checks should be implemented at the bedside when epidural medications are initiated and when rates or doses are changed [47-49].

3.3. Parenteral nutrition support

Nearly 40% of adult critically ill patients have a high risk of malnutrition, which definitely increases the incidence of mortality and poor prognosis. As a therapy, nutrition supplements have become important and necessary. In general, the individual benefits and risks of parenteral nutrition (PN) and enteral nutrition (EN) have been elucidated gradually. Because of cheaper, safer, and more physiologic, EN remains the preferred choice. But EN alone usually is not able to meet the energy targets owing to gastrointestinal intolerance. Parenteral nutrition (PN) therapy is a complex and critical therapy that requires special clinical knowledge, skills, and practice experience to avoid errors in prescribing, compounding, and clinical management of patients. It involves the IV administration of nutritionally sufficient and balanced formulations to supply essential nutrients to patients who are unable to tolerate oral or enteral feeding due to dysfunctional or inaccessible gastrointestinal (GI) tract. Over the years, PN has become an important primary and adjunctive therapy in various clinical conditions and disease states for both the acutely ill hospitalized patients and in the long-term setting for selected patients in the home. The PN formulations are complex admixtures that consist of multiple components, including both macronutrients (amino acids, dextrose, and IVFEs) and micronutrients (electrolytes, vitamins, and trace elements). When all the daily nutritional requirements are exclusively supplied to the patient by PN formulations, the therapy is called total parenteral nutrition (TPN). The PN formulations must meet the nutritional requirements of the patient according to patient age, energy expenditure, and clinical status to ensure that the appropriate nutrients are provided to patient and to avoid under- or overnutrition. Although being lifesaving for many patients, PN therapy is a high-risk feeding modality that can be associated with some complications. An incompatible, unstable, or contaminated intravenous infusion may result in harm to patients, including serious morbidity and even mortality. Therefore, PN formulations must be compounded under strict aseptic techniques according to validated pharmaceutical compounding procedures. Broyles et al reported the positive impact of pharmacists' interventions on improving fluid balance in fluid-restricted ICU patients receiving PN. The practice of permissive underfeeding in the medical or mixed medical-surgical ICU is supported by multiple small studies that suggest improved clinical outcomes compared with full feeding, potentially due to fewer complications from hyperglycemia, electrolyte imbalances, and feeding intolerances. Arabi et al found that permissive underfeeding was associated with lower (but non–statistically significant) 28-day mortality compared to target feeding [50-52].

4. Pharmacist on the Pediatric Intensive Care Practice

Pharmacists are considered an integral part of the multidisciplinary team in ICU patient care, although their level of involvement in the critical care practice is variable. Studies have shown that a pharmacist's involvement in critical care rounds is associated with fewer adverse effects and alone may be associated with lower mortality among ICU patients. The American Academy of Pediatrics in 2003 proposed that inclusion of a pharmacist in the critical care team can help decrease medication errors. With transitions occurring in the field of clinical pharmacy, it is important to define the role of the clinical pharmacist on the multidisciplinary team and to highlight the value of the position, which includes enhancing the safety and quality of patient care, in addition to financial savings. Clinical pharmacists have been a part of the PICU team at our institution since 2003, with evolution of their role and involvement over time. The pharmacists working in the PICU have either completed a pediatric pharmacy residency or departmental pediatric pharmacy training. The use of antibiotics in PICU is very high (ranging from 65% to more than 95%) due to several reasons including high incidence of community-acquired sepsis, healthcare-associated infections or as a postoperative prophylaxis. This high antibiotic use leads to several problems including development of antibiotic resistance, drug toxicity and drug interactions. Pharmacist-led ASP in PICU ensured 64% reduction in antibiotics use and 58% cost reduction both in terms of DOT and COT. Having a pharmacist on a rounding team in an ICU has been shown to reduce the incidence of ADEs by two thirds. Pharmacist-monitored TPN proved cost effective in comparison with the standardized solution without pharmacist monitoring. Thus, clinical pharmacists can not only improve drug safety, but also serve to lower costs, improve quality of pharmacotherapy, coordinate the relationship with other departments [53-55].

5. Interventions to reduce medication errors in NICU

Medication errors represent a significant but often preventable cause of morbidity and mortality in neonates. Neonates are more prone to medication errors at each

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stage of the medicine management process due to the increased need for calculations, dilutions, and manipulations of medications. Furthermore, many medications are used off-label in the neonatal setting, meaning that they are not specifically licensed for use in neonates and are therefore often only available in adult formulations and concentrations. As a result, prescribing and administration challenges often places neonates at risk of potentially fatal 10-fold or 100-fold dosing errors. There is also the associated challenge of limited dosing protocols and evidence-based information regarding the efficacy, safety, dosing, pharmacokinetic, and clinical use of medications in neonates. In addition, relative physiological immaturity means that neonates have less capacity in being able to buffer unintended consequences of medication errors. Such susceptibility towards medication errors in neonates, as previously described, is further emphasized by previous research that observed that medication errors with the potential to cause significant harm were three times more likely to occur in the NICU than in adult wards. Furthermore, an analysis of all medical errors occurring within the NICU identified that medication errors were the single largest contributor, nearly 50% of all errors. Given the complexity of medication use in neonates, the high frequency in which high-risk medications are used and the potential for serious adverse events of even minor medication errors, intervention strategies to increase medication safety in neonatal care should be regularly reviewed. The identification and evaluation of such interventions are of critical importance in assisting healthcare systems and providers in understanding, implementing and augmenting interventions to reduce neonatal medication errors. Several international organizations have encouraged the conduct of pharmaceutical clinical trials with newborns in an attempt to overcome a number of barriers that have been identified such as ethical issues involving this vulnerable population, low accrual rates because of the small size of this population, small volume of biological samples that can be obtained from neonates, changing pharmacokinetics and pharmacodynamics with the postnatal age, as well as financial considerations. The incidence of off-label and unlicensed medicines prescribed in NICU varies from 34% to 95.6% and from 5.7% to 34.6%, respectively. Furthermore, 44% to 100% of all neonates hospitalized at NICUs are administered at least one off-label or one unlicensed medicine. The lack of information about the safety and efficacy of drugs increases the risk of poor clinical outcomes, of ADRs and medication errors when off-label and unlicensed medicines are prescribed to neonates. The conversion of solid to liquid pharmaceutical forms represents about one-sixth of the unlicensed drugs administered in NICUs, and this practice occurs mostly with cardiovascular medicines because of the unavailability in the market of liquid formulations adequate for administration to the neonatal population, a reality observed in several countries. Drug shortages affected many agents used in NICUs, which can have quality and safety implications for patient care, especially in extremely low birth weight infants. Neonatologists must be aware of current shortages and implement mitigation strategies to optimize patient care. In the context of the continuous quest to improve the care of the neonates especially the critically ill premature infants, the extended role of pharmacists in the process of parenteral nutrition order writing and effective participation in decision-making especially in the neonatal population is increasingly important [56-61].

6. **Pharmacists in CCU**

The in-hospital mortality rate of acute myocardial infarction (AMI) has dramatically decreased due to the treatment at the coronary care unit (CCU), especially with the progress of arrhythmia therapy and reperfusion therapy. On the other hand, severe heart failure and multiple organ failure are increasing due to aging populations and multiple organ diseases. As a result, patients with AMI without complications are less likely to be admitted to the CCU, and cardiologists staying in the CCU have also decreased. The mortality rate is high when complications such as cardiogenic shock, cardiac rupture, and in-hospital cardiac arrest occur in AMI, therefore careful intensive care even in low-risk AMI is necessary. Therefore, for the critical care of cardiovascular diseases, it is necessary to convert from CCU to the cardiovascular intensive care unit. DRPs that were suspected to cause or contribute to a possibly fatal outcome were determined by clinical pharmacist service in patients hospitalized in a cardiology ward. Correction of these DRPs by physicians after pharmacist's advice caused a significant decrease in mortality as analyzed by PS matching. In patients with CVDs, the frequency of DRPs has been reported to be as high as 68%. Cardiovascular drugs, such as antithrombotic agents, anticoagulants, hemostatic agents, and cardiac glycoside, are commonly implicated in FADE due to suboptimal medication use in CVD. Nosocomial infections in patients in cardiology departments rely on factors such as old age, HF, invasive procedures, concomitant diseases, and inappropriate use of antimicrobial drugs. These infections ultimately increase the risk of death for these patients. The clinical pharmacists can play an important role by intervening and correcting DRPs at a hospital cardiology unit. It is likely that the clinical pharmacy intervention is best implemented in the cardiology ward if the clinical pharmacist discusses the DRPs face-to-face with the physicians. A pharmacist's clinical services in the CCU allowed for significant estimated reductions in total drug costs [62-64].

7. **Education and Training ICU Pharmacists**

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As healthcare system has begun to place more emphasis on the provision of direct patient care activities and adherence to clinical guidelines, the profession of pharmacy has adapted to provide services, and practitioners, that meet these demands. A rising proportion of end-of-life care takes place in the ICU. Nearly 30% of Medicare patients used the ICU in their last month of life, increased from 24% a decade ago. Training for ICU pharmacotherapy is usually not the focus of many undergraduate pharmacy curricula and ICU clinical rotations/clerkships are often viewed by students as 'difficult to pass' rotations. Therefore, students' interest in ICU as a practice area is not widespread, limiting the qualified recruitment pool when a position is secured. Fortunately, with dedicated courses in ICU pharmacotherapy appearing in the elective portion of some pharmacy curricula, the addition of board certification in Critical Care Pharmacy by the Board of Pharmacy Specialties in the U.S., more and more training programs and opportunities will be forthcoming to help close the qualified personnel shortage and needs gap. In Japan, initiation of the reimbursement from the government to monitor patients in ICU and the foundation of certified emergency medicine and critical care specialist resulted in the increased number of ICU pharmacists. Pharmacists keen on a career in critical care need to understand that this is a complicated area and that things do not always end well for patient. Ongoing professional development and collegial support is even encouraged internationally. This may include undertaking more research or developing better ways of working with team and developing treatment plans, prescribing medications and leading a pain, agitation and delirium service, ensuring patients received the correct sedatives, opioid analgesics and antipsychotics. The interventions listed above are only a few of many responsibilities of a critical care pharmacist. These pharmacists may also work up patients, and round with the multidisciplinary team. In addition, critical care pharmacists communicate current drug shortages and substitutions to the team on their unit. Overall, working in the intensive care unit appears to provide critical care pharmacists the opportunity to use their clinical knowledge to enhance patient care as a valued member of the interprofessional team. Quality of palliative care training in critical care medicine programs and the use of bedside tools were independently associated with reduced ICU use at the end of life. Hospital and medical education leaders have worked to address concerns about the increasing amount and significant variation in end-of-life ICU use. Individual institutions have developed and evaluated a variety of interventions that include a more proactive approach to the provision of palliative care, educational initiatives targeting ICU staff, and bedside tools for communication and symptom management. Innovations in workforce training and technology specific to the ICU may be useful in addressing the shortage of intensivist physicians, yielding benefits to patients and payers [65-71].

8. Epilogue

Even as the scope of pharmacy practice expands, impediments to optimal delivery of pharmaceutical care remain. These include shortages of pharmacists, increasing complexity of medication regimens, and increasing acuity of patients and the associated workload. Pharmacy technicians are well positioned to augment direct patient care services because of their knowledge of the medication distribution system in their respective health care centers. Pharmacy technicians with additional training and support in the clinical area increase the work efficiency of pharmacists in the ICU, thereby making it possible to extend pharmacy services in direct patient care to a larger number of patients during the pharmacists' work day. Recent literature indicates that more active participation of pharmacists in the pharmacological treatment of critically ill patients is desirable. Moreover, according to the literature, pharmacists' activities in the ICU should not be limited to providing advice to the staff but should also include active participation in decision-making regarding the maintenance of pharmacological treatment.

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