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Review Article

Clinical Impact of Pharmacist Presence in ICU Medical Team on Mortality Rate

Behzad Nili-Ahmadabadi[1], Mauro Luisetto[2], Hossein Nili-Ahmadabadi[3], Heba Nasser[4], Ghulam Rasoul Mashori[5], Mohammad Nili-Ahmadabadi[6]

1. Behzad Nili-Ahmadabadi, *PharmD*, Nano Drug Delivery (*a product development firm*), Chapel Hill NC, USA, behznili@nanodd.com, +1 (919) 617-NANO
2. Mauro Luisetto, *PharmD/PhD*, Hospital Pharmacist, Pharmacologist, European Specialist in Laboratory Medicine, maurolu65@gmail.com, Via Stradella, 26, Piacenza, ER, Italy
3. Hossein Nili-Ahmadabadi, *MD*, Gastroenterologist, Assistant Professor, Yasuj University of Medical Sci., Faculty of Medicine, Yasuj, Iran
4. Heba Nasser, *PharmD/PhD*, Microbiology & Immunology, Faculty Member at Heliopolis University, nassihebat@gmail.com, heba.nasser@hu.edu.eg
5. Ghulam Rasoul Mashori, *PhD in Clinical Pharmacology*, Full Professor & Director, Peoples University of Medical & Health Sciences for Women, Islamabad, Pakistan, mashori.286@gmail.com
6. Mohammad Nili-Ahmadabadi, Intern at Mindcracy & Nano Drug Delivery, WhatsApp: +98-939-9908601, mohammad_nili@yahoo.com

Abstract. Studies indicate alarmingly high number of death, by medical errors, especially in the US [23]. This review article aims to use studies around the world in order to examine the role clinical pharmacists can play, as proactive health team members in an Intensive Care Unit (ICU), in preventing health risks, particularly those ending in life losses. It also examines clinical pharmacist interventionist role by focusing on optimizing the quality of pharmacotherapy and patient safety. The goal of creating an advanced medical treatment integrated team is already a trend in western countries and pharmacist roles in clinical decisions is expanding, in a very specialized fashion. This therefore although puts pharmacists under a greater burden of responsibility than ever before, but it is well justified, since it prevents a considerable number of health risks, by achieving a relevant reduction in mortality rates, and at the same time cuts down unnecessary expenses. According to ASHP Guidelines [20]: ”pharmacist should function as a liaison between pharmacy and other clinical staff in different departments such as anesthesiology, surgery and antibiotic use. ”The paper examines the role of the clinical pharmacists as experts of excellence in drug use and its impact in ICU that will eventually reflect in not only reducing mortality rates and improving clinical outcomes but also lowering considerably the costs of drugs, medical devices, consequential costs caused by medical errors, number of recovery days in the hospital and more. This can be obtained by using clinical pharmacist to guard, oversee, both adjust/correct therapies and take a task of using a management tool, in every day ICU’s activities. Based on biomedical literature, we can observe a general improvement in different clinical outcomes and as a result a noticeable reduction in mortality rates, when a clinical pharmacist is a permanent member of the medical team. In brief words, we are here to help not only in increasing life quality of the patients in need of a functional healthcare system, but also in removing unnecessary cost burdens, which eventually prevents economy turmoil.

Keywords: Intensive Care Unit, ICU, Clinical Outcomes, Mortality Rate, Costs, Cost Containment, Pharmaceutical Care, Anesthesiology, Gastroenterology, Hematology, Medical Imaging, Health Care Ethics, Evidence-Based Medicine, Professional Development, Pharmacy Service, Communication Barriers, eLearning, Social Networking

Introduction

What we are witnessing is that citizens around the world are massively distancing themselves from modern medicine and seeking traditional herbal or ancient practices. However, we clinicians not only do not admit that there are very good reasons behind this phenomenon but also, instead of looking to fix the problems, subconsciously react and immediately point our finger towards traditional medicine, as non-scientific and baseless.

I think it's long overdue that we instead of invalidating traditional medicine, seriously look within our own domain and analyze what part of modern medicine is either dysfunctional or going in the wrong direction.

While no one doubts that there are many unqualified traditional natural supplement manufacturers, while no one denies that there are many claims in herbal medicine that are not based on solid clinical research evidence and some are founded on even false claims or often speculations, but if the traditional medicine is not reliable it doesn't mean the modern medicine is working or there is no room for criticism on very commonly accepted undisputable medical principles or widely accepted medications. We pharmacists and physicians are so firmly certain that basing on anything outside our text books, is dangerous, since only modern medicine is pure science. Sometimes, we take this to an undisputable level, claiming that there is no way to save peoples' lives other than what we practice in our clinics and hospitals.

However, the truth is that modern medicine not that failed in curing disorders or diseases, it has even created many ***modern diseases***, commonly known as ***so-called side effects***. Besides that there are even so many incidents that often take peoples' lives, for no reason whatsoever. If one looks even into his close circle, can find at least 4-5 cases who themselves were victims of such medical negligence. There are even incidents when hospitals caused health damage or killed patients, instead of holding themselves accountable and fixing the damage, if possible, they'll try to cover them up, shamelessly ignore and walk away or admit the guilt.

We cannot murder defenseless people who trusted us and name it error. **There is no room for error or even mistake when we are dealing with life and death.**

We cannot walk away from our responsibilities or stifle controversy, we must rather welcome it. Unless we prosecute the killer, this killing will not stop. It's about time to be candid about our errors, for as a wise man once said: "*an error does not become a mistake until you refuse to correct it.*

Instead of taking advantage of people's medical science ignorance, downgrading patients or squashing the truth, we have to accept full responsibility for our errors, and we must expect the public to point them out, when we miss them. After all, we are paid to cure people not to kill. Yes, I'm using the term killing, because that's what it is [21, 23].

But the truth is far from this utopia. As the Athenian lawmaker Solon: "*decreed it a crime for any citizen to shrink from controversy*", we shall welcome, if not for public health, at least for the sake of holding our team responsible and accountable. John F. Kennedy once said: "*without debate, without criticism, no administration and no country can succeed and no republic can survive*" and I'd say: "*without debate, without criticism, no side effect can be detected and no drug, sorry poison, can be banned*".

No one can doubt today, that most of these strict regulations, implemented by health authorities, such as FDA, were not initiated by universities, NIH, FDA, department of health or pharmaceutical laboratories. They came into existence by peoples' complaints, by these so called

"*conspiracy activists*" or law firms; that is a fact. You don't expect a pharmaceutical manufacturer volunteers to expose the side effects of its own products or a hospital admits an error that took someone' life on its own, do you? The truth is modern medicine has failed, not only in medical errors, but also in many other aspects of the science itself, from:

- how these clinical trials are run, by people whose driving force is not necessarily saving peoples' lives, to
- how the clinical trials are run, by what kind of methods and protocols and how the conclusions are drawn?" Can we really deduce that inflammation is causing cancer by simply putting a group of patients on NSAIDs? Inflammation is a normal physiological response that causes injured tissue to heal. Inflammation is the immune system's response to infection and injury. An inflammatory process starts when a group of hormones are released by the damaged tissue. In response, white blood cells make substances that cause cells to divide and grow to rebuild tissue to help repair the injury, where NSAIDs block the biosynthesis of all Protaglandines and Protacyclines, all over the body, so isn't safer to run a separate study for every single of these 30+ different types of Protaglandines and Protacyclines, and not systemically, but rather where the so-called inflammation is happening? Can we really establish a "*scientific conclusion*" by a term we have created, and named it "*inflammation*" to push nonsteroidal anti-inflammatory drugs (NSAIDs)? Is it really true that all Protaglandines and Protacyclines cause cancer? Here is a statement from National Cancer Inst.: "*Many studies have investigated whether anti-inflammatory medications, such as aspirin or non-steroidal anti-inflammatory drugs, reduce the risk of cancer. However, a clear answer is not yet available. For more information, see no easy answers about whether aspirin lowers cancer risk* [24-26]". Is it really true that every time the bad guy is the natural biochemical/physiological mechanisms of our body system? Are we here to believe that blocking systemically several mediators of many processes of immune system reduces risk of cancer? Where did our logics go? You mean crippling immune system helps us not getting cancer? Immune system is supposedly the very intelligent targeting system to eat cancer even when raises its head. Immune system is the only force that kills cancer right after it was born. In fact, some novel cancer treatments, work through enabling immune system that was put to sleep by no one else but NSAIDs and Glucocorticoids, to now recognize and see cancerous cells and eventually eat them up. Or is this another desperate effort to shift the blame away from the real causes of cancer, namely the chemicals we instill into our own body every day, maybe NSAIDs [30] that we try to make them look like angles or maybe preservatives [37-55] which like their sister NSAIDs dysfunction the immune system? In fact, it is well known that NSAIDs even inhibit antibody production in human cells, besides that they can cause a host of other diseases, such liver damage, renal failure, aseptic meningitis and can interfere with bone fracture healing [30-36]. Do you really think it is wise to block 30+ very important hormones that control every single physiological process? NSAIDs are the most widely used xeno-agents in the world. Obviously, not everybody is following the status quo or turning a blind eye. In fact, thanks to many scientists with critical and independent thinker mindset, this group of drugs (NSAIDs) has recently come under scrutiny because of recent focus in the literature on the various adverse effects that can occur when applying NSAIDs. **But my issue** is not just NSAIDs; it **is the modality and methodology used in clinical research itself**, although the use of NSAIDs is a big problem, which shall not be ignored at all. You use them when you catch cold, when pull your teeth, you have back pain, cannot walk, have headache, sneeze, caught, fever, painful menstruation or dysmenorrhea, you name it. In many of these cases it's misusing NSAIDs everywhere, when patient doesn't need anything." to

- ”even, how we made vocabularies for diseases, for instance, whether anxiety or being a little down (as we give a scary name like depression to it) is really a pathological state to begin with?
    - And do we really have to put these defenseless children on psychotropic drugs for unjustified and ridiculous reasons, messing up their entire CNS hormonal balance, which works similarly to the wiring system of an electronic chip?”
    - Is there anyone that can testify “inflammation” is a disease or rather a defense mechanism, by which, the super intelligent organism puts a blockade, a concrete wall, on poisons or microbes so they cannot access the blood stream? So why are we using the scary term “flame” for it?
    - Is there anyone that can testify “anxiety” is a disorder or disease or rather a sophisticated technology of the mind to alert you from outside possible dangers? Without anxiety, our response to stressful situations, an Iraqi or Syrian mother and dad who have only 2-3 hours, until they have to witness the death of their entire family by some military-grade mercenaries, an icy road at night, an impending exam, a lecture at the university or symposium, a big dinner party at the white house we have to attend, might be inadequate and lead to disastrous consequences. Anxiety is a way our body is telling us we have to do something. It’s meant to make sure we are extra vigilant and ensure that we will be well equipped to successfully, escape from danger or accomplish our tasks and goals. The real individual who needs anxiolytic drugs is some psycho, *sorry* psychologist who is so **anxious to drug** and **mess up** the **CNS hormonal balance** of your **5-year old child**. But sadly, the current medical community is in complete denial. It says: “*anxiety **disorders** are actually quite common and it has been estimated that over **one quarter of the general population** will experience a real anxiety disorder during their lifetime. Commonly anxiety disorders co-exist with other medical conditions, especially **depression**.”* [4] Is there anyone else noticing an agenda to drug the society, from their early childhood? I know many would say, but this is exaggerated. No it’s not. The problem you overlook or turn a blind eye on it does not go away; it keeps bouncing into your face.
    - Is there anyone that can testify “depression” is a disorder or disease, a pathological state or is rather a physiological state in which we are being prepared to accumulate our talents to analyze our mistakes, enabling us to come up new plans with a more efficient strategy or with minimal resources with maximum efficiency?
    - And the same goes on with a little trouble with breathing, when often clinicians label it as potential threats of asthma or epilepsy
- “and in what extent we are overprescribing, overdosing or mis-prescribing these very unfriendly molecules to biological systems” and “who is writing these leaflets, training us, physicians and pharmacists and what are the incentives, behind all these trainings” to
- “how these pharmaceutical molecules have been evolved and how we pharmaceutical chemists, ruthlessly, add extremely toxic moieties, from dangerous polycyclic aromatic rings to radical generating groups, such as Hydrazines (R_1-NH-NH-R_2) [1, 2], and Nitro (NO_2-) [3], to alkylating agents (-C-X), such as trifluoromethyl (CF_3-), dichloroacetyl (CCl_2-CO-) and many others, which obviously readily bond to most nucleophilic moieties such as amino (:N-), thio (:SH), hydroxy (-Ö-H) groups, or aromatic clouds, which exist in every biomolecule, from DNA to functional proteins to enzymes of the organism, unleashing weird **merciless diseases**

(which we give them an innocent name, like: **adverse reactions** or **side effects**) from tissue damages to DNA cleavage and eventually cancer". It reminds me of the term "*collateral damage*". In fact, "*effetti collaterali*" in Italian stands for "*side effects".*

So, this building, which we call it medicine, from its science, to its research labs, all the way to operation rooms, needs not a retouch or paint; this building is rotten from its very foundations.

Now this review article aims not to emphasize on those 99% of the above failures, but rather to make a desperate effort to reduce mortality rates of poor citizens due to unjustified negligence, which we call them "*collateral damage*", sorry "*errors*" and in this case, we restricted ourselves specifically to at least ICU. We are here to see if there is a difference, if some clinicians can take a task of guarding other ones in their team from making fatal mistakes in the process of treatment within the ICU. Did you know that in US alone, the number of death caused by medical errors in July 2015 exceeded 200,000 people in a year [27] and is rampantly increasing? Researchers from Johns Hopkins University School of Medicine, in May 2016 found that deaths from medical errors may be responsible for more than a quarter of a million deaths annually [23]. Data in the studies was taken from a combination of Medicare and 13 other hospitals, which researchers examined to determine that the estimated annual rate of deaths from medical errors is 251,454 in the US [21, 22]. That means it's not getting any better, it's actually getting worse. What did us physicians, nurses and pharmacists do to stop this killing? Well, I'd not call this "*error*", or even genocide, I'd call it a disaster, since it's more similar to a high magnitude earthquake, and it's happening every single year! Now this is not cancer that you'd say you cannot prevent it.

This article reviews studies and conducts a conclusive assessment on the impact and effectiveness of a clinical pharmacist, as a proactive health team member in an Intensive Care Unit (ICU) in centrally mortality but also in morbidity rates. It also evaluates the clinical pharmacist interventionist role with a focus on optimizing the quality of pharmacotherapy and patient safety. The goal is to create an advanced medical treatment integrated team. Now the good news is in western countries, such as USA, Europe, Canada, etc, this trend of using specialized clinicians trained for specific roles has already begun; therefore pharmacist's role in clinical decisions is increasing. Pharmacists today are not only under a greater burden of responsibility than ever before but also they are going through specialized training, as are taking canalized and differentiated roles.

Following, we list examples of proposed roles and activities that a pharmacist can play in pharmaceutical care, in this case, in ICU:

- Medication histories verification
- Allergy detection verification
- Pharmaceutical medication history review
- Antimicrobial stewardship
- Verifying whether there is a necessity in continuing or stopping the medication during an acute/severe medical condition
- Participate in discussions between physicians, patients and family members in order to help making the best decision regarding treatment options
- Drug-related problems evaluation and coming up with solutions
- Drug therapy assessment, therapeutic management regarding dosage errors in a fashion to avoid too high or too low levels
- Toxicity check-up, evaluation and monitoring
- Pharmacokinetic monitoring, Therapeutic Drug Monitoring (TDM)
- Assessment of treatment efficacy and safety, as well as costs

- Nutrition consultation, parenteral nutrition prescription evaluation, assisting physicians in prescribing drugs in pain therapy
- Therapy adjustment evaluation
- Checking and managing, in details, all reanimation pharmacological aspects
- In order to avoid often life-threatening errors, pharmacist participates in all pharmacological aspects such as prescription, dosage adjustment and modality, especially in disease-drug, drug-drug, drug-food interactions of the following drug classes:
    1. Anesthetics
    2. Muscle Relaxants
    3. Analgesics
    4. Antimicrobials
    5. Fluids
    6. Emergency Drugs
    7. Oxygen
    8. Blood Derivates
    9. Blood
- Recording and documenting all the activities and events for every case in the patient's medical record
- Drug information compatibility data verification, particularly those iv
- Educating healthcare professionals, such as nurses, physicians, etc, including those of ICU, on the pharmacological aspects and usage of drugs and medical devices
- Recruit, coordinate and enroll hospital pharmacists in residency or fellowship programs, as well as launching pharmacist ICU training programs, critical care rotations
- Advanced heart life support principles
- Providing up-to-dates and continuing educational programs on pharmacological aspects of drugs and medical devices to all healthcare professionals
- Educating medical personnel about the role of pharmacists as part of the multidisciplinary health-care team
- Investigational drugs management in the process of clinical trials/research
- Participating in designing and writing clinical research/trials protocol, as well as enrolling patients for such studies
- Evaluating laboratory results, imaging data as well as clinical research and personal data and accordingly intervening the adjustment of the related pharmacological aspects of the treatment, on a case by case basis
- Statistical data analysis and research activities of morbidity, costs, drug use, the number of hospital recovery days, antimicrobial use, etc
- Writing and preparing manuscripts for clinical trial protocols, scientific publications, articles, conferences, posters, educational lectures, etc
- Writing and preparing case reports
- Document services provided to the ICU
- Economical impact assessment of drug use and services provided in the ICU
- Designing and writing entire new academic university pharmacy courses and programs, including books, procedures, lectures, etc
- Ethical committee activity, monitoring and reporting adverse drug events to hospital committee
- Developing and implementing healthcare policies and protocols, for different novel drug products

- Medication use evaluations, costs management, appropriate use of blood derivates, disinfectants antiseptics, antimicrobials and other drugs
- Recommendations regarding medication regiment review, appropriate antibiotic therapy and duration, drip rates and titration for vasocontrictor agents, iv compatibility, stability, anticoagulants and fluids (electrolytes and colloids)
- Pharmacological and medical history data collection and evaluation, allergy evaluation
- Along with other healthcare professionals the pharmacist is responsible in developing and writing not only emergency drug check lists, but also protocols of pharmaceutical care starting from surgery room setting, to ICU, pre-surgery preventive antimicrobial treatment, infectious disease therapy, severe sepsis, all kinds of shocks, such as septic, cardiologic, brain, etc all the way to analgesics, anesthetics and tromboprophylactics
- Risk assessment, ADR (Adverse Drug Reactions) reporting
- Medication to stop, or switch from iv to oral
- Post operative complication and need for therapy changes
- Pharmacists are providing drug and medical devices information service, to healthcare professionals
- Along with physicians, pharmacists are participating in patient care rounds
- Counseling on toxicological emergencies, antidotes, support therapies, steps in detoxifications/decontaminations, following to the protocol guidelines, step by step, toxicology lab data, target organ specific toxicity
- Risk evaluation in anesthetic procedure

Materials and Methods

We have researched and gathered in biomedical database some relevant research works, in which engaged pharmacists in ICU and other severe conditions in order to evaluate the clinical effects, as an observational study. Our emphasis was to assess clinical pharmacist presence in medical teams.

Results

We here report the following findings and valuable pieces of works, upon which we depict our conclusion:

Katayama T. *el al* [11] reported

> *medical treatment integrated team is now advancing, although pharmacist's role in clinical decision is increasing; and pharmacists have a greater burden of responsibility than before.*

Hisham M. *et al* [12] in their article: "***Impact of clinical pharmacist in an Indian Intensive Care Unit***" stated:

> *"A critically ill patient is treated and reviewed by physicians from different specialties; hence, polypharmacy is very common.*
>
> *This study was conducted to assess the impact and effectiveness of having a clinical pharmacist in an Indian Intensive Care Unit (ICU). It also evaluates the clinical pharmacist interventions with a focus on optimizing the quality of pharmacotherapy and patient safety.*
>
> *The prospective, observational study was carried out in medical and surgical/trauma ICU over a period of 1 year.*

During the study period, average monthly census of 1032 patients got treated in the ICUs. A total of 986 pharmaceutical interventions due to drug-related problems were documented, whereof medication errors accounted for 42.6% (n = 420), drug of choice problem 15.4% (n = 152), drug-drug interactions were 15.1% (n = 149), Y-site drug incompatibility was 13.7% (n = 135), drug dosing problems were 4.8% (n = 47), drug duplications reported were 4.6% (n = 45), and adverse drug reactions documented were 3.8% (n = 38). Drug dosing adjustment done by the clinical pharmacist included 140 (11.9%) renal dose, 62 (5.2%) hepatic dose, 17 (1.4%) pediatric dose, and 104 (8.8%) insulin dosing modifications. A total of 577 drug and poison information queries were answered by the clinical pharmacist.

Clinical pharmacist as a part of multidisciplinary team in our study was associated with a substantially lower rate of adverse drug event caused by medication errors, drug interactions, and drug incompatibilities."

McNeely EB *et al* [13] in "***Treatment Considerations and the Role of the Clinical Pharmacist Throughout Transitions of Care for Patients with Acute Heart Failure***" reported the following:

"Heart failure is associated with increased risk of morbidity and mortality, resulting in substantial health-care costs.

Clinical pharmacists have an opportunity to reduce health-care costs and improve disease management as patients transition from inpatient to outpatient care by leading interventions to develop patient care plans, educate patients and clinicians, prevent adverse drug reactions, reconcile medications, monitor drug levels, and improve medication access and adherence.

Clinical pharmacists are able to reduce rates of hospitalization, readmission, and mortality.

In addition, care by clinical pharmacists can improve dosing levels and adherence to guideline-directed therapies.

A greater benefit in patient management occurs when clinical pharmacists collaborate with other members of the health-care team, emphasizing the importance of heart failure treatment by a multidisciplinary health-care team.

Education is a key area in which clinical pharmacists can improve care of patients with heart failure and should not be limited to patients.

Clinical pharmacists should provide education to all members of the health-care team and introduce them to new therapies that may further improve the management of heart failure. "

Kang JE *et al* [14] in their 2016 article: "***Pharmacist-involved care for patients with heart failure and acute coronary syndrome: a systematic review with qualitative and quantitative meta-analysis***" concluded:

"Many trials have indicated that interventions by pharmacists resulted in beneficial outcomes with positive effects on cardiovascular diseases.

The interventions through pharmacist-involved pharmaceutical care in patients with heart failure (HF) and acute coronary syndrome (ACS) were reviewed systemically and examined.

A systematic literature search was conducted to identify relevant articles describing pharmacist interventions in HF and ACS. Most studies were evaluated qualitatively, and the strength of evidence was graded according to the Agency for Healthcare Research and Quality (AHRQ) guidelines. Some of the studies were also assessed by a meta-analysis.

All-cause hospitalization showed improvement in the pharmaceutical care group.

However, the strength of evidence for the majority of outcomes with pharmaceutical care, except direct performance measures such as prescription rates, was either insufficient or low."

Sai-Ping Jiang *et al* [16] in "***Implementation of pharmacists' interventions and assessment of medication errors in an intensive care unit of a Chinese tertiary hospital***" said:

"This study aimed to report interventions administered by clinical pharmacists and analyze medication errors in an intensive care unit (ICU) in a tertiary hospital in People's Republic of China.

A prospective, noncomparative, 6-month observational study was conducted in a general ICU of a tertiary hospital in the People's Republic of China. Clinical pharmacists performed interventions to prevent or resolve medication errors during daily rounds and documented all of these interventions and medication errors.

During the 6-month observation period, a total of 489 pharmacist interventions were reported. Approximately 407 (83.2%) pharmacist interventions were accepted by ICU physicians.

The incidence rate of medication errors was 124.7 per 1,000 patient-days. Improper drug frequency or dosing (n=152, 37.3%), drug omission (n=83, 20.4%), and potential or actual occurrence of adverse drug reaction (n=54, 13.3%) were the three most commonly committed medication errors. Approximately 339 (83.4%) medication errors did not pose any risks to the patients. Antimicrobials (n=171, 35.0%) were the most frequent type of medication associated with errors.

Medication errors during prescription frequently occurred in an ICU of a tertiary hospital in the People's Republic of China. Pharmacist interventions were also efficient in preventing medication errors".

MacLaren R *et al* [15] in a 2008 article: "***Clinical and economic outcomes of involving pharmacists in the direct care of critically ill patients with infections***" said:

"To determine whether the absence or presence of clinical pharmacists in intensive care units (ICUs) results in differences in mortality rates, length of ICU stay, and ICU charges for Medicare patients with nosocomial-acquired infections, community-acquired infections, and sepsis.

ICU outcome data were drawn from the 2004 modified Medicare provider analysis and review. Depending on the infection studied, the involvement of clinical pharmacists was evaluated in 8,927-54,042 patients from 265 to 276 hospitals.

Mortality rates, length of ICU stay, Medicare charges, drug charges, and laboratory charges for each of the infections categorized according to the absence or presence of clinical pharmacists. Compared to ICUs with clinical pharmacists, mortality rates in ICUs that did not have clinical pharmacists were higher by 23.6% ($p < 0.001$, 386 extra deaths), 16.2% ($p = 0.008$, 74 extra deaths), and 4.8% ($p = 0.008$, 211 extra deaths) for nosocomial-

acquired infections, community-acquired infections, and sepsis, respectively. Similarly, ICU length of stay was longer by 7.9% (p < 0.001, 14,248 extra days), 5.9% (p = 0.03, 2855 extra days), and 8.1% (p < 0.001, 19,215 extra days) for nosocomial-acquired infections, community-acquired infections, and sepsis, respectively. ICUs that did not have clinical pharmacists had greater total Medicare billings of 12% (p < 0.001, $132,978,807 extra billing charges), 11.9% (p < 0.001, $32,240,378 extra billing charges), and 12.9% (p < 0.001, $224,694,784 extra billing charges) for nosocomial-acquired infections, community-acquired infections, and sepsis, respectively. Similar findings were observed for Medicare drug charges and laboratory charges.

The involvement of clinical pharmacists in the care of critically ill Medicare patients with infections is associated with improved clinical and economic outcomes. Hospitals should consider employing clinical ICU pharmacists"

Again **MacLaren R** *et al* [17] in 2009 in "***Effects of pharmacist participation in intensive care units on clinical and economic outcomes of critically ill patients with thromboembolic or infarction-related events***":

"To assess the effects of clinical pharmacist participation in the care of critically ill Medicare patients with thromboembolic or infarction-related events (TIE) on clinical and economic outcomes.

In this retrospective database review (September 1, 2004-August 31, 2005), Outcomes data evaluated included mortality rates, length of intensive care unit (ICU) stay, total Medicare charges, drug and laboratory charges, and rates of bleeding complications. In addition, outcomes related to the bleeding complications (transfusions, mortality rate) were assessed. Patient outcomes in ICUs with clinical pharmacy services were compared with patient outcomes in ICUs without these services. Clinical pharmacy services were defined as direct patient care services provided by a pharmacist specifically devoted to the ICU;

Involving clinical pharmacists in the direct care of intensive care patients with TIE was associated with reduced mortality, improved clinical and charge outcomes, and fewer bleeding complications. Hospitals should promote direct involvement of pharmacists in the care of patients in the ICU."

James Gallagher *et al* [18] in: "***Cost-outcome description of clinical pharmacist interventions in a university teaching hospital BMC Health Services***" believe:

"*Pharmacist interventions are one of the pivotal parts of a clinical pharmacy service within a hospital. This study estimates the cost avoidance generated by pharmacist interventions due to the prevention of adverse drug events (ADE).*

A total cost avoidance of €708,221 was generated. Input costs were calculated at €81,942. This resulted in a net cost benefit of €626,279 and a cost benefit ratio of 8.64:1. The most common type of intervention was the identification of medication omissions, followed by dosage adjustments and requests to review therapies.

This study provides further evidence that pharmacist interventions provide substantial cost avoidance to the healthcare payer."

Dr. **Candice R. Preslaski**, *et al* in: "***Recent Advances in Chest Medicine Pharmacist Contributions as Members of the Multidisciplinary ICU Team***" [28] wrote:

"*Augmented by technology and resource utilization, this shift in roles has allowed pharmacists to provide valuable services in the form of assisting physicians and clinicians*

with pharmacotherapy decision-making, reducing medication errors, and improving medication safety systems to optimize patient outcomes. Documented improvements in the management of infections, anticoagulation therapy, sedation, and analgesia for patients receiving mechanical ventilation and in emergency response help to justify the need for clinical pharmacy services for critically ill patients.

Contributions to quality improvement initiatives, scholarly and research activities, and the education and training of interdisciplinary personnel are also valued services offered by clinical pharmacists.

Partnering with physician and nursing champions can garner support from hospital administrators for the addition of clinical pharmacy critical care services.

The addition of a pharmacist to an interprofessional critical care team should be encouraged as health-care systems focus on improving the quality and efficiency of care delivered to improve patient outcomes."

According to the article: "***Pharmacist Contribution as Members of Multidisciplinary Intensive Care Unit (ICU) Team 2013***" [28]:

"*Critical care pharmacy has evolved over the past 30 years and is now recognized by the pharmacy profession and critical care practitioners as an advanced discipline within pharmacy practice.*

Moreover, technological advances (eg, computerized provider order entry, integrated health-care records, automated distribution systems, robotic fill devices, bar coding), scope of practice changes (eg, technician check technician), safety and cost-containment mandates, and competitive pressures are enabling pharmacists to be physically present in the ICU, often providing direct patient care and acting as the expert pharmacotherapy manager of a multidisciplinary ICU team.

Direct patient care is described in the Scope of Pharmacy Practice as the pharmacist's observation of the patient and his or her contributions to the selection, modification, and monitoring of patient-specific drug therapy through collaborative practice with an interprofessional team or another health-care provider.

Evaluation and verification of medication orders, to dispensing and assisting with administration of medications, to collaborative drug therapy management where pharmacists are authorized to select medications for identified medical conditions, adjust dosage regimens to optimize pharmacotherapy, monitor key vital signs and order laboratory tests, provide drug information, and develop and evaluate therapeutic management policies.

The paradigm for critical care pharmacy services is the 2000 Society of Critical Care Medicine (SCCM)/American College of Clinical Pharmacy position paper, which defines the fundamental, desirable, or optimal activities across clinical and nonclinical domains (Table 1).4 Fundamental activities are services that must be provided for the safe delivery of pharmaceutical care to all patient populations; desirable activities add clinical functions necessary for the specialized care of critically ill patients; and optimal activities reflect an integrated, specialized, and dedicated model of direct patient care functions aimed at optimizing outcomes. In the interest of promoting these activities, the SCCM suggests that pharmacists are essential for the delivery of quality care to critically ill patients and recommends the integration of a dedicated, proactive, and physically present pharmacist on the ICU team as an essential component of a multidisciplinary approach to critical care.

Role and Impact of Direct Critical Care Pharmacy Services:

Pharmacist delivery of direct, proactive, patient-centered care has been associated with both perceived and actual improvements in patient outcomes.

A 2007 analysis of 2,836,991 patients across 885 hospitals showed that hospital-wide mortality rates decreased as the pharmacist-to-occupied bed ratio increased.

Specific Pharmacy Services Associated with Favorable Healthcare Outcomes

Pharmacy Service Annual Deaths Avoided per Hospital

Targeting Specific Therapeutic Practice Domains

These studies suggest a global improvement in care associated with the institution of direct patient care pharmacy services in the ICU.

In practice, many clinical pharmacy activities are directed toward specific therapeutic practice domains where outcomes can be more clearly demonstrated and, thus, the presence of a dedicated pharmacist can be more easily justified.

Therapeutic practice domains may be comprehensive but usually are focused on capturing the sickest patients or targeting certain medications, such as those highlighted by patient safety initiatives or known to cause the most serious adverse events (eg, vasoactive agents, sedatives/analgesics, electrolytes, anticoagulants, insulin).

Antimicrobial Therapy

Critical care clinical pharmacists receive extensive training in infectious disease pharmacotherapy to complement their training in other domains of critical care practice. Moreover, the literature suggests the benefit of clinical pharmacist activity as it pertains to infectious disease pharmacotherapy in critically ill patients.

Additionally, deescalation of antimicrobial therapy in response to specific culture findings may reduce the emergence of antimicrobial resistance.

Guidelines from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America state that a clinical pharmacist with infectious disease training should be a core member of the multidisciplinary antimicrobial stewardship team.

The impact of the addition of a clinical pharmacist to an antimicrobial control program was evaluated in a Veteran Affairs medical center. Over a 2-year period, the pharmacist reviewed 1,329 orders for restricted and nonformulary antibiotics for appropriateness on the basis of presumed infection, culture results, formulary availability, and dosing. The pharmacist recommended changes in > 50% of orders, with most changes related to spectrum of activity, formulary substitution, or dose adjustments. These interventions were associated with shorter lengths of stay (10.8 days vs 13.2 days, $P < 0.001$) and decreased mortality (6.61% vs 8.28%, $P = 0.007$) compared with the period before the implementation of an antimicrobial control program directed by a clinical pharmacist.

A similar impact was seen when pharmacists managed surgical antimicrobial prophylaxis. A survey and database review of 242,704 Medicare surgical patients from 806 different hospitals showed that pharmacist-managed antimicrobial prophylaxis was associated with significant improvement in clinical outcomes, such as decreased surgical site infections and length of stay. Nearly 19% of the hospitals included had pharmacist-managed surgical prophylaxis. In hospitals that did not offer pharmacist-managed antimicrobial

prophylaxis, annual death rates were 52% higher, with 105 excess deaths (OR, 1.54; 95% CI, 1.46–1.63; P < 0.0001); length of hospital stay was 10.2% longer, with 167,941 excess patient days (P < 0.0001); and infection complications were 34.3% higher (OR, 1.52; 95% CI, 1.40–1.66; P < 0.0001) than in those with pharmacist involvement.

Clinical pharmacists provide expertise in pharmacokinetics and pharmacodynamics essential for dosing considerations in critically ill patients. Vancomycin and Aminoglycosides are the most common drug therapies managed by a clinical pharmacist. A database review of pharmacist management of Vancomycin and Aminoglycosides was evaluated in a study population comprising 199,082 Medicare patients treated in 961 hospitals. Hospitals with pharmacist-managed Vancomycin or Aminoglycoside therapies had lower mortality (17% vs 18%, P < .0001); shorter lengths of stay (11.56 ± 18.73 days vs 12.98 ± 18.66 days, P < 0.0001); and fewer adverse events, including hearing loss (4.6% vs 6.8%, P < 0.0001) and renal impairment (25.8% vs 34.5%, P < 0.0001).

Similarly, individualized pharmacokinetic monitoring performed by a clinical pharmacist was associated with less Aminoglycoside-associated nephrotoxicity compared with physician-monitored therapy in a retrospective case-control study of 2,405 patients (7.9% vs 13.2%, P = 0.02).

Compared with ICUs with clinical pharmacists, mortality rates in ICUs that did not have clinical pharmacists were higher for nosocomial-acquired infections, community-acquired infections, and sepsis by 23.6% (386 excess deaths, P <0.001), 16.2% (74 excess deaths, P = 0.008), and 4.8% (211 excess deaths, P = 0.008), respectively. Similarly, ICU length of stay was longer for all infection categories by 7.9% (14,248 excess days, P < 0.001), 5.9% (2,855 excess days, P = 0.03), and 8.1% (19,215 excess days, P < 0.001), respectively.

Anticoagulation Therapy

Critically ill patients requiring anticoagulation often have multiple comorbid conditions that require a delicate balance between treatment of a thromboembolism and avoidance of a detrimental bleeding event. Coupled with the need to manage these therapies in a time-sensitive manner, anticoagulation in the ICU becomes increasingly complex.

Additionally, regulatory standards from the Joint Commission are placing greater importance on the safety and management of inpatient anticoagulation. As pharmacologic experts, clinical pharmacists can provide valuable services that aid in improving safety and clinical care in critically ill patients requiring anticoagulation.

Clinical pharmacists often manage clinical pathways and guidelines to aid in the administration of anticoagulants in the ICU. These pathways frequently empower pharmacists and nurses to independently direct anticoagulant dosage regimens under the guidance of a predefined protocol.

In the case of heparin infusions in patients with DVT, such pathways reduced the time to achieve therapeutic activated partial thromboplastin time (aPTT) from a mean of 54 h before the implementation of the pathway to only 11 h after implementation.

Similar outcomes were documented in an 802-bed university hospital where pharmacists managed direct thrombin inhibitors for the treatment of heparin-induced thrombocytopenia.23 The time to achieve the therapeutic aPTT was reduced by 12.5 h (P < .001), and the proportion of time within the therapeutic aPTT range was increased by 32% (P < .001).

Combining the results of the 2006 survey of ICU pharmacy services with the Expanded Modified Medicare Provider Analysis and Review, mortality rates were 37% higher in ICUs without direct patient care clinical pharmacy services (OR, 1.41; 95% CI, 1.36–1.46) for patients with thromboembolic or infarction-related events.24 ICUs without a clinical pharmacist also had a 49% greater incidence of bleeding complications (OR, 1.53; 95% CI, 1.46–1.60), which was associated with a higher likelihood for the need for blood transfusions (OR, 1.47; 95% CI, 1.28–1.69) and a greater amount of blood product administration (6.8 ± 10.4 units/patient vs 3.1 ± 2.6 units/patient, P = 0.006).

Before the requirement of an inpatient anticoagulation program, it was found that pharmacist-managed anticoagulation was associated with reductions in mortality, hospital lengths of stay, and blood transfusions.

Additionally, the pharmacist-managed patients had fewer readmission rates for bleeding or thrombosis within 1 to 3 months after discharge.

Sedation and Analgesia

Pharmacist involvement in maintaining patient comfort has focused on adherence to clinical practice guidelines, reduction of prescribing variability, increased appropriate drug selection, and reduction of drug costs.

The implementation of a sedation scoring tool and sedation guideline with pharmacist-driven drug selection and dose adjustments of benzodiazepines and Fentanyl decreased the incidence of agitation (22.4%-11%, P < 0.001) and pain (9.6%-5.9%, P < 0.05) while improving the proportion of time patients were at the goal level of sedation (17.2%-29.6%, P < 0.01).

In another study where clinical pharmacists concurrently evaluated all patients receiving mechanical ventilation and continuous sedation and made recommendations to adhere to the approved sedation guidelines of the institution, the intervention group (n = 78) demonstrated a shortened duration of mechanical ventilation (178 ± 178 h vs 338 ± 348 h, P < 0.001), ICU length of stay (238 ± 206 h vs 380 ± 325 h, P = 0.001), and hospital length of stay (369 ± 274 h vs 537 ± 350 h, P = 0.001) compared with a historical cohort (n = 78). The daily interventions made by the clinical pharmacist during the implementation phase included adding a sedative agent (32%), discontinuing a sedative agent (20%), decreasing the sedative dose (18%), supplementing a bolus agent (11%), and adding as-needed agents (9%).

Emergency Response

Most critical care pharmacists receive training in advanced cardiac life support (ACLS) as well as other emergency situations such as trauma resuscitation, stroke, and ST-segment elevation myocardial infarction.

This training combined with their expert knowledge of medications provides opportunities for clinical pharmacists to be valuable members of a resuscitation response team, which has been associated with reduced mortality.

Reducing Adverse Drug Events

Critically ill patients are at high risk for ADEs because of the severity of disease; organ dysfunction; and number, complexity, and duration of medications administered.

Numerous published reports identified clinical pharmacists as optimal providers to identify and reduce medication errors and ADEs through medication profile review and adverse drug reaction (ADR) management and attendance during patient care rounds.

Pharmacist management of ADRs is associated with reduced mortality. Specifically, increasing clinical pharmacist staffing from one to five pharmacists per 100 occupied beds was associated with a 48% decrease in ADRs.

During the 8-month study period, the presence of a pharmacist during rounds was associated with a reduction in the total number of preventable ADEs (33 vs 11.6 per 1,000 patient days, P < 0.001) and order-writing ADEs (10.4 vs 3.5 per 1,000 patient days, P < 0.001), whereas no changes occurred in the cardiac ICU. Of 366 interventions made by the pharmacist, 362 (99%) were accepted by the physicians and primarily related to the fundamental activities of order clarification (45%), drug information (25%), and alternative therapy recommendation (12%).

Identification of drug-drug or drug-disease interactions is a fundamental service of the medication profile review performed by clinical pharmacists.

Prolongation of the corrected QT interval (QTc) is a serious adverse effect of certain medications. When a standardized algorithm for monitoring patients who receive QTc-prolonging medications was implemented at a tertiary academic medical center, the incidence of QTc prolongation was significantly lower in the 77 patients observed by a clinical pharmacist compared with 72 control group patients (19% vs 39%, P = 0.006).

Economic Considerations

It has been estimated across all hospital patients that the return on investment of a clinical pharmacist's salary is about 9:1, strictly from cost avoidance. This ratio approaches 25:1 in the ICU, suggesting that the benefit of clinical pharmacy services may be optimized in patients in the ICU.

Of note, this benefit-cost ratio may underestimate the true value of the clinical pharmacist because it does not account for a potential decreased mortality or shortened length of ICU stay.

The Affordable Care Act emphasizes greater efficiency within US health-care systems. Clinical pharmacists in the ICU can aid in improving the delivery of safe and efficient care to critically ill patients while reducing ADEs and medication errors. A common barrier in many institutions is securing the salary support to justify the hiring of dedicated critical care pharmacists. For example, if the support comes from the pharmacy department, these salaries detract from other departmental initiatives that may provide obvious financial and patient safety rewards (eg, hiring technicians, purchasing automated distribution systems or robotic fill devices, implementing advanced computer technologies). The economic benefit of clinical pharmacists, on the other hand, may only be realized through reduction in variable costs, such as drug expenditures and cost avoidance. However, the current budgeting system used in many institutions may penalize some departments, even when the institution as a whole benefits. An example is the use of a newer, more expensive sedative agent that reduces ventilator and hospital days but at the expense of the pharmacy budget. With the evolution of health-care models that promote greater efficiency and safety, increased reimbursements accrued by meeting quality metrics should be redistributed to hospital departments to offset the increased costs. In the case of most hospital pharmacy departments, the fixed budget must be delicately balanced by optimizing drug therapies to improve patient outcomes while

dedicating clinical pharmacist personnel to support patient care services and by maintaining a positive return on investment. For this reason, critical care physician and nurse champions are essential in promoting resources needed for the clinical pharmacist because they may advocate for these roles on the basis of improved patient care, safety, and clinical outcomes. These partnerships, in collaboration with pharmacy administration, may garner support from hospital executives and help to define the roles and responsibilities of the clinical pharmacist so that expectations are realized.

The literature reviewed herein is limited by a lack of robust, prospective, randomized trials and consists primarily of database, retrospective cohort, and preintervention / postintervention study designs. Given the inability to control for factors such as therapeutic advancements in critical care medicine and the increasing heterogeneity of patients over time, it is difficult to attribute the results reported in the literature solely to clinical pharmacist service in intensive care. Moreover, there exists a likely possibility of publication bias in favor of positive results that challenge a robust interpretation and application of study results. Additionally, there are few data on the impact of desirable or optimal clinical pharmacy services, such as education, scholarship, and committee service, in addition to pharmacotherapy management. Future studies should focus on quantifying clinical pharmacist contributions to clinical care in blocked study design to control for the aforementioned variations.

Critical care pharmacists are pharmacotherapy experts and offer unique skills and insight into the care of critically ill patients.

Patient's safety and clinical outcome are considerably enhanced when a clinical pharmacist proactively participates, as a permanent member of the multidisciplinary ICU team.

The focused assessment by the clinical pharmacist to focus on the patients in critical conditions especially those in specific therapeutic practice domains, such as antimicrobial management, anticoagulation, sedation and analgesia, and emergency response, have been justified by not only noticeably saving so many lives but also helping to fiscally contain their service costs.

As a conclusion,

Therefore, in an era focused on improving health-care efficiency, the persistent presence of clinical pharmacists positively contributed to the overall delivery of care for critically ill patients, in a prominent fashion.

Discussions

What we have observed was, when clinical pharmacist is part of the medical team, a general improvement occurred on many clinical outcomes in ICU, reducing the mortality rate, in a prominent fashion.

So the question is, "who will be responsible for the death of a patient if there is a chance of a mistake in choosing, say the appropriate to the pathological conditions of the patient of an anesthetic"? The presence of a clinical pharmacist, in the medical team, besides saving patient's life, improves clinical outcome when for example an expensive transplant is in the process, and the patient would lose his/her life anyways, if a clinical pharmacist would not participate. This is just a minute example amongst many; the same is valid for complicated cardiovascular,

gastroenterology and neurological surgeries, as well as some treatments of cancer patients and this is just to mention few examples; the list does not stop here.

So, after all the events we have observed, through other studies, collected in this paper, "does anyone even doubt in *the ethical necessity of proactive presence of a clinical pharmacist or at least a doctor of pharmacy, with extensive knowledge of pharmacological parameters of the current medications used in public or private healthcare institutions, as a permanent member of the ICU medical team*"?

Conclusions

Considering the increasing number of life losses and medical damages, posed by healthcare bodies to patients and under the light of current results, including those presented in this review article, we see is incumbent, morally and ethically, upon all the healthcare authorities, including the federal legislative branch, to ask institutions involved to strictly apply this working method in the ICU settings, in order to both prevent a **considerable number of health risks, by achieving a relevant reduction in mortality rate**, and contain unnecessary expenses. This not only reduces nation's burden that on its part would reflect on the life quality of every ordinary citizen but also opens the hands of the health authorities to give a higher quality, more generous and unrestrained service to those who really need.

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