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# Bioavailability of Orally Administered Drugs in Critically Ill Patients

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## Abstract

Critically ill patients managed in the Intensive Care Unit (ICU) suffer from several pathophysiological alterations due to critical illness resulting in potential changes in the pharmacokinetics of drugs including systemic absorption. Nevertheless, these patients are still given some medications in unadjusted doses thereby putting the patients at a risk for therapy failure. The objective for this study was to summarize the available evidence regarding oral drug absorption in the ICU. A literature search of the databases MEDLINE, EMBASE, and PubMed was conducted on (February 24, 2020). Articles discussing the rate and/or extent of orally administered drugs in critically ill patients were included. A total of 58 studies were found: 17 interventional studies, 33 observational studies (30 prospective, 3 retrospective) and 8 case reports. A total of 43 articles reported altered drug absorption in critically ill patients suggesting the need for alternative measures to facilitate treatment success. The absorption of orally administered drugs may be altered in critically ill patients. Measures for altered drug absorption in critically ill patients were suggested such as holding tube feeding before and after medication administration, increasing doses of orally administrated drugs and using alternate routes of administration.

## Keywords

bioavailability, critical illness, drug absorption

## Introduction

Critically ill patients are those who are at risk of developing, or have, life-threatening organ dysfunction and require management at the Intensive Care Unit (ICU). Evidence-based drug therapy guidelines in various disease states are not always applicable to critically ill patients since these patients have several pathophysiological alterations due to critical illness. Pathophysiological changes can include altered plasma protein binding, altered renal drug clearance, changes to gastric pH and absorption, and reductions in hepatic blood flow or enzyme activity.[1,2] These changes can affect the pharmacokinetics (PK) of different drugs. Despite having multiple risk factors for altered PK, critically ill patients are still given some medications in unadjusted doses thereby putting them at a risk for therapy failure, longer hospitalizations and increased adverse drug events.[1,3] One important consideration in critically ill patients is the possibility of altered rate and extent of oral drug absorption, the process of movement of the drug from the site of administration to the systemic circulation. There have been multiple reports of altered drug absorption in critically ill patients; however, clear guidance on how to manage those alterations is lacking.[1,3]

The aim of this review is to summarize the available evidence regarding drug absorption of orally administered drugs at the ICU. The factors contributing to altered drug absorption will also be described and discussed for each drug, when available. The available evidence will be summarized, and recommendations will be provided for each included drug based on the quality of the available evidence.

## Literature Search

A comprehensive literature search of the databases MEDLINE (1946 to September 16, 2019), EMBASE (1974 to September 17, 2019) and PubMed (1946 to 16 September

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2019) was conducted. The search was repeated on February 24, 2020 to capture any additional studies since the original search. The following keywords were used: ("gastrointestinal absorption" OR "absorption*" OR "absorb*" OR "biological bioavailabilit*" OR bioavailabilit*) AND ("intensive care unit*" OR "ICU" OR "intensive treatment unit*" OR "intensive therapy unit*" OR "critical care unit*" OR "critical* ill*" OR "terminal care" OR "terminal* ill*) AND ("oral*" OR "orally" OR "enteral*" OR "feeding tube"). Articles discussing absorption rate and extent of orally administered drugs, either by mouth or feeding tubes, in critically ill patients managed at the ICU were included. Non-English studies that could not be translated to English by using an online translator tool, non-human studies and reviews were excluded. Articles discussing bioavailability without providing PK data were excluded. Following duplicates removal, title and abstract screening was conducted to exclude articles not fulfilling the inclusion criteria. Then, full text screening was conducted. If there was any doubt regarding the relevance of any of the articles, discussion among authors was done to reach a consensus. The data collected included author and year of publication, study type, dose and name of the drug, number, sex and age of participants, bioavailability, area under the concentration-time curve (AUC), drug concentrations, factors altering drug absorption and clinical implications. The level of evidence for each recommendation was graded using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria.[4]

## Results of Literature Search

Literature searches from all databases resulted in 2542 articles. Following abstract and title screening, 122 articles remained. After full text screening, a total of 58 articles were included in this review: 17 interventional studies, 33 observational studies (30 prospective, 3 retrospective) and 8 case reports. Of all included articles, 5 were abstracts and 1 a letter to the editor. A summary of studies discussing altered drug absorption in critically ill patients (43 studies) is provided in Supplementary Tables 1 (adults) and 3 (pediatrics). The remaining 15 studies reporting unaltered drug absorption are presented in Supplementary Table 2.

## Antiepileptic Drugs

The incidence for seizures at the ICU ranges from 3.3-34%. Head trauma, stroke, and electrolyte abnormalities are common conditions in patients managed at the ICU and are risk factors for developing seizures.[5] Knowledge of the pharmacokinetics of antiepileptic drugs including the bioavailability is of importance since most of these drugs are with a narrow therapeutic range.

### *Phenytoin*

Phenytoin is an antiepileptic drug that undergoes saturable elimination and follows a nonlinear PK profile with a disproportionate increase in serum concentration with increasing doses. The recommended reference range for phenytoin is between 10-20 mg/L (40-80 μmol/L). Two studies have reported that phenytoin plasma concentrations decrease by up to 75% when administered via enteral feeding tubes in patients receiving continuous tube feeding.[6,7] This reduction in drug concentrations has been attributed to an interaction between phenytoin and the enteral feeding formulas. Meat-based formulas seemed to have the lowest interaction.[8] Reported strategies to overcome this interaction include increasing the dose of phenytoin or holding tube feeds before and/or after drug administration.[6,9] However, it is unclear how long and when tube feeds should be held. One study found that holding tube feeds for one hour before and after phenytoin administration increased the propensity for achieving therapeutic drug concentrations.[9] In contrast, Maynard et al[8] have reported that holding tube feeds for 2 hours before and after drug administration did not improve drug concentrations.[8] Lastly, two studies reported a risk of supratherapeutic phenytoin concentrations with holding tube feeds 2 hours before and/or after drug administration.[7,10] While holding enteral nutrition may improve drug concentrations, the effects of significant nutritional delivery interruption with frequent phenytoin administrations must be considered in context of the patient.

In conclusion, there is moderate evidence suggesting that enteral feeding should be held for one to two hours before and/or after phenytoin administration to avoid interactions with the enteral formula. Therapeutic drug monitoring (TDM) is important when using phenytoin to ensure safe drug concentration and avoid toxicity. As, phenytoin displays saturable kinetics, dose adjustments must be done with caution if the levels are low or high, especially in the presence of hypoalbuminemia. Dose increases or decreases can range from 30 to 100 mg/day if phenytoin levels are below or above the reference range, respectively. Always consider the patient's clinical status before ordering a phenytoin level. If holding tube feeds is not an option, administration of the IV formulation of phenytoin or fosphenytoin may be an alternative. Fosphenytoin is dosed in phenytoin equivalent units with 1.5 mg fosphenytoin equaling 1 mg phenytoin.

### *Levetiracetam*

Levetiracetam, a broad-spectrum antiepileptic drug, is widely used in critically ill patients since it has a rapid onset of action, is well tolerated, and has minimal drug interactions. Levetiracetam is available in a parenteral formulation. TDM is not typically recommended, and dosage adjustments should be made based on clinical status. However, it has been suggested that TDM may be beneficial in populations where altered pharmacokinetics are expected such as critically ill patients, pediatrics, the elderly and those exhibiting augmented renal clearance.[11] Mink et al[12] have reported that mean levetiracetam concentrations declined by 30% after switching from

parenteral to enteral administration.[12] Higher levetiracetam doses can be considered when using the enteral route in critically ill patients, but the evidence is very low and further studies are needed.

### Phenobarbital

Phenobarbital is a barbiturate antiepileptic drug. The usual bioavailability in healthy adults is reported to be >90%, making it relatively simple to convert between parenteral and oral dosages. The recommended reference range for phenobarbital is 15-40 mg/L (43 to 172 mmol/L). No reports of phenobarbital bioavailability among critically ill adult patients were found. Marsot et al and Williams et al have reported that the enteral bioavailability of phenobarbital ranges between 49-85% in neonates in the ICU.[13,14] Reduced bioavailability in neonates has been attributed to the difference in gastric pH between adults and neonates. When switching from parenteral to enteral route, therapeutic drug monitoring might be considered to ensure concentrations are within the reference range.

### Valproic Acid

Valproic acid is available in enteral and parenteral forms. Mink et al[12] have reported that enteral administration of valproic acid resulted in equivalent mean serum concentrations compared to IV administration.[12] Based on this, it appears that critically ill patients may have complete enteral absorption and 1:1 IV to PO dose conversion could possibly be utilized. However, since only one observational study was found, the evidence is considered very low. Therapeutic drug monitoring is recommended in situations of uncontrolled seizure activity despite adequate valproic acid dosing or where dose-dependent adverse effects are suspected.

### Carbamazepine

Miles et al have reported that enteral administration of 8-10 mg/kg carbamazepine suspension resulted in rapid control of generalized convulsions and partial seizures in pediatrics, but the absorption was delayed in one patient receiving enteral feeding. Based on this one patient, the authors concluded that avoiding enteral feeds may be needed if the effect from carbamazepine is required quickly.[15]

## Antimicrobials

Serious infections are often treated using IV antimicrobials in critically ill patients to ensure therapeutic drug concentrations are reached. Enteral administration is restricted to patients who have a functional GI tract and can absorb the drug. This route may be an alternative to IV antimicrobials depending on the infection. If possible, clinicians may wish to use the enteral route given its benefits including earlier discharges, good tolerability, and reduced costs.[3]

### Fluoroquinolones

Fluoroquinolones are concentration-dependent antimicrobials, meaning the concentration must be above the minimum inhibitory concentration (MIC) of the pathogen to be effective.[16] Fluoroquinolones are used for many Gram-negative bacterial infections and are often seen in critically ill patients. Drug interactions with fluoroquinolones are common which can make their use more complicated than other antimicrobial classes. Given that they are commonly used, understanding the factors that affect their use is necessary.

Ciprofloxacin is available in both enteral and parenteral formulations. It is well absorbed with 500 mg PO every 12 hours provideing a similar AUC to 400 mg IV every 12 hours.[17] Enteral absorption of ciprofloxacin has been studied among critically ill patients. One study evaluated oral administration of ciprofloxacin after abdominal surgery and found that drug concentrations immediately after surgery are decreased.[18] In ICU patients it is unclear if enteral feeding affects ciprofloxacin absorption. Debon et al[19] found no difference in absorption when tube feeds were administered with either 500 mg or 750 mg oral ciprofloxacin doses.[19] In contrast, de Marie et al and Mimoz et al saw a decrease in $C_{max}$ when a 750 mg enteral dose was given with tube feeds.[20,21] Additionally, Cohn et al[18] has found that giving 750 mg PO twice daily to mechanically ventilated critically ill patients gave similar AUC and $C_{max}$ levels as a single 500 mg PO dose in non-critically ill patients.[18] Given that fluoroquinolones are concentration-dependent antimicrobials, it is important to consider whether $C_{max}$ is above MIC; Debon et al[19] have reported that both 500 mg and 750 mg enteral doses resulted in concentrations above MIC for many pathogenic bacteria.[19]

De Smet et al and Kees et al have investigated moxifloxacin. Both authors reported that administration of 400 mg daily enterally is not equivalent to 400 mg daily given parenterally in ICU patients, with the enteral bioavailability reported to be approximately 77% in both studies. The first mentioned study also reported that $C_{max}$ declined approximately 45% after enteral administration.[22,23]

The PK parameter to assess fluoroquinolone efficacy should be either $C_{max}$ or AUC.[16] For ciprofloxacin there is some evidence to support enteral administration in critically ill patients with functioning GI tracts; some studies showed a decrease in $C_{max}$ (partly due to interactions with tube feeds) and some demonstrated similar AUC between the enteral and parenteral routes.[18-21] Increasing ciprofloxacin doses when enterally administering to critically ill patients could be considered along with monitoring of clinical status to ensure adequate drug absorption. The data are much more limited for moxifloxacin suggesting the risk of lower efficacy with enteral administration compared to parenteral administration in

critically ill patients. The evidence is moderate for ciprofloxacin and very low for moxifloxacin.

In contrast, some fluoroquinolones have not shown altered drug absorption in critically ill patients. One study found that enteral and parenteral administration of 500 mg levofloxacin resulted in equivalent exposure in critically ill patients; however, these patients had no renal or GI dysfunction and were relatively stable.[24] Kanji et al[25] have reported that tube feeding does not affect the bioavailability of 400 mg gatifloxacin, but critical illness results in variability that may limit the use of enteral formulations.[25] The evidence is very low for both drugs since only one observational study each was found and all studies had small sample sizes.[24,25]

### Cephalosporins

Cephalosporins are bactericidal beta-lactam antimicrobials. One cephalosporin, cefroxadine, was studied to determine the bioavailability in critically ill patients. Cefroxadine is nearly 100% orally absorbed due to its stability in an acidic environment.[26] However, Beyssac et al[27] have reported a 30% decline of cefroxadine $C_{max}$ in patients receiving continuous tube feeding.[27] The evidence is very low since only one observational study was found. Cefroxadine has been removed from market, and conclusions cannot be extended to other orally administered beta-lactam antimicrobials.

### Other Antimicrobials

Chin et al have investigated the PK of trimethoprim-sulfamethoxazole in both critically ill and non-critically ill HIV-patients. The authors reported that oral bioavailability of trimethoprim was 97.5%, and sulfamethoxazole 86.2% in critically ill patients, compared with 101.8% and 99.1% in non-critically ill patients, respectively. However, conclusions regarding critically ill HIV-patients were based on only four patients which limits the generalizability of the study.[28] Closely monitoring response to therapy in critically ill patients is important.

### Antifungals

Invasive fungal infections are serious complications in critically ill patients. These infections are a major cause of morbidity and mortality at the ICU.[29] Antifungal medications are used for both prophylaxis and treatment of fungal infections.[30] Commonly used antifungal medications include azole drugs. This class includes agents such as fluconazole, posaconazole, itraconazole and voriconazole. The bioavailability of these agents is variable and ranges from roughly 55% with itraconazole to >90% with fluconazole and may be affected by gastric pH or food intake.[31]

The bioavailability of fluconazole in the critically ill has been evaluated and results are mixed. Barquist et al[32] reported a decrease in AUC with enteral administration in critically ill patients after laparostomy.[32] While fluconazole is typically well absorbed in healthy patients, several studies have reported variable enteral bioavailability in critically ill patients with estimates ranging from 77% to 124%.[30,33-36] These studies also evaluated the effect of enteral nutrition on fluconazole concentrations; two studies found that tube feeds decreased fluconazole absorption and two studies found no effect from tube feeds. Additionally, one study found that holding tube feeds for 1 hour after fluconazole administration resulted in serum drug concentrations above MIC for most *Candida* sp.[37]

Posaconazole concentrations may be decreased in critically ill patients. Two studies observed inadequate drug concentrations with 200 mg and 400 mg doses of posaconazole given enterally, and it was suspected that concomitant tube feeds or proton pump inhibitors (PPI) use may have contributed to the observed drug levels.[38,39] Similarly, itraconazole concentrations are decreased after enteral administration in patients who have undergone bone marrow transplants, and it was speculated this was due to increased gastric pH.[40] On the other hand, Karoubi et al have reported in a conference abstract a mean voriconazole bioavailability of 106% in mechanically ventilated critically ill patients on continuous tube feeding. Investigated doses were 4 mg/kg IV every 12 hours for 3 days, followed by 5 mg/kg enterally every 12 hours.[41] The authors have concluded that enteral administration of voriconazole after initial IV therapy may be appropriate.

In conclusion, the evidence regarding enteral absorption of azole antifungals is limited. Drug concentrations may be reduced by continuous tube feeding or increased gastric pH, except for voriconazole, and these factors should be considered when selecting an agent for antifungal therapy.

## Gastric Acid Suppressing Medications

Gastric acid suppressants are routinely used at the ICU for both prevention and treatment of several conditions, including GI bleeding, gastroesophageal reflux disease and peptic ulcer disease.

### Proton-Pump Inhibitors

PPIs are available in oral and parenteral formulations. As discussed earlier they can affect the absorption of other medications, but their absorption can also be impaired. Olsen et al has compared parenteral and enteral administration of lansoprazole in critically ill patients. The authors have found that enteral administration of lansoprazole results in a decreased bioavailability and AUC, yet results in increased acid suppression compared to parenteral dosing.[42] The quality of evidence is moderate and enteral administration of lansoprazole could be considered when treating critically ill patients.

### Anticholinergics

Investigations have shown that acetylcholine has a role in the regulation of gastric acid secretion; the anticholinergic pirenzepine prevents gastric acid secretion by selective blocking of

muscarinic receptors. This drug is well tolerated with a low incidence of antimuscarinic side effects such as dry mouth and GI dysmotility. Tanswell et al have reported a 50% rise in bioavailability in critically ill patients; however, this rise was determined to not be clinically relevant as pirenzepine has a wide reference range and minor adverse effects. Given the safety of pirenzepine, dose adjustment in critically ill patients is likely unnecessary. The evidence is considered very low.[43]

### Histamine H2-Receptor Antagonists

Histamine H2-Receptor Antagonists are used for stress ulcer prophylaxis among other uses and may be seen in an ICU setting. Pemberton et al have reported that postoperative critically ill patients absorbed enough ranitidine to reach therapeutic concentrations using either 300 or 500 mg doses. Tube feeding was held for one hour after drug administration in this study.[44] The evidence is considered moderate and critically ill patients could be treated using unadjusted doses of ranitidine for stress ulcer prophylaxis.

## Cardiovascular Medications

### Verapamil

Verapamil is used in hypertension and atrial fibrillation, among other indications. It is available in both enteral and parenteral formulations, and its bioavailability in healthy patients is 20-35%. Verapamil is usually well tolerated with moderate side effects. Woodcock et al[45] have reported that its oral bioavailability appears to be lower in critically ill patients than in healthy volunteers.[45] The authors also saw changes in verapamil clearance and concluded that differences in verapamil kinetics exist between critically ill and healthy patients.

### Acetylsalicylic Acid

Acetylsalicylic acid (ASA) irreversibly inhibits platelet function at low dose. It is frequently used as secondary prevention after a heart attack or stroke, and clinicians are likely to see ASA in critically ill patients. Schoergenhofer et al have investigated different formulations of ASA in patients managed in the ICU. The authors have reported that chewable tablets result in an 8% decline in concentrations, and enteric-coated tablets result in a 35% decline compared with parenteral administration. The blood samples were drawn one hour after administration and no difference in platelet aggregation inhibition was observed between the formulations.[46] Given that platelet inhibition did not change, critically ill patients may be treated with any of the studied ASA formulations.

### Clopidogrel

Clopidogrel is a P2Y12 platelet aggregation inhibitor. It may be seen in critically ill patients, especially if they have a cardiac history. Součková et al have reported that the bioavailability and platelet aggregation inhibition of clopidogrel is significantly impaired after enteral administration in critically ill patients who had undergone cardiopulmonary resuscitation and acute percutaneous coronary intervention (PCI). The authors reported platelet inhibition of only 9% after 24 hours in these patients, compared with 45% in stable patients.[47] Based on this, critically ill patients may be at risk of insufficient platelet inhibition after enteral administration of clopidogrel. As no IV formulation of clopidogrel is available, alternative antiplatelet agents for critically ill patients after PCI should be considered. The evidence is considered very low and further studies should be carefully considered before action is taken. Alternate P2Y12 inhibitors include ticagrelor and prasugrel, but no studies were found for these agents.

### Clonidine

Clonidine stimulates α2-adrenergic receptors and has sedative and antihypertensive effects. One study has investigated enteral absorption of clonidine in pediatric postoperative cardiac patients. The authors reported that the majority reached therapeutic drug concentrations, but enteral absorption was delayed by approximately 127 minutes.[48] It is possible that postoperative cardiac pediatrics could be treated with enteral clonidine; however, if a rapid effect is necessary other options should be considered.

## Other Medications

### Melatonin

Melatonin is a hormone with several functions in critically ill patients. The primary function is regulation of the sleep cycle. In addition, melatonin also works as a hypnotic, antioxidant, analgesic and antiseptic regulator. Several studies have reported that critically ill patients have impaired concentrations of melatonin during hospitalization; however, it is not clear if this phenomenon is due to reduced production or higher consumption of melatonin as an antioxidant. Due to this, critically ill patients are often treated with exogenous melatonin.[49,50] Several studies have evaluated melatonin administration in the ICU. Three studies have reported supra-physiologic melatonin levels after enteral administration, with doses ranging from 3 to 10 mg.[49,51,52] Mistraletti et al has reported tube feeds may facilitate melatonin absorption, and Bourne et al have observed carryover effects with administration of 10 mg doses.[49,52] Given the carryover effects with higher doses, it may be reasonable to start with lower doses and titrate up.

### Fludrocortisone

Polito et al have investigated enteral absorption after a single dose of 50 μg in patients with sepsis. The authors reported that drug concentrations were undetectable in 33% of the patients,

and it was theorized that decreased absorption may have contributed to this observation; other factors may have contributed to the undetectable level, including concomitant therapy with PPIs.[53] As fludrocortisone is not available as an IV formulation, alternate agents may be considered if concerns about enteral absorption are present.

### Acetaminophen

Acetaminophen is a non-narcotic analgesic agent used for fever and mild to moderate pain in both adults and pediatrics. Acetaminophen is well tolerated and safe in recommended doses. It is available in oral, IV, and rectal forms, though rectal administration can cause a 10 to 20% reduction in bioavailability compared to oral forms.[54] Additionally, the acetaminophen test is often used for investigations of delayed gastric emptying and intestinal absorption in critically ill patients.[55] Berger et al have reported impaired enteral absorption of acetaminophen on day one after cardiac surgery in adults managed at the ICU. The authors reported a 60% decline in AUC compared with healthy subjects and attributed this to pyloric closure as post-pyloric delivery did not show a decrease in AUC. However, the absorption capacity was similar to healthy subjects on day three, and absorption was observed to be negatively related to opiate dose.[56] Ariano et al[57] have reported an enteral bioavailability of 75% in critically ill patients, compared with 88% in healthy subjects.[57] Additionally, Kleiber et al[58] have reported the chance of reaching therapeutic drug concentration after oral administration with a 15 mg/kg dose is 2.5 times less likely compared with IV administration in pediatrics, but increased oral doses carried a risk of overdosing.[58] Critically ill patients could be given acetaminophen enterally without dose adjustments, but parenteral administration is preferred if delayed gastric emptying is expected. The evidence is considered very low since only observational studies were found.

### Metformin

Metformin is a widely used drug for the treatment of diabetes mellitus type 2. In healthy adults, bioavailability is typically 50 to 60% and it starts working within days.[59] Given how common it is, practitioners are likely to see patients in the ICU who use metformin. Metformin must often be held in critically ill patients to prevent acute kidney injury, but it may be seen again after patients are more stable.[60] Mojtahedzadeh et al have compared oral metformin monotherapy, IV insulin monotherapy, and metformin/insulin combination therapy for glycemic control in critically ill patients. The authors reported that both AUC and Cmax after monotherapy with metformin were lower than seen in healthy subjects; however, no significant difference in glycemic control was observed between the groups.[61] Based on this, patients in the ICU could be treated orally with metformin with results similar to those in non-critically ill patients.

### Tacrolimus

Tacrolimus is an immunosuppressant agent commonly used after organ transplantation. It has a narrow therapeutic margin and requires therapeutic drug monitoring. One study evaluating tacrolimus in transplant patients showed no difference in dose requirements when patients received continuous tube feeding compared to when feeds were held.[62] Given this, oral administration may be appropriate with no required dosage increase. The evidence is considered very low as only one small observational study was found. In addition, tacrolimus could be administered intravenously in addition to reports of sublingual administration.[63]

### Aminophylline

Aminophylline is a bronchodilator that when administered, it releases theophylline in the body, the active component (theophylline: aminophylline dose conversion is 0.8:1).[64] One prospective study found near 100% bioavailability in critically ill patients that was not affected by three different enteral feed formulas.[65] It is possible that in this population enteral administration could be used without dosage adjustment.

### Thyroxine

Thyroxine was investigated in an interventional study in solid organ donors. The authors have found that thyroxine appears to be well absorbed in this population.[66] Given the moderate level evidence, unadjusted doses of thyroxine may be appropriate for solid organ donors in the ICU.

### Oseltamivir

Oseltamivir is an antiviral medication commonly used to treat influenza infections. Three studies evaluating oseltamivir in critically ill patients found that absorption did not appear to be altered in critically ill patients.[67-69] Doses ranged from 75 mg BID to 150 mg BID and were administered through feeding tubes by dissolving the capsule contents in water.

### Potassium Chloride

Potassium is typically well absorbed after enteral administration in healthy patients. One study evaluated the effect of parenteral and enteral administration of potassium chloride in critically ill patients and found no difference in mean response after IV or enteral administration.[70] While the evidence is very low, enteral administration of potassium chloride with monitoring of therapy is appropriate.

## Factors Altering Drug Absorption

Critically ill patients are at risk of altered drug absorption due to multiple factors. First, these patients have several

pathophysiological alterations from critical illnesses which may affect the drug absorption and put the patients at a higher risk for therapy failure. Despite this, there are few studies evaluating drug absorption in critically ill patients and use of drugs in off-label regimens is not uncommon.[3,71] Second, critically ill patients are exposed to various interventions due to their critical illness such as tube feeding, which also may alter drug absorption.[71] The following section will discuss some factors in critically ill patients that may affect drug absorption.

### Perfusion Alterations

Hypotension and shock states are two common conditions observed in critically ill patients. As a compensatory mechanism, these conditions increase the blood flow toward vital organs which will automatically decrease the perfusion to remaining organs, such as the GI tract. These perfusion alterations in the GI tract may reduce the systemic absorption of drugs from the intestines.[71]

### Gastrointestinal Alterations

GI alterations in critically ill patients may affect the drug PK in several ways. These patients often suffer from intestinal atrophy, motility dysfunction, delayed gastric emptying, and pH alterations which may affect drug absorption.

Surgeries, nutrition intolerance and hemodynamic instability are some reasons why critically ill patients may be withheld oral or enteral nutrition. A lack of enteral nutrition can affect GI maintenance and proliferation since these processes are dependent on and stimulated by food in the gut. Some studies have also reported that starvation leads to intestinal atrophy and surface area changes due to decreased villus height and crypt depth.[71] This reduction in surface areas can lead to a decrease in drug absorption.

Critically ill patients often have motility dysfunction of the stomach and small intestine due to surgery, immobility or administration of opioids for analgesia.[3,71] Capdevila et al[72] have reported that approximately 50% of all patients managed at the ICU suffer from pain during their hospitalization and are in need for analgesia.[72] Motility dysfunction leads to impaired absorption capacity and this state is generally more pronounced in the acute phase of critical illness making the enteral route of administration untrustworthy. Hypomotility improves when the patients recover from their illnesses.[3,71] On the other hand, some GI conditions may increase the absorption capacity of different drugs. Two cases have been found where the bioavailability of orally administered vancomycin was increased, when vancomycin is normally poorly absorbed from the gut. All patients suffered from colitis and were managed at the ICU.[73,74]

Another common GI alteration in critically ill patients is delayed gastric emptying. Nguyen et al[75] have reported that up to 60% of all patients managed in the ICU suffer from delayed gastric emptying.[75] Since most drugs are absorbed through the small intestines, delayed gastric emptying will delay the time to peak concentration of the drug, and thereby the onset of action.[1] Ways to measure gastric emptying include the acetaminophen test and scintigraphy, the latter being the gold-standard.[55,76]

Lastly, pH alterations in the GI tract are also common in this patient population. Proton-pump inhibitors and H2-antagonists are routinely used in critically ill patients for stress ulcer prophylaxis.[43] These medications will elevate gastric pH thereby affecting the absorption of drugs that require an acidic environment to be absorbed.[3]

### Enteral Feeding

Enteral feeding tubes enable nutrition and drug delivery to patients that are mechanically ventilated or unable to swallow. However, there are some complications associated with enteral feeding and drug administration via feeding tubes. First, drugs can adhere to the plastic of the feeding tube resulting in reduced drug delivery and thereby drug absorption. Second, enteral feed formulas may alter pH in the GI tract and affect the bioavailability of different drugs. Another potential risk is that some enteral feed ingredients can bind directly to drugs and reduce their absorption.[1] Phenytoin and ciprofloxacin are examples of those drugs whose bioavailability is affected when administered via enteral feeding tube. In addition, the extent of the interaction may also depend on the composition of the enteral formula.

### Pharmacokinetic Changes

The bioavailability of drugs is a function of GI absorption, hepatic first pass metabolism, and GI metabolism, if any. Therefore, drugs that undergo extensive first pass metabolism may have increased systemic exposure if hepatic function is impaired, as is often seen in critically ill patients. These patients can also experience overall reduced drug clearance. This reduced clearance enhances systemic exposure despite altered drug absorption. Furthermore, critically ill patients are often treated with multiple medications, potentially resulting in drug interactions that could contribute to altered bioavailabilities.

## Limitations

This review has several limitations. The studies included in this review are of varying quality. Each was rated based on the GRADE criteria, as mentioned above. Observational studies, interventional studies, and case reports were included in this review. Observational studies carry more bias than interventional studies, and case reports are considered to be the lowest quality evidence. While recommendations were able to be made for some drugs given the moderate level of evidence, other drugs did not have enough evidence to make clear recommendations. For drugs with low or very low evidence,

**Table 1.** Summary of Recommendations in Critically Ill Patients Based on Available Evidence.

| Drug | Suggested Measures | Suggestion Basis |
|---|---|---|
| Antiepileptic Drugs | | |
| Phenytoin | •Oral administration: Hold TF for 1-2 hours before and after drug administration<br>•TDM is important<br>•Parenteral formulation is available | Moderate evidence<br>•Four studies: Three observational; one interventional<br>Four case reports<br>•Three studies had sample sizes ≥20 participants[6-10,78,79] |
| Valproic acid | •Oral administration: No dose increase required<br>•Parenteral formulation is available | Very low evidence<br>•One observational study<br>•Sample size ≥20 participants[12] |
| Levetiracetam | •Oral administration: Consider using higher doses<br>•Parenteral formulation is available | Very low evidence<br>•One observational study<br>•Sample size ≥20 participants[12] |
| Carbamazepine | •Oral administration of suspension in pediatrics: No dose increase required<br>•Avoid co-administration of TF if the effect is desired to come quickly | Very low evidence<br>•One observational study<br>•Sample size ≤20 participants[15] |
| Phenobarbital | •Oral administration after switch from parenteral route in neonates: Higher doses might be required<br>•TDM is important •Parenteral formulation is available | Very low evidence<br>•Two observational studies<br>•Both studies had sample sizes ≥20 participants[13,14] |
| Antimicrobials | | |
| Ciprofloxacin | •Unfunctional GI tract or unsure: Use parenteral administration<br>•functional GI tract: Oral administration: Consider higher doses<br>•Parenteral formulation is available | Moderate evidence<br>•Six studies: Five observational, one interventional<br>•One study had a sample size ≥2018-21,80,81 |
| Moxifloxacin | •Prefer parenteral administration | Very low evidence<br>•Two observational studies<br>•One study had a sample size ≥20[22,23] |
| Cefroxadine | •Oral administration: Consider higher doses | Very low evidence<br>•One observational study<br>•Sample size ≥20 participants[27] |
| Gatifloxacin | •Oral administration: Highly variable; consider injectable formulation | Very low evidence<br>•One observational study<br>•Sample size ≤20 participants[25] |
| Levofloxacin | •Oral administration: No dose increase required | Very low evidence<br>•One observational study<br>•Sample size ≤20 participants[24] |
| Trimetoprim-sulfamethoxazole | •Oral administration: No dose increase required | Very low evidence<br>•One observational study<br>•Sample size ≤20 participants[28] |
| Antifungals | | |
| Fluconazole | •Oral administration: Consider higher doses | Moderate evidence<br>•Six studies: Four observational, two interventional<br>•One study had sample size ≥20 participants[30,32,34-37] |
| Posaconazole | •Parenteral administration preferred<br>•If oral administration used, avoidance of PPI therapy and holding TF may be required | Moderate evidence<br>•Adults; two studies: One observational, one interventional<br>•Pediatrics; one case report<br>•One study had sample size ≥20 participants[38,39,82] |
| Itraconazole | •Oral administration: Consider higher doses avoid co-administration of PPI | Very low evidence<br>•One case report[40] |

*(continued)*

**Table 1.** (continued)

| Drug | Suggested Measures | Suggestion Basis |
|---|---|---|
| Antiepileptic Drugs | | |
| Voriconazole | •Oral administration: Consider higher doses; continuous TF may be appropriate<br>•TDM is available | Very low evidence<br>•One observational study<br>•Sample size ≤20 participants[41] |
| Gastric acid suppressing medications | | |
| Lansoprazole | •Acid suppression is unaffected<br>•Oral administration: No dose increase required | Moderate evidence<br>•One interventional study<br>•Sample size ≤20 participants[42] |
| Pirenzepine | •Acid suppression is unaffected<br>•Oral administration: No dose increase required | Very low evidence<br>•One observational study<br>•Sample size ≥20 participants[43] |
| Ranitidine | •Oral administration: No dose increase required | Moderate evidence<br>•One interventional study<br>•Sample sizes ≤20 participants[44] |
| Cardiovascular medications | | |
| Verapamil | •Bioavailability appeared to be slightly reduced<br>•Oral administration: No dose increase required | Very low evidence<br>•One observational study<br>•Sample size ≤20 participants[45] |
| Acetylsalicylic acid | •Antiplatelet effect is unaffected<br>•Oral administration: No dose increase required | Moderate evidence<br>•One interventional study<br>•Sample size ≥20 participants[46] |
| Clopidogrel | •Stable patients: Oral administration: No dose increase required<br>•Unstable patients after CPR and acute PCI: Oral administration: antiplatelet effect might be impaired | Very low evidence<br>•One observational study<br>•Sample size ≤20 participants[47] |
| Clonidine | •Delayed absorption in postoperative cardiac pediatric patients<br>•Oral administration:no dose increase required | Very low evidence<br>•One observational study<br>•Sample size ≤20 participants[48] |
| Other medications | | |
| Melatonin | •Oral administration: Start dosing at low doses and titrate as needed | Moderate evidence<br>•Four interventional studies<br>•Two studies had sample sizes ≥2049-52 |
| Tacrolimus | •Oral administration in transplant patients: No dose increase required; continuous TF may be used •TDM is available | Very low evidence<br>•One observational study<br>•Sample size ≤20 participants[62] |
| Fludrocortisone | •Stable patients: Oral administration: No dose increase required<br>•Unstable patients: Consider use of an alternate agent | Very low evidence<br>•One observational study<br>•Sample size ≥20 participants[53] |
| Acetaminophen | •Adults: Oral administration: No dose increase required; Parenteral administration preferred if delayed gastric emptying expected (e.g., post-operative patients)<br>•Pediatrics: No dose increase required; Parenteral administration preferred if delayed gastric emptying expected | Very low evidence<br>•Adults; two observational studies<br>•Pediatrics; one observational study<br>•One study had sample size ≥20 participants[56-58] |
| Metformin | •Glycemic control is unaffected<br>•Oral administration: No dose increase required | Moderate evidence<br>•One interventional study<br>•Sample size ≥20 participants[61] |
| Aminophylline | •Oral administration: No dose increase required | Very low evidence<br>•One observational study<br>•Sample size ≤20 participants[65] |
| Thyroxine (T4) | •Oral administration: No dose increase required | Moderate evidence<br>•One interventional study<br>•Sample size ≥20 participants[66] |

*(continued)*

**Table 1.** (continued)

| Drug | Suggested Measures | Suggestion Basis |
|---|---|---|
| Antiepileptic Drugs | | |
| Oseltamivir | •Oral administration: No dose increase required | Very low evidence<br>•Two observational studies; one case report<br>•All studies had sample sizes ≤20 participants[67-69] |
| Potassium chloride | •Oral administration: No dose increase required | Very low evidence<br>•One observational study<br>•Sample size ≥20 participants[70] |

BID, twice a day; CPR, cardiopulmonary resuscitation; F, bioavailability; PCI, percutaneous coronary intervention; PO, per oral; TDM, therapeutic drug monitoring; TF, tube feeding.

clinicians should evaluate the risks and benefits of using the drug in the context of their patients. The number of participants is also an important consideration when discussing the strength of a study. Many included studies had small sample sizes, and a limitation with small sample sizes is that the study may not have sufficient power to detect differences between groups. Small studies may also result in false-positive results leading to inaccurate conclusions; Hachshaw et al had reported that studies performed on <20 participants are likely too small for all investigations.[77]

For several agents included in this review there have been reference ranges established for therapeutic drug concentrations. These exist to try and maximize benefit while minimizing known risk of harm for drugs with narrow therapeutic range. TDM can be a very useful tool when assessing these medications and possible drug interactions, but it cannot be used alone. Drug levels must always be interpreted in the clinical context of each patient, for example whether a seizure has been terminated or not, and a drug level outside the reference range may not always require action from the prescriber.

There are several factors that limit the generalizability of the included studies. First, critically ill patients are a heterogeneous group in terms of etiology, age, and disease severity. Second, given the populations studied, it is difficult to apply the evidence to patients in critical care, especially if they would not meet the inclusion criteria for the relevant study. Lastly, many studies were done in a small population or are low-quality evidence. While the evidence around drug absorption in critical care is limited, we may less likely get large-scale studies given the population of interest and the ability to critically evaluate the applicability of a study to each patient.

## Conclusion and Suggested Recommendations

Critically ill patients suffer from several pathophysiological alterations and medical interventions due to critical illness which may affect enteral absorption of various drugs. Despite known concerns around drug absorption in ICU patients, some drugs are still given enterally, or in unadjusted doses, and may put patients at a higher risk of therapy failure. To manage altered drug absorption in critically ill patients, some adjustments may be necessary. This review discussed the available evidence for drug absorption and provides some guidance for managing enteral drug administration in patients treated in the ICU. A summary of the suggested recommendations are depicted in Table 1.

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### Supplemental Material

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