

CRITICAL CARE PHARMACY HANDBOOK 2013



**Clinical Pharmacy Working Committee
(Critical Care Subspecialty)
Pharmaceutical Services Division,
Ministry of Health**

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MESSAGE



The discipline of critical care pharmacy practice evolved over the years to become an essential component of the multidisciplinary team in the intensive care unit (ICU). Pharmacists are required to work closely with other healthcare providers in promoting health, preventing disease complications, as well as to assess and monitor medication use assuring that drug therapy regimens are safe and effective.

A description of pharmacy services and pharmacist activities in a critical care setting will assist practitioners and administrators in establishing or advancing this specialized pharmacy services. This handbook elaborates the role of pharmacists and pharmacy services in the care of the critically ill patients. It presents information on the fundamentals of critical care practice from a pharmacist's perspective. The availability of this handbook will guide the critical care pharmacists in their practice and help in the expansion of quality critical care pharmacy services throughout Ministry of Health (MOH) facilities.

I would like to commend the Clinical Pharmacy Working Committee (Critical Care subspecialty), Pharmaceutical Services Division, Ministry of Health for their contribution and commitment to the publication of this handbook.

Thank you.

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CHAPTER 1

1.1 THE ROLE OF PHARMACIST IN CRITICAL CARE

The discipline of critical care pharmacy practice evolved over the past 25 years to become an essential component of the multidisciplinary team in the intensive care unit (ICU). In Malaysia, Clinical Pharmacy Working Committee (Critical Care Pharmacy Subspecialty), Pharmaceutical Services Division (PSD), Ministry of Health (MOH) Malaysia has been established in 2006 to assist all pharmacists in the critical care setting in providing the best care to critically ill patients. Training centres in critical care pharmacy has also been established by PSD, MOH for short term attachment programme to train new pharmacists in critical care setting in ensuring the best pharmaceutical care provided by pharmacists.

Pharmacists established clinical practices consisting of therapeutic drug monitoring, nutrition support and participation in patient care rounds. Pharmacists also developed efficient and safe drug delivery systems with the evolution of critical care pharmacy satellites and other innovative programs.

1.2 CRITICAL CARE PHARMACIST ACTIVITIES

- Participates in ward rounds as a member of the multidisciplinary critical care team to provide pharmacotherapeutic management for all ICU patients
- Performs medication history taking and medication reconciliation reviews to determine which maintenance drugs should be continued during the acute illness
- Prospectively evaluates all drug therapy for appropriate indications, dosage, drug interactions and drug allergies
- Monitors the patient's pharmacotherapeutic regimen for effectiveness and adverse drug reactions (ADR) and intervenes as needed
- Evaluates all orders for parenteral nutrition and recommends modifications as indicated to optimize the nutritional regimen
- Identifies ADR and assists in their management and prevention and develops process improvements to reduce drug errors
- Uses the medical record as one means to communicate with other health care professionals and to document specific pharmacotherapeutic recommendations
- Provides pharmacokinetic monitoring when a targeted drug is prescribed
- Provides drug information and intravenous compatibility information to the ICU team
- Maintains current tertiary drug references
- Provides drug therapy related education to ICU team members
- Documents clinical activities that include general pharmacotherapeutic monitoring, pharmacokinetic monitoring, ADEs, education and other patient care activities

- Acts as a liaison between pharmacy, nursing and the medical staff to educate health professionals regarding current drug-related procedures, policies, guidelines and pathways
- Contributes to the hospital newsletters and drug monographs on issues related to drug use in the ICU
- Implements and maintains departmental policies and procedures related to safe and effective use of drugs in the ICU
- Provides consultation to hospital committees such as Pharmacy and Therapeutics, when critical care pharmacotherapy issues are discussed
- Identifies how drug costs may be minimized through appropriate use of drugs in the ICU and through implementation of cost-containment measures
- Participates in quality assurance programs to enhance pharmaceutical care
- Maintains knowledge of current primary references pertinent to critical care pharmacotherapy
- Participates in training pharmacy students, residents and fellows through experiential critical care rotations, where applicable
- Coordinates the development and implementation of drug therapy protocols or critical care pathways to maximize benefits of drug therapy
- Participates in research design and data analysis where applicable
- Contributes to the pharmacy and medical literature for examples case reports, pharmacokinetic and pharmacoeconomic reports

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CHAPTER 2

2.1 DEEP VEIN THROMBOSIS PROPHYLAXIS

2.1.1 Introduction

A vast number of critically ill patients have at least one risk factor for venous thromboembolism (VTE) and with other additional specific risk factors such as respiratory & cardiovascular failures, obesity, smoker, surgery, trauma, malignancy, elderly, immobility and having central venous catheters.

VTE which defined as an event due to thrombus formation is manifested as deep vein thrombosis (DVT) or pulmonary embolism (PE). VTE is one of the most common and detrimental complication in these patients, attributing to about 10% of hospital mortality. Therefore, patients' risk of developing VTE should be assessed (e.g. high, moderate to low risk) and appropriate pharmacological & non-pharmacological management should be commenced.

2.1.2 Definitions⁵

DVT is defined as a clot that occurs in the deep veins of the extremities. Further sub classifications include symptomatic versus asymptomatic and proximal (above the knee) versus distal (below the knee).

PE is defined as being a clot usually originating from a DVT that travels to the pulmonary vasculature where it becomes an embolism and thereby impedes gas exchange distal to embolism.

2.1.3 Indications for Prophylaxis

All adult inpatients will be assessed for their risk of VTE that include the background history and acute or sub acute precipitating factors which are shown in **Table 2**. Clinicians will need to use their own judgment in addition to the guideline to determine the best method of reducing the risk of VTE in each individual patient. It is the combined responsibility of the physician and other healthcare staff including the clinical pharmacist and nursing staff to ensure all patients at risk for VTE have received appropriate prophylaxis when needed.¹

a. Low-risk groups ¹

- Patients with minor trauma or minor medical illness at any age, in the absence of thrombophilia, previous DVT or PE.
- Patients undergoing minor surgery (duration under 30 minutes) at any age, in the absence of other risk factors.
- Patients undergoing major surgery (duration over 30 minutes) who are aged under 40 years and have no additional risk factors.

b. Moderate risk groups ¹

- Patients undergoing major general, urological, gynaecological, cardiothoracic, vascular, or neurological surgery who are aged > 39 years or with other risk factors
- Patients immobilised with acute medical illness
- Major trauma

- Minor surgery or trauma or illness in patients with previous deep vein thrombosis, pulmonary embolism, or thrombophilia.

Table 2: Venous Thromboembolism – Risk Factors ⁶

Background Factors	Precipitating Factors
<ul style="list-style-type: none"> • Age > 40 years • Marked obesity (BMI >30) • Immobility / bed rest / pharmacological paralysis / sedation • Pregnancy / Puerperium • Stroke / spinal cord injury • High dose estrogens • Previous DVT or PE • Thrombophilia <ul style="list-style-type: none"> - Deficiency of antithrombin, protein-C or protein-S - activated protein-C resistance - antiphospholipid antibody or • Lupus anticoagulant 	<ul style="list-style-type: none"> • Trauma or surgery, especially of pelvis, hip, lower limb • Malignancy especially pelvic, abdominal, metastatic • Cardiac / respiratory failure • Recent myocardial infarction • Paralysis of lower limb(s) • Severe infection • Inflammatory bowel disease • Nephrotic syndrome • Polycythemia • Paraproteinemia • Paroxysmal nocturnal hemoglobinurea • Bechet's disease • Burns • Mechanical ventilator

c. High-risk groups¹

- Fracture or major orthopaedic surgery of pelvis, hip, or lower limb.
- Major pelvic or abdominal surgery for cancer.
- Major surgery, trauma, or illness in patients with previous deep vein thrombosis, pulmonary embolism, or thrombophilia.
- Lower limb paralysis (for example, hemiplegic stroke, paraplegia).
- Critical lower limb ischaemia or major lower limb amputation.
- Spine fracture

2.1.4 Methods of Prophylaxis

There are two method of prophylaxis of DVT, which are¹:

- a. Pharmacological methods :
- Standard heparin (usually in low dosage)
 - Low molecular weight heparins
 - Oral anticoagulant such as warfarin
 - Aspirin

**Pharmacological prophylaxis should not be initiated in patients with high risk factors of bleeding, unless the risk of VTE outweighs the risk of bleeding.*

- b. Mechanical methods - increase venous outflow and/or reduce stasis within the leg veins :
- Graduated compression stockings (GCS)
 - Intermittent pneumatic compression (IPC) devices
 - Venous foot pump (VFP)

Table 2.1: Recommended DVT prophylaxis for surgical procedures and medical conditions ⁸

Surgery/Condition	Recommended Prophylaxis	Comments
General Surgery Low risk: minor procedures, <40 years old, no additional risks	None	Early ambulation
General Surgery Moderate risk: Minor procedure but with risk factor, nonmajor surgery age 40-60 with no risks, or major surgery <40 years with no risks	Heparin, LMWH, ES, or IPC	Heparin 5000 – 7500 iu bd OR LMWH (daily dose according to manufacturer) with IPC or ES. * LMWH and heparin has comparable efficacy for DVT prophylaxis. ^{8,9} The clinical advantages of LMWH over LDUH is its once-daily administration and the lower risk of heparin-induced thrombocytopenia (HIT), BUT LMWH is more costly. ¹⁰
General Surgery High risk: Non-major surgery over age 60 or over age 40 with risks.	Heparin , LMWH	Heparin 5000 – 7500 iu tds OR LMWH (daily dose according to manufacturer) *In high-risk general surgery patients, higher doses of LMWH provide greater protection than lower doses. ³
General Surgery Very high risk: Major surgery over age 40 plus prior VTE, cancer or hypercoagulable state	LMWH combined with ES or IPC	LMWH (daily dose according to manufacturer) *May consider post discharge LMWH or perioperative warfarin
Elective Hip Replacement	LMWH or warfarin	May combine with ES or IPC; start LMWH 12 hours before surgery, 12-24 hours after surgery, or 4-6 hours after surgery at half the dose for initial dose for at least 10 days. Start warfarin preoperatively or immediately after surgery, target INR 2.0-3.0. Extended prophylaxis is recommended for up to 28 to 35 days after surgery. ⁸
Elective Knee Replacement	LMWH or warfarin	Both LMWH and warfarin resulted in significantly fewer proximal DVTs compared with LDUH or IPC (p<0.006 for each comparison). ¹¹ Pooled data from 5 trials that directly compared LMWH with warfarin showed rates of proximal DVT of 3.4% and 4.8%, respectively. ⁸
Hip Fracture Surgery	LMWH or warfarin	
Neurosurgery	IPC, LDUH or LMWH	Mechanical method is preferred, however if heparin is to be initiated, it shall be administered post 48-72hrs of the surgery.
Trauma	LMWH with ES or IPC	If high risk of bleeding, may use ES and/or IPC alone.
Acute Spinal Cord Injury	LMWH	Continue LMWH during rehabilitation or convert to warfarin (target INR 2.5).

Medication Class	Unfractionated heparin	Low molecular weight heparin		Indirect Factor Xa Inhibitor
Medication	Heparin	Enoxaparin	Tinzaparin ¹⁷	Fondaparinux
Duration	5 days OR until hospital discharge if this is earlier than 5 days.	<p>Surgical case¹⁴ 7-10 days or longer if there is a risk of DVT and until patient ambulatory.</p> <p>Medical case¹⁴ 6 – 14 days</p>	7-10 days	<p>Orthopedic and abdominal surgery¹⁵ 5 to 9 days after surgery</p> <p>In patient undergoing hip fracture surgery 9 to 24 days (consider the risk)</p> <p>Medical patients with DVT risk 6 to 14 days</p>
Monitoring	<p>Platelet count, full blood count.</p> <p>Recommendation: the platelet count is monitored in patients receiving heparin for more than five days, and that heparin is stopped immediately if thrombocytopenia occurs.</p>	<p>Platelet count, full blood count</p> <p>Risk of thrombocytopenia (happen between 5th and the 21st day following the beginning of enoxaparin therapy). If significant decrease (30 to 50% of initial count), the treatment should be discontinued and switch to other alternative.</p>	Platelet count, full blood count	<p>Full blood count, serum creatinine, and occult blood testing of stools are recommended. PT and APTT are insensitive measures.¹⁶</p>
Contraindication¹⁶	<p>- bleeding disorders</p> <p>- a history of allergy either to enoxaparin, heparin or other low molecular weight heparin ¹</p>			<p>- Hypersensitivity to fondaparinux</p> <p>- severe renal impairment (CLCr <30 mL/min)</p> <p>- body weight <50 kg (prophylaxis)</p> <p>- active major bleeding</p> <p>- thrombocytopenia</p> <p>- bacterial endocarditis</p>
Precaution¹⁶	<p>Hypersensitivity to drug.</p> <p>May cause thrombocytopenia. Discontinue and consider alternative if platelet are < 100,000/mm³ or /and thrombosis develop.</p>	<p>Recent or anticipated neuraxial anesthesia (epidural or spinal anesthesia) are at risk of spinal or epidural hematoma and subsequent paralysis.</p>	<p>Recent or anticipated neuraxial anesthesia (epidural or spinal anesthesia) are at risk of spinal or epidural hematoma and subsequent paralysis. Consider risk versus benefit.</p>	<p>Same with enoxaparin.</p> <p>Not to be use interchangeable (unit-for-unit) with heparin, LMWH or heparinoids.</p>

Medication Class	Unfractionated heparin	Low molecular weight heparin		Indirect Factor Xa Inhibitor
Medication	Heparin	Enoxaparin	Tinzaparin ¹⁷	Fondaparinux
	In neonate suggest to use preservative free as some preparation contained large amount benzyl alcohol (> 100 mg/kg/day) that can cause fatal toxicity (gaspings syndrome).	Consider risk versus benefit. Risk of thrombocytopenia. Caution in patient with renal failure; dosage adjustment need for CrCl < 30mL/min.	Risk of thrombocytopenia.	Use caution in patient with moderate renal dysfunction. Patient with severe hepatic impairment with elevation in prothrombin time.
Side effect	Thrombocytopenia occurs in about 3-4% of patients given prophylactic heparin. Allergic reactions (including skin necrosis), raised serum transaminase concentrations, and osteoporosis with long term use (especially in pregnancy) ¹	1 to 10% risk¹⁶ CNS: fever, confusion, pain Dermatology: erythema, bruising, hematoma at site of injection GI : nausea, diarrhea Hematologic : hemorrhage, thrombocytopenia Hepatic : ALT/ALP increase		> 10% - Fever, nausea, anemia ¹⁶ 1- 10% Edema, hypotension, insomnia, dizziness, headache, confusion, rash, purpura, bullous eruption, hypokalemia, constipation, vomiting, diarrhea, dyspepsia, moderate thrombocytopenia, increase in liver enzyme. ¹⁶
Drug interaction	Increased effect/toxicity if use with anticoagulant, thrombolytics, dextran and drug affect platelet function (e.g. aspirin, NSAIDs, dipyridamole, ticlopidine, clopidogrel), cephalosporins which contain MTT (methylthiotetrazole) chain (e.g. cefoperazone high dose >6g) and parenteral penicillins (may inhibit platelet aggregation). ¹⁶ Decreased effect if use with Nitroglycerin (IV) that may occur in high dosages. ¹⁶	Increased effect/toxicity if use with anticoagulant, thrombolytics, dextran and drug affect platelet function (e.g. aspirin, NSAIDs, dipyridamole, ticlopidine, clopidogrel), cephalosporins which contain MTT chain and parenteral penicillins (may inhibit platelet aggregation). ¹⁶		Increased effect/toxicity if use with anticoagulants, antiplatelet agents, drotrecogin alfa, NSAIDs, salicylates and thrombolytic agents. ¹⁶
Special instruction	There is an increased risk of wound haematomas, which can be minimised by avoiding injections close to wounds. ¹		All disposable tinzaparin syringes contain an air bubble which does not have to be pressed out before administering the injection.	To avoid loss of medicinal product when using prefill syringe do not expel the air bubble from the syringe before the injection. ¹⁵

2.2 STRESS-RELATED MUCOSAL DISEASE

2.2.1 Introduction

Stress-related mucosal disease (SRMD) is an acute condition which erosion of the gastric mucosa occur secondary to a physiologic stress.¹ SRMD encompasses with 2 types of mucosal lesions which are stress-related injury, (diffuse, superficial mucosal damage) and discrete stress ulcers (deep focal lesions that penetrate the submucosa).⁹ Clinical trials have estimated gastrointestinal (GI) bleeding in 3% to 6% of intensive care unit (ICU) patients.

The etiology of SRMD is multifactorial and complex. Patients with head injury or burns are at the highest risk of SRMD due to gastric acid secretion resulting from vagal stimulation. Other critically ill patients appear to develop SRMD as a result of diminished mucosal defenses and hypoperfusion.⁴ The longer the gastric pH remains below 4 the greater the risk of hemorrhage. There is a strong relationship between duration of mechanical ventilation, duration of intensive care stay and incidence of ulceration.⁵

In critically ill patients requiring mechanical ventilation and use of a nasogastric tube, acute GI bleeding may become clinically evident, with a bloody gastric aspirate or the appearance of coffee ground materials in the gastric aspirate. Hematemesis or melena may be the first sign of bleeding in patient without nasogastric tube. Unexplained hypotension or a decrease greater than 2g/dL in hemoglobin level should prompt evaluation for bleeding in the upper GI tract.

2.2.2 Prevention Strategies

- a. **High risk patient**^{3,13} – *all patients to receive prophylaxis*
 - Mechanical ventilation > 48 hours
 - Coagulopathy
 - History of previous GI hemorrhage
 - Current outpatient PUD treatment or prophylaxis
 - Central nervous system (CNS) injury (subarachnoid hemorrhage (SAH) /cardiovascular attack (CVA) – hemorrhagic or ischemic)
 - Sepsis with or without organ dysfunction
 - Vasopressor/Inotropic prescription
- b. **Moderate risk patient** – *consider prophylaxis*
 - Chronic NSAID or aspirin use
 - High dose prolonged steroid treatment (>250mg/day of hydrocortisone or equivalent)
 - ICU stay > 10 days
- c. **Low risk patient or tolerating per oral diet/Full gastric enteral feeds**
 - no prophylaxis or discontinue prophylaxis
- **Discontinuation**

Once patient is tolerated to full feeding and has no more risk factors, prophylactic therapy may be discontinued. This is important to avoid

unnecessary drug interaction, adverse effects (pneumonia) and increased cost.

- **Safety**

Unnecessary prophylactic stress ulcer therapy might lead to severe complication and the most common complication is pneumonia.¹⁰ The hypothesis is based upon the concept that higher pH relates to overgrowth of gastric microbes and leads to upper tracheal colonization. This concept partnered with microaspiration of intubated patients lying supine may increase the nosocomial pneumonia rate. The ability to reliably maintain a pH < 4 will decrease the rate of pneumonia. Furthermore, gastric acid is an important defense against the acquisition of *C. difficile* spores, and the use of acid suppressive agent has been associated with *C. difficile* infections.⁸

2.2.3 Stress Ulcers Prophylaxis in Patient With Nasogastric Feeding

The administration of gastric nutrition reduces, but does not eliminate, the risk of GI hemorrhage. Any patient predicted to be mechanically ventilated > 48 hours and without a contraindication to gastric enteral nutrition, is encouraged to have nasogastric nutrition initiated within 72 hours of admission when a nasoenteric tube is in-situ.

2.2.4 Prophylaxis Agents for SRMD

Many agents are available for the use of patients who are at risk for SRMD. The agents include histamine type 2 receptor antagonists (H₂RAs), proton pump inhibitors (PPIs), sucralfate, antacids, and prostaglandin analogs (Table 2.3).

Clinical trials reveal that H₂RAs are the most widely used first-line agents. Although the bioavailability of oral H₂RA more excellent compared to intravenous, the evidence of efficacy have been shown in intravenous administration.³

Multiple studies have examined the effects of PPIs in ICU patients, but all have been small and many measured intermediate endpoints.⁷ Furthermore, although PPIs never been demonstrate to reduce the rate of bleeding from stress ulceration (as compared to placebo), these agents are commonly prescribed for the prevention of this condition. A recent meta-analysis did not find strong evidence that PPIs were different from H₂RA in term of stress-related GI bleeding prophylaxis, pneumonia and mortality among ICU patients.⁸

Sucralfate is not recommended for prophylaxis of stress ulcer as it is inferior to H₂RA and can clog enteral feeding tubes.³ The largest randomized controlled trial to date involved 1200 mechanically ventilated patients has determined that ranitidine was significantly better than sucralfate in reducing clinically important SRMD bleeding (odds ratio [OR]: 0.44; 95% confidence interval [CI]: 0.21-0.92).⁷

Antacids also are not used to prevent of stress ulcers because of large and frequent dosing (30-60 mL, every 1 - 4 hours), constipation, diarrhea, electrolytes abnormalities, fluctuating gastric pH and can clog enteral feeding tubes.³

Table 2.3: Drugs to prevent SRMD¹²

Drug Classes	Histamine Type 2 Receptor Antagonists	Proton Pump Inhibitors		
Drugs	Ranitidine	Esomeprazole	Omeprazole	Pantoprazole
Dosage	Adult Normal Dose Oral : 150 mg bd IV : 50 mg Q8H Dose Adjustment CrCl < 50 ml/min Oral : 150 mg od IV : 50 mg every 18-24 hours; adjust dose cautiously if needed Hemodialysis: Adjust dosing schedule so that dose coincides with the end of hemodialysis.	40 mg daily (IV, nasogastric tube, PO) <i>* Esomeprazole is the S-isomer of omeprazole</i>	20-40 mg daily (PO, nasogastric/ jejunal, duodenal tube)	40 mg daily (IV, nasogastric tube, PO)
Monitoring	Liver enzyme, serum creatinine, sign and symptoms of PUD, occult blood with GI bleeding, renal function.	Liver enzyme		
Contraindication	Hypersensitivity to the component of the formulation			
Precaution	Use in caution in patient with hepatic impairment and renal impairment	Severe liver dysfunction may require dose adjustment	Bioavailability may increase in the elderly, Asian population, and with hepatic dysfunction	IV preparation contain edentate sodium (EDTA); use caution in patient who are at risk for zinc deficiency if other EDTA containing solution are co-administered
Adverse Reactions	Arrhythmias, dizziness, headache, mental confusion, rash, anemia, thrombocytopenia, leucopenia, hepatic failure and pneumonia	Headache, nausea, flatulence, diarrhea, constipation, abdominal pain, hypertension, hyponatremia, pneumonia	Headache, dizziness, diarrhea, abdominal pain, pneumonia	Headache, diarrhea, flatulence, abdominal pain, abnormal liver function test

Drug Classes	Histamine Type 2 Receptor Antagonists	Proton Pump Inhibitors		
Drugs	Ranitidine	Esomeprazole	Omeprazole	Pantoprazole
Drug Interaction	<p>CYP450 effect</p> <p>Increase effect: Phenytoin, Midazolam</p> <p>Decrease effect: Atazanavir, Alprazolam, Ketoconazole, Itraconazole,</p>	<p>CYP450 effect</p> <p>Increase effect: Methotrexate, Phenytoin, Warfarin</p> <p>Decrease effect: Atazanavir, Indinavir, Ketoconazole, Itraconazole, Clopidogrel, Mycophenolate mofetil, Cyanocobalamine</p>	<p>CYP450 effect</p> <p>Increase effect: Methotrexate, Clonazepam, Midazolam, Diazepam, Digoxin, Warfarin</p> <p>Decrease effect: Ketoconazole, Itraconazole, Atazanavir, Indinavir, Clopidogrel, Mycophenolate mofetil</p>	<p>CYP450 effect</p> <p>Increase effect: Methotrexate, Warfarin</p> <p>Decrease effect: Atazanavir, Indinavir, Ketoconazole, Itraconazole, Mycophenolate mofetil, Cyanocobalamine</p>
Special Instruction	First line in treatment of SRMD	<p>Stability of PPIs after reconstitution</p> <p>After reconstitution with 10 ml of isotonic sodium chloride solution, intravenous omeprazole /pantoprazole can be administered as a rapid injection over 2 minutes or it can be stores for up to 2 hours at room temperature.</p> <p>Intravenous admixtures of pantoprazole can be prepared by mixing with 100 ml of isotonic sodium chloride solution, 5% dextrose in water, or lactated Ringer's solution to achieve a final concentration of 0.4 mg/ml. This solution can be stored for up to 24 hours at room temperature. This admixture can be administered over 15 minutes. ¹¹</p>		

2.3 NEUROMUSCULAR BLOCKING AGENTS (NMBA) IN CRITICALLY ILL PATIENTS

2.3.1 Introduction

The use of neuromuscular blocking agents in the ICU remains a problematic issue, especially since the indications for the pharmacologic paralysis of ICU patients are unclear. The current recommendations are that muscle relaxants be used to facilitate mechanical ventilation in patients whom sedation alone is inadequate in providing effective mechanical ventilation.¹ However, NMBAs may also improve chest wall compliance, prevent respiratory dyssynchrony, and reduce peak airway pressures. Besides that, muscle paralysis may also reduce oxygen consumption by decreasing the work of breathing and respiratory muscle blood flow.² The decision to treat a patient in the ICU with NMBAs is difficult as it depends on individual practitioner preference than by standards based on evidence-based medicine.¹

2.3.2 Neuromuscular Transmission and Blockade

Due to the multiple complications associated with NMBAs, they should be the last drug of choice used in critically ill patients. They are classified based upon their structure, mechanism of action and pharmacokinetic properties. Structurally, NMBAs have either an aminosteroidal such as pancuronium,

vecuronium and rocuronium or benzylisoquinolinium nucleus such as atracurium and cisatracurium. In term of pharmacokinetic properties, NMBAs differ in their duration of action and route of elimination. Besides that, they differ in the degree of histamine release, vagal block, risk of prolonged blockade and cost.³

Neuromuscular blocking agents are structurally related to Acetylcholine (Ach) and act by interfering with the binding of Ach to the motor endplate. They are divided into depolarizing or nondepolarizing agents based upon their mechanism of action.⁴

- Depolarizing NMBAs bind to cholinergic receptors on the motor endplate, causing initial depolarization on the endplate membrane followed by blockade of neuromuscular transmission. Because calcium is not resequenced in the sarcoplasmic reticulum, muscles are refractory to repeat depolarization until depolarizing NMBAs diffuse from the receptor to the circulation and are hydrolyzed by plasma pseudocholinesterase.
- Nondepolarizing NMBAs competitively inhibit the Ach receptor on the motor endplate. Drug binding to the Ach receptor either prevents the conformational change in the receptor or physically obstructs the ion channels so that an endplate potential is not generated.

2.3.3 Neuromuscular Blocking Agents

- *Succinylcholine*

Succinylcholine produces the most rapid onset of neuromuscular block of all NMBDs. Succinylcholine is currently the only available depolarizing NMBA and is not used for long-term use in ICUs. Succinylcholine can cause cardiac arrest from hyperkalaemia in the critically ill.¹

- *Atracurium*

Atracurium is an intermediate acting NMBA with minimal cardiovascular adverse effects and is associated with histamine release at higher doses. Atracurium has been administered to various critically ill populations, including those with liver failure, brain injury or multiple organ dysfunction syndromes (MODS) to facilitate mechanical ventilation. Recovery of normal neuromuscular activity usually occurred within one to two hours after stopping the infusions and is independent of organ function. Long term infusions have been associated with the development of tolerance, necessitating significant dose increases or conversion to other NMBAs. Atracurium has been associated with persistent neuromuscular weakness as other NMBAs.¹

- *Pancuronium*¹

Pancuronium is a long acting, non-depolarizing compound which has vagolytic effects (more than 90% of ICU patients will have an increase in heart rate of ≥ 10 beats/min), which limits its use in patients who cannot tolerate an increase in heart rate such as patients with cardiovascular disease. In patients with renal failure or cirrhosis, neuromuscular blocking effects of Pancuronium are prolonged because of its increased elimination half-life and the decreased clearance of its 3-hydroxypancuronium metabolite that has one-third to one-half the activity of Pancuronium.

For patients for whom vagolysis is contraindicated (e.g. those with cardiovascular disease), NMBAs other than Pancuronium may be used. Cisatracurium or Atracurium is recommended for patients with significant hepatic or renal disease because of their unique metabolism.

- *Rocuronium*

Rocuronium is a nondepolarizing NMBA with a monoquaternary steroidal chemistry that has an intermediate duration of action and has a very rapid onset of action. The onset is more rapid than with any other non-depolarizing agent and almost as quick as with succinylcholine. The duration of action of Rocuronium is similar to Vecuronium. Rocuronium offers no advantage over vecuronium except in bolus doses for tracheal intubation in the critically ill especially when succinylcholine is contraindicated.⁹

- *Vecuronium*

Vecuronium is an intermediate acting NMBA that has a structural analogue of Pancuronium and is not vagolytic. It is excreted through renal (35%) and bile (50%). Thus, patients with renal impairment and hepatic insufficiency will have decreased drug requirements to maintain adequate blockade. Vecuronium has been reported to be more commonly associated with prolonged blockade once discontinued, compared with other NMBAs and therefore it is being used with decreased frequency in ICU.¹

- *Cisatracurium*¹

Cisatracurium is an isomer of atracurium and classified as intermediate-acting benzyloiso-quinolinium NMBA that is increasingly used. Cisatracurium causes minimal cardiovascular effects and has a lesser tendency to produce mast cell degranulation than atracurium. It is metabolized by ester hydrolysis and Hofmann elimination (a pH & temperature-dependant clinical process), thus, the duration of blockade should not be affected by renal or hepatic dysfunction.

The pharmacological properties of the NMBAs are listed in **Table 2.4**.

2.3.4 Complications of NMBAs

There are two possible complications related to prolonged paralysis following discontinuation of NMBAs. The first is known as “prolonged recovery from NMBAs”, defined as an increase (after cessation of NMBA therapy) in the time to recovery of 50–100% longer than predicted by pharmacologic parameters, which might be due to the accumulation of NMBAs or metabolites. These steroid-based NMBAs such as vecuronium are associated with reports of prolonged recovery and myopathy since steroid-based NMBAs undergo extensive hepatic metabolism and produce active drug metabolites. NMBAs should be discontinued as soon as possible in patients receiving NMBAs and corticosteroids.

Acute quadriplegic myopathy syndrome (AQMS) is another complication of NMBAs. It presents with a clinical triad of acute paresis, myonecrosis with increased creatine phosphokinase (CPK) concentration, and abnormal electromyography (EMG). Other factors that may contribute to the development of this syndrome include nutritional deficiencies, concurrent drug administration

with aminoglycosides or cyclosporine, hyperglycemia, renal and hepatic dysfunction, fever and severe metabolic or electrolyte disorders.¹

2.3.5 Monitoring Parameters

All patients on NMBA should be assessed both clinically and by train-of-four (TOF) monitoring, with a goal of adjusting the degree of neuromuscular blockade to achieve one or two twitches. Before initiating neuromuscular blockade, patients should be medicated with sedative and analgesic drugs to provide adequate sedation and analgesia in accordance with the physician's clinical judgment to optimize therapy. By monitoring patients on the depth of neuromuscular blockade will lead to the usage of lowest NMBA dose and subsequently minimize adverse events.¹

2.3.6 Special Population

Obese

Obesity does not appear to alter the pharmacokinetics or pharmacodynamics of succinylcholine or rocuronium. These agents therefore can be dosed according to actual body weight rather than predicted body weight. However, for artacurium and vecuronium, they have a prolonged duration of action if they are dosed according to actual body weight.^{10,11} Therefore, NMBA are ideally given according to ideal body weight, except for succinylcholine or rocuronium.¹²

Pregnant¹³

Succinylcholine remains the agent of choice to assist in intubation during pregnancy, using total body weight. The use of a nondepolarizing neuromuscular blocking agent for anesthesia maintenance requires strict monitoring. In obstetrics, the use of a neuromuscular blocking agent may expose the neonate to partial paralysis that may be detected by a thorough clinical examination.

Asthma

NMBAs can theoretically induce bronchospasm by inducing histamine release or by reacting with muscarinic receptors. It has been suggested that those NMBA that cause histamine release (atracurium), or that block M₂ muscarinic receptors be avoided in the treatment of the acute asthmatic.¹⁴ It has been shown that muscle weakness developed in asthmatic patients who have received both NMBs and corticosteroids. Although guidelines do not exist, it would be prudent to monitor CPK, and to minimize the dose.

Table 2.4: Pharmacological properties of neuromuscular blocking agents (NMBAs)

	Succinylcholine	Atracurium	Rocuronium	Pancuronium	Vecuronium	Cisatracurium
Dose	<p>Muscle relaxant as an adjunct to anaesthesia</p> <p><u>Initial test dose:</u> IV injection: 5-10mg may be given. Usual single dose 0.3-1.1mg/kg. Max: 100mg according to depth and duration of relaxation required. IM inj: 2.5-4mg/kg. Max: 150mg</p>	<p>1. Adjunct to general anaesthesia (for surgery or intubation)</p> <p><u>Initial:</u> IV injection : 0.3 – 0.6 mg/kg ^{6,7} Maintenance: IV injection : 0.1 – 0.2 mg/kg ^{6,7}</p> <p>OR</p> <p>IV infusion : 5 – 10 mcg/kg/min (300 – 600 mcg/kg/hr).^{6,7}</p> <p>2. Intensive care</p> <p><u>Initial:</u> IV injection: 0.3 – 0.6 mg/kg. ^{6,7}</p> <p><u>Maintenance:</u> IV infusion: 4.5 – 29.5 mcg/kg/min (usual: 11 – 13 mcg/kg/min). ^{6,7}</p>	<p>1. Surgery procedures (Intubation)</p> <p><u>Initial:</u> IV injection : 0.6 mg/ kg. ^{6,8} Maintenance: IV injection : 0.15 mg/ kg (Elderly : 0.075 – 0.1 mg/kg)^{6,8}</p> <p>OR</p> <p>IV infusion: 0.3 – 0.6 mg/kg/h (Elderly: 0.4 mg/kg/h). ^{6,8}</p> <p>2. Intensive care</p> <p><u>Initial:</u> IV injection : 0.6 mg/ kg ^{6,8}</p> <p><u>Maintenance:</u> IV infusion : 0.3 – 0.6 mg/kg/h for first hour then adjusted according to response ^{6,8}</p>	<p>1. Neuromuscular blockade</p> <p><u>Initial:</u> IV injection : 0.06 – 0.1 mg/kg or 0.05 mg/ kg after initial dose of succinylcholine for intubation. ⁵ Maintenance: IV injection 0.01 mg/ kg 60 – 100 min after initial dose, then 0.01 mg/kg every 25 – 60 min. ⁵</p> <p>2. Intensive care</p> <p>IV injection : 0.05 – 0.1 mg/kg bolus followed by 0.8 – 1.7 mcg/kg/min once recovery from bolus seen or 0.1 – 0.2 mg/kg every 1-3 hours. ⁵</p>	<p>1. Surgery procedures (Intubation)</p> <p><u>Initial:</u> IV injection : 0.08 – 0.1 mg/kg or 0.04-0.06 mg/kg after initial dose of succinylcholine for intubation. ⁵ Maintenance: succinylcholine for intubation. ⁵ Maintenance: IV injection 0.01-0.015 mg/kg 25-40 min after initial dose, then 0.01-0.015 mg/kg every 12 – 15 min ⁵. May be administered as continuous infusion at 0.8-2 mcg/kg/min.</p> <p>2. Intensive care</p> <p>IV injection: 0.05- 0.1 mg/kg followed by 0.8-1.7 mcg/kg/min once recovery from bolus seen or 0.1 – 0.2 mg/kg every 1-3 hours. ⁵</p>	<p>1. Surgery procedures (Intubation)</p> <p><u>Initial:</u> IV injection : 0.1mg/ kg after initial dose of succinylcholine for intubation. ⁵ Maintenance: IV injection 0.03 mg/ kg 40-60 min after initial dose, then at 20 min intervals. ⁵</p> <p>2. Intensive care</p> <p>Begin infusion at a dose of 3mcg/kg/min with dosage ranges of 0.5-10mcg/kg/min. ⁵</p>
Onset	2 – 3 min ⁵	2 – 3 min ⁵	1 – 2 min (within 4 min) ⁵	2 – 3 min ⁵	2.5 – 3 min ⁵	2 – 3 min ⁵
Duration	10 – 30 min ⁵	20 – 35 min ⁵	~ 30 min 5	60 – 100 min ⁵	20 – 40 min ⁵	20 – 35 min ⁵

	Succinylcholine	Atracurium	Rocuronium	Pancuronium	Vecuronium	Cisatracurium
Monitoring	Vital signs (heart rate, blood pressure, oxygenation during admission, temperature); serum K ⁺ and Ca ²⁺ , assisted ventilator status, neuromuscular function with a preperal nerve stimulator. ⁵	Vital signs (heart rate, blood pressure, respiratory rate); renal function and liver function. ⁵	Peripheral nerve stimulator measuring twitch response; heart rate, blood pressure, assisted ventilation status. ⁵	Heart rate, blood pressure, assisted ventilation status. ⁵	Blood pressure, heart rate. ⁵	Vital signs (heart rate, blood pressure, respiratory rate). ⁵
Contraindications	Hypersensitivity to succinylcholine or any component of the formulation, acute phase of injury following major burns. ⁵	Hypersensitivity to atracurium besylate or any component of the formulation. ⁵	Hypersensitivity to rocuronium or any component of the formulation. ⁵	Hypersensitivity to pancuronium or any component of the formulation. ⁵	Hypersensitivity to vecuronium or any component of the formulation. ⁵	Hypersensitivity to cisatracurium besylate or any component of the formulation. ⁵
Precautions	Caution in children and adolescent. Acute rhabdomyolysis with hyperkalemia, ventricular arrhythmias and cardiac arrests reported in children with undiagnosed skeletal muscle myopathy. Caution in patients with extensive or severe burns; risk of hyperkalemia increased following injury. ⁵	Reduce initial dose and inject slowly over 1-2 min in patients in whom substantial histamine release will be potentially hazardous (patients with clinically important cardiovascular disease). ⁵ Increased sensitivity in patients with myasthenia gravis and Eaton-Lambert syndrome. ³	Caution in patients with valvular heart disease, pulmonary impairment; ventilation must be supported during neuromuscular blockade. ⁵ Increased sensitivity in patients with myasthenia gravis and Eaton-Lambert Syndrome. ³	Ventilation must be supported during neuromuscular blockade. ⁵ Use with caution in patients with renal and/or hepatic impairment (adjust dose appropriately). ⁵ Increased sensitivity in patients with myasthenia gravis and Eaton-Lambert syndrome. ⁵	Ventilation must be supported during neuromuscular blockade. ⁵ Caution in patients with renal and/or hepatic impairment (adjust dose appropriately). ⁵ Increased sensitivity in patients with myasthenia gravis and Eaton-Lambert syndrome. ⁵	Increased sensitivity in patients with myasthenia gravis and Eaton-Lambert syndrome. ⁵

	Succinylcholine	Atracurium	Rocuronium	Pancuronium	Vecuronium	Cisatracurium
Side effects	<p>Frequency not defined:</p> <p>Cardiovascular: Arrhythmias, bradycardia, cardiac arrest, hyper-/hypotension, tachycardia</p> <p>Dermatologic: Rash</p> <p>Gastrointestinal: excessive salivation.⁵</p> <p>Neuromuscular & skeletal: jaw rigidity, postoperative muscle pain, rhabdomyolysis.⁵</p> <p>Respiratory: apnea, respiratory depression.⁵</p> <p>Endocrine & metabolic: hyperkalemia.</p>	<p>1 – 10% :</p> <p>Cardiovascular: Bradycardia, flushing, hypotension, tachycardia.³</p> <p><1% : Broncheal secretions, erythema, itching, urticaria, wheezing.³</p>	<p>>1% :</p> <p>Cardiovascular: Transient hypertension and hypotension.³</p> <p><1% (Limited to important or life-threatening): Abnormal ECG, anaphylaxis, arrhythmia, bronchospasm, edema, hiccups, nausea, rash, rhonchi, shock, tachycardia, wheezing, vomiting.³</p>	<p>Frequency not defined:</p> <p>Cardiovascular: elevation in pulse rate, elevated blood pressure and cardiac output, tachycardia, edema, skin flushing, circulatory collapse.⁵</p> <p>Dermatologic: Rash, itching, erythema, burning sensation along the vein.⁵</p> <p>Gastrointestinal: excessive salivation.⁵</p> <p>Neuromuscular & skeletal: profound muscle weakness.⁵</p> <p>Respiratory: wheezing, bronchospasm.⁵</p>		
Drug interactions	<p>Succinylcholine</p> <p><i>Increased effect :</i> Aminoglycosides, colistimethate, cyclophosphamide, lithium, loop diuretics, magnesium salts, polymyxin B, procainamide, vancomycin</p> <p><i>Decreased effect :</i> Loop diuretics.⁵</p> <p><i>Increased effect :</i> Aminoglycosides, beta blocker, calcium channel blocker, clindamycin, imipenem, quinolones, tetracycline, vancomycin, macrolides, loop diuretics (frusemide), ketamine, magnesium sulphate, procainamide, and quinidine. May increase risk of myopathy when used with high-dose corticosteroids for extended periods.⁵</p> <p><i>Decreased effect :</i> Carbamazepine (chronic use), phenytoin (chronic use), theophylline, sympathomimetics.⁵</p> <p>Atracurium</p>					

2.4 SEDATION, ANALGESIC AND DELIRIUM IN CRITICALLY ILL PATIENTS

2.4.1 Introduction

Sedatives agents and analgesics are often used to facilitate patient tolerance of invasive mechanical ventilation.¹ Patients undergoing mechanical ventilation experience significant stress superimposed on their acute medical problem, ranging from anxiety about their surroundings and condition to distress with potential pain from necessary nursing care and procedures.² The goals of sedation and analgesia in this context include decreasing pain and anxiety, reducing the stress response, and facilitating nursing care.¹ Choice of agents can be based on many factors, including the relative needs for sedation and analgesia, pharmacodynamics, pharmacokinetics, route and ease of administration, tolerance and cost.¹³

Recent evidence indicates that the choice of sedating agents, frequency of administration and regular assessment of sedation contribute to patient outcomes such as length of stay in the ICU, days of mechanical ventilation, and rate of self-extubation.^{1,2} Titrating the dose of sedative medications based on a sedation scale will help prevent over-sedation and treat under-sedation. Over-sedation can increase time on ventilator support and prolong ICU duration of stay and under-sedation can cause hypercatabolism, immunosuppression, hypercoagulability and increased sympathetic activity.^{3,4}

Improving sedation management through sedation protocols and interventions such as daily interruption of sedation is an increasing focus of quality improvement initiatives in critical care.⁴ In 2000, Kress and co-workers showed that daily withholding of sedative agents led to reduced length of ICU stay, less ventilator time, fewer ICU complications and fewer neurological investigations. Subsequent studies by the same group demonstrated daily sedation withholding to be safe in patients with ischaemic heart disease and that it reduces the psychological sequelae of critical illness. Sedation withholding is now part of the 'Ventilator Care Bundle', as outlined by the UK Department of Health and recommended by the Surviving Sepsis Campaign.³

Assessment of sedation level is carried out mainly by nurses or critical care physicians by assessing patient responses to simple stimuli.³ Sedation-agitation scales can be used to identify and quantify agitation and to grade the depth of sedation.⁵ ICU Management Protocol 2012, by Ministry of Health Malaysia, suggested that patients are to be assessed for sedation and agitation based on the Revised Riker Sedation-Agitation Scale (SAS) or Richmond Agitation and Sedation Scale (RASS) every 4 hours and titrate the sedative infusion rate with the aim of keeping the SAS between -1 to +1 or RASS between -2 to +1.⁶

Exception to keeping within the targeted score (should be sedated to achieve SAS of -2 to -3 or RASS of -3 to -5)⁶:

- Head injured on cerebral protection
- Septic shock on high inotropic support (IV Noradrenaline >0.15mcg/kg/min or Dopamine >15mcg/kg/min or Adrenaline >0.15mcg/kg/min)
- ARDS on high ventilatory support (FiO₂ >0.6 and PEEP >12)
- Tetanus

Table 2.5: Revised Riker Sedation Agitation Scale⁶

Score	Description	Definition
+3	Agitated and restless	<i>When awoken or otherwise, pulling at ETT, trying to remove catheters or requires physical restraints</i>
+2	Awake but mildly agitated	<i>Anxious but mildly agitated. Attempts to sit up but calms down with verbal instructions</i>
+1	Awake and calm	<i>Awake, calm and easily follows commands</i>
0	Aroused by voice and remains calm	<i>Awakens easily to verbal stimuli. Remains awake, calm and easily follows command</i>
-1	Aroused by movement	<i>Awakens to loud verbal stimuli or gentle shaking. Has eye contact for at least 10 seconds but drifts off to sleep</i> OR <i>Awakens to loud verbal stimuli or gentle shaking and follows simple commands</i>
-2	Aroused by painful stimuli	<i>Localising or flexion to pain. Does not communicate or follow commands</i>
-3	Unarousable	<i>Extension, minimal or no response to painful stimuli</i>

Table 2.6: Richmond Agitation and Sedation Scale⁶

Score	Description	Definition
+4	Combative	<i>Overtly combative or violent; immediate danger to staff</i>
+3	Very agitated	<i>Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff</i>
+2	Agitated	<i>Frequent non purposeful movement or patient-ventilator dyssynchrony</i>
+1	Restless	<i>Anxious or apprehensive but movements not aggressive or vigorous</i>
0	Alert and calm	
-1	Drowsy	<i>Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact to voice i.e eye contact >10 seconds with verbal stimulation</i>
-2	Light sedation	<i>Briefly (less than 10 seconds) awakening with eye contact to voice i.e eye contact <10 seconds with verbal stimulation</i>
-3	Moderate sedation	<i>Any movement but no eye contact to verbal stimulation</i>
-4	Deep sedation	<i>No response to voice, but any movement to physical stimulation</i>
-5	Unarousable	<i>No response to voice or physical stimulation</i>

2.4.2 Sedative Agents

- *Benzodiazepines*

Benzodiazepines such as midazolam, diazepam and lorazepam act by potentiating the activity of gamma-aminobutyric acid (GABA) which is the major inhibitory neurotransmitter in the central nervous system. The rate of benzodiazepines onset of action is determined by its ability to cross the blood brain barrier. The relatively lipophilic benzodiazepine have faster onset than the relatively water soluble benzodiazepines.

Midazolam is the most commonly used benzodiazepine for ICU sedation. It is a short acting, water soluble benzodiazepine that undergoes extensive oxidation in the liver to form water soluble hydroxylated metabolites, which are excreted in urine. However, the primary metabolite, namely 1-hydroxymethylmidazolam, has mild CNS depressant activity and may accumulate in the critically ill patient especially in the case of kidney failure. Medications that interfere with the cytochrome P450 enzyme will decrease metabolization of midazolam. During short term infusions, midazolam is generally safe and effective sedative agent. However, during continuous infusions, accumulation of midazolam can occur because of the large volume distribution.⁷

- *Propofol*

Propofol is a sedative-hypnotic agent with a rapid onset and offset action.⁷ It may be preferred to facilitate earlier weaning and extubation.^{13,14} Propofol acts on the GABA receptor like the benzodiazepines although the site of action on this receptor is different.⁷

It is available for intravenous administration and dissolved in fat emulsion. It has extremely rapid distribution and metabolism (by hepatic conjugation) responsible for promptly patient arousal after a single dose or interruption of drug infusion. Its metabolites are excreted by kidneys. Its formulation causes a transient elevation of triglyceride level and has some allergic properties. It has respiratory and cardiovascular depressant effects with minimal influence on heart rate. Hepatic and renal diseases have little impact on the pharmacokinetics of propofol.

Propofol infusion syndrome is a rare but serious and potentially fatal adverse effect, typically seen with infusion rates >5 mg/kg/h for more than 48 hours. This syndrome is characterized by dysrhythmias, heart failure, metabolic acidosis, hyperkalemia and rhabdomyolysis.⁷

***Note: 1 ampoule of Propofol-Lipuro® 1% (20ml) = 2g of fat (18kcal). Different product may confer different calorie which may be considered when formulating for patient's feeding.**

- *Dexmedetomidine*

Dexmedetomidine is a centrally acting α_2 -agonist with sedative and analgesic properties. The sedative properties are facilitated through the locus coeruleus site in the CNS and the analgesic effects may occur via activation of the α_2 receptors by accentuating the action of opioids. It causes no significant effect on respiratory drive, even when used with opioids.

The main adverse drug effect are primarily related to cardiovascular including hypotension and bradycardia, particularly when loading dose are used, thus, loading dose is not recommended.^{7,12}

Most studies involving dexmedetomidine have evaluated postoperative ICU patients and demonstrated efficacy for short-term sedation and analgesic sparing. Although dexmedetomidine is labeled in some countries only for sedation less than 24 hours, it appears to have a promising potential as an effective sedative agent in critically ill patients and can be used safely up to 7 days, with stable and predictable hemodynamic effects on induction and cessation.^{7,23}

- *Ketamine*

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist with sedative, analgesic and bronchodilator properties. It produces a state of dissociative anaesthesia, profound analgesia, and amnesia and serves as a potent bronchodilator which is beneficial in asthmatic and chronic obstructive pulmonary disease patients. Ketamine has been reported to produce opioid dose sparing and good patient acceptance.^{9,24,26}

Ketamine is not routinely used as a sedative infusion due to the sympathetic nervous system stimulation resulting in increased cardiac work, blood pressure, pulse rate and a rise in cerebral metabolic oxygen consumption. As a phencyclidine analogue, it has some of the psychological adverse effects found with that hallucination and delirium, especially in adults, but these can be avoided if administered concomitantly with a benzodiazepine.^{24,27}

Continuous infusion ketamine may likely be utilized safely as adjunctive sedative and analgesic therapy in mechanically ventilated medical ICU patients if concomitant benzodiazepine therapy is provided.²⁵

Table 2.6: Comparison of Sedative Agents

	Midazolam	Propofol	Dexmedetomidine	Ketamine
Dose	<p><u>Initial dose :</u> 0.01 - 0.05 mg/kg over several min. ^{9,10,11}</p> <p><u>Maintenance dose :</u> 0.02 – 0.1 mg/kg/h. ^{9,10,11}</p>	<p>1) Monitored anaesthesia care sedation</p> <p><u>Initial dose :</u> 100 – 150 mcg/kg/min (6 – 9 mg/kg/h) IV infusion. ^{9,10}</p> <p><u>Maintenance dose:</u> 25 – 75 mcg/kg/min (1.5 – 4.5 mg/kg/h) IV. ^{9,10}</p> <p>2) Sedation for mechanically ventilated ICU patient</p> <p><u>Initial dose :</u> 5 mcg/kg/min (0.3 mg/kg/h) IV infusion for 5 min then titrate in 5 - 10 mcg/kg/min (0.3 - 0.6 mg/kg/h) increments every 5-10 min to achieve desired sedation level. ^{9,10}</p> <p><u>Maintenance dose:</u> 5 - 50 mcg/kg/min (0.3 - 3 mg/kg/h) or higher. ^{9,10}</p>	<p><u>Initial dose :</u> 1 mcg/kg over 10 mins. ^{9,10}</p> <p><u>Maintenance dose :</u> 0.2 – 0.7 mcg/kg/h for a maximum of 24 hours. ^{9,10}</p>	<p><u>Initial dose:</u> 0.2 - 0.75mg/kg.⁹</p> <p><u>Maintenance dose:</u> 2 - 7 mcg/kg/min (0.12-0.42 mg/kg/hr).⁹</p>
Onset	1- 5 min ⁹	30 - 45 sec ⁹	5 - 10min ^{9,20}	30 - 40sec ^{9,20}
Duration	~ 2 hours ⁹	20 - 75min ⁹	60 - 120min (dose dependent) ⁹	5 - 10min (IV) ⁹

	Midazolam	Propofol	Dexmedetomidine	Ketamine
Elimination	Hepatic Cytochrome P450 3A4, active metabolite excreted renally ¹²	Hepatic conjugation ¹²	Hepatic including glucuronidation and CYP2A6 ¹²	Hepatic N-demethylation ²⁰
Cardiac effects	Important depressant effect ^{9,10}	Important depressant effect ^{9,10}	Important depressant effect ^{9,10,12}	Important stimulant effects ⁹
Respiratory effects	Important depressant effect ^{9,10}	Important depressant effect ^{9,10}	Minimal depressant effect ^{9,10,12}	Bronchodilatory effect ⁹
Analgesia	None ⁹	None ⁹	Yes ⁹	Yes ^{24,26}
Monitoring	Respiratory and cardiovascular status, blood pressure. ^{9,11}	Anaphylactic reactions, blood pressure, cardiorespiratory depression, fever, propofol infusion syndrome, hyper- triglyceridemia. ¹⁰	Level of sedation, blood pressure, heart rate, respiration, rhythm, pain control. ⁹	Heart rate, blood pressure and cardiac function. Respiratory rate and transcutaneous O ₂ saturation. ⁹
Contraindication	Hypersensitivity to midazolam and its components including benzyl alcohol (cross- sensitivity with other benzodiazepines may exist). ^{9,10} Narrow-angle glaucoma and pregnancy. ^{9,10}	Hypersensitivity to propofol. ⁹ Allergy to eggs, egg products, soybeans or soy products. ^{9,10}	Hypersensitivity to dexmedetomidine and its components. ⁹ Use outside of intensive care setting. ⁹	Hypersensitivity to ketamine or any component of the formulation. Condition in which an increase in blood pressure would be hazardous. ⁹
Precaution	May cause severe respiratory depression, respiratory arrest or apnea. ⁹ May cause hypotension – hemodynamic events are more common in paediatric patients or patients with hemodynamic instability. ⁹	Use slower rate of induction in elderly. ⁹ May cause anaphylactic reaction, life threatening. ¹⁰ Do not administer with blood or blood products through the same IV catheter. ⁹	Use cautiously in elderly patients; hypotension and/or bradycardia may be more pronounced. ¹⁰ Use caution in patients with heart block, bradycardia, severe ventricular dysfunction, hypovolemia, diabetes and chronic hypertension. ⁹	May cause CNS depression. May cause dependence and tolerance with prolonged use. Postanesthetic emergence reactions which can manifest as vivid dreams, hallucinations, and/ or frank delirium may occur. Rapid IV administration or overdose may cause respiratory depression or apnea.

	Midazolam	Propofol	Dexmedetomidine	Ketamine
	Hypotension and/or respiratory depression may occur frequently in patients who have received narcotic analgesics. ⁹	Abrupt discontinuation can result in rapid awakening, anxiety, agitation and resistance to mechanical ventilation. ^{9,10}		Use with caution in patients with coronary artery disease, catecholamine depletion, hypertension and tachycardia. Use with caution in patients with cerebrospinal fluid pressure elevation. Use with caution in the chronic alcoholic or acutely alcoholic intoxicated.
Side effects COMMON ^{9,10,11,12}	Gastrointestinal: N & V Neurologic: Excessive somnolence, headache Respiratory: Cough Others: Hiccoughs	Gastrointestinal: N&V Musculoskeletal: Involuntary movement	Gastrointestinal: Nausea, xerostomia	Cardiovascular: Hypertension, tachycardia Neurologic: Emergence from anesthesia, psychiatric sign or symptom
SERIOUS ¹⁰	Cardiovascular: Cardiac arrest usually in combination with CNS depressant drug; hypotensive episode Neurologic: Involuntary movement Psychiatric: Agitation Respiratory: Apnea, respiratory arrest with CNS depressant drug, desaturation in paediatric patients, respiratory depression, respiratory obstruction	Cardiovascular: Bradyarrhythmia, heart failure Gastrointestinal: Pancreatitis Immunologic: Anaphylaxis Neurologic: Seizure Respiratory: Apnea, respiratory acidosis Renal: Acute renal failure Others: bacterial septicemia, propofol infusion syndrome	Cardiovascular: Atrial fibrillation, bradyarrhythmia, cardiac dysrhythmia, hypertension, hypotension, tachycardia Respiratory: Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation, pleural effusion, pulmonary congestion, respiratory acidosis	Cardiovascular: Bradyarrhythmia, cardiac dysrhythmia, hypotension Immunologic: Anaphylaxis Respiratory: Apnea, laryngeal spasm, pulmonary edema, respiratory depression

	Midazolam	Propofol	Dexmedetomidine	Ketamine
Drug Interaction¹⁰	Atazanavir (contraindicated, theoretical) Diltiazem (moderate, probable) Indinavir (contraindicated, theoretical)	Oxycodone (major, theoretical)	Oxycodone (major, theoretical)	Oxycodone (major, theoretical) Tramadol (major, theoretical)
Advantages	Shorter acting if preserved organ function ¹² Fast onset ¹²	Short acting ¹²	Very short duration ¹² Has some analgesic properties ¹²	Attenuates the development of acute tolerance to opioids ²⁰
Disadvantages	Many drug interactions. Active metabolite accumulates in renal failure. ¹²	Reduces blood pressure. Increase serum triglyceride. Pancreatitis. Propofol infusion syndrome. ¹²	Reduces blood pressure and heart rate. Not approved for use >24 hour in some countries, some studies are longer. ^{12,23}	May cause hallucinations and other psychological disturbances. ²⁰

2.4.3 Analgesic Agents

Opioids remain as the mainstay drug for analgesic therapy in ICU patients.⁷ It function through stimulation of receptors, principally via μ_1 and μ_2 opioid receptors.¹² All opioids produce a dose-dependent respiratory depression and this depression is increased when use in combination with benzodiazepine.^{7,12}

- *Morphine*

Morphine is the oldest and most hydrophilic opioids in current use. Its peak effect is more delayed (30min) as compared with more lipid soluble opioids such as fentanyl (2 - 4min).¹⁶ It is metabolize in the liver to 80% of inactive morphine-3-glucuronide, which has no analgesic action or neurotoxicity and 20% of active morphine-6-glucuronide which is a potent analgesic having 20 to 40 times the activity of morphine. Both metabolites are eliminated by the kidney and therefore accumulate in patients with renal dysfunction. It should be avoided in patients with renal insufficiency.^{7,12,15} Primary non-opioid receptor adverse effect of morphine is histamine release which can cause mild hypotension, tachycardia and possibly bronchospasm.¹⁶

- *Fentanyl*

Fentanyl is the preferred analgesic agent for critically ill patients with hemodynamic instability. It is a potent synthetic opioid with approximately 100 times the potency of morphine.^{15,16} It has a similar profile of opioid receptor-based adverse effects as morphine but does not cause histamine release.¹⁶ Fentanyl has a rapid onset of action due to its high lipophilicity and short duration

of action from its rapid redistribution from CNS to other tissues.^{7,12,16} However, higher doses will saturate lipid stores so that clearance of larger cumulative doses is dependent on longer elimination mechanisms. The pharmacokinetics of fentanyl is not altered by liver or kidney dysfunction.¹⁶

- *Remifentanyl*

Analgesia-based sedation with remifentanyl has been introduced as an option in ICU patients. Remifentanyl, a derivative of fentanyl, is a short-acting opioid with unique properties. No histamine release is associated with this drug and thus, it is recommended to be used in patient with pulmonary disease requiring opioids administration.²⁹

Remifentanyl is metabolized by unspecific esterases that are widespread throughout the plasma, red blood cells, and interstitial tissues with no active metabolite, whereas elimination of other opioids requires hepatic biotransformation and renal excretion. Therefore, there is no accumulation in patients with hepatic and renal failure. The context-sensitive half-time (the time required for the drug's plasma concentration to decrease by 50% after cessation of an infusion) of remifentanyl is consistently short (3.2 minutes), even after an infusion of long duration (> 8 hours).^{7,20}

Table 2.7: Comparison of Analgesic Agents

	Morphine	Fentanyl	Remifentanyl
Dose	<u>Initial dose:</u> 0.01-0.15mg/kg every 1-2hours as needed ⁹ <u>Maintenance dose:</u> 0.07-0.5mg/kg/hr ⁹	<u>Initial dose:</u> 0.35-1.5mcg/kg every 30-60min as needed ⁹ <u>Maintenance dose:</u> 0.7-10mcg/kg/hr ⁹	<u>Initial dose:</u> 1mcg/kg over 30-60sec ⁹ <u>Maintenance dose:</u> 0.6-15mcg/kg/hr ⁹
Onset	5-20 min ^{9,11,12}	2 - 5 min ¹²	1-3 min ^{9,20}
Duration	2-4 hours ^{12,16}	0.5 – 1 hours ⁹	0.3 – 0.6 hours ⁹
Elimination	Hepatic conjugation; active metabolite excreted renally. ¹²	Hepatic CYP450 3A4. ¹²	Hydrolysis by esterases. ^{9,20}
Monitoring	Pain relief. Respiratory and CNS status. Blood pressure. ⁹	Pain relief. Respiratory and CNS status. ⁹ Blood pressure, heart rate. ^{9,10}	Respiratory and cardiovascular status. ⁹
Contraindication	Hypersensitivity to morphine sulfate or any product component. Acute or severe asthma. Known or suspected paralytic ileus. patients. ^{9,11}	Hypersensitivity to fentanyl or any product component. Acute or severe asthma. Known or suspected paralytic ileus.	Hypersensitivity to remifentanyl, fentanyl analogs or any component of the component of the formulation.

	Morphine	Fentanyl	Remifentanyl
Contraindication	<p>Opioid non-tolerant</p> <p>Significant respiratory depression, especially in unmonitored settings that lack resuscitative equipment.¹⁰</p> <p>During labor when a premature birth is anticipated.^{9,11}</p> <p>Within 2 weeks of MAO inhibitors.¹¹</p>	<p>Opioid non-tolerant patients.</p> <p>Significant respiratory depression, especially in unmonitored settings that lack resuscitative equipment.¹⁰</p> <p>Within 2 weeks of MAO inhibitors.¹¹</p>	<p>Not for intrathecal or epidural administration due to the presence of glycine in the formulation.⁹</p>
Precaution	<p>May cause CNS depression.</p> <p>May cause hypotension, orthostatic hypotension and syncope.</p> <p>May cause respiratory depression, especially in elderly debilitated patients, hypoxia or hypercapnia.</p> <p>Use with caution in patients with adrenal insufficiency, biliary tract dysfunction, acute pancreatitis.</p> <p>Use with caution in patients with history of drug abuse or acute alcoholism.</p> <p>Use with caution in renal/hepatic impairment, head trauma, seizure, thyroid dysfunction.⁹</p>	<p>May cause CNS depression.</p> <p>May cause respiratory depression, especially in elderly debilitated patients, hypoxia or hypercapnia.</p> <p>Use with caution in patients with history of drug abuse or acute alcoholism.</p> <p>Use with caution in bradycardia, bradyarrhythmias, renal/hepatic impairment, head trauma.⁹</p>	<p>May cause hypotension</p> <p>Use with caution in patient with hypovolemia, cardiovascular disease (including acute MI) or drugs which may exaggerate hypotensive effects.</p> <p>Safety and efficacy for postoperative analgesic or monitored anaesthesia care have not been established in children.</p> <p>Rapid IV infusion may result in skeletal muscle and chest wall rigidity, impaired ventilation or respiratory distress/ arrest; nondepolarizing skeletal muscle relaxant may be required.⁹</p>
Side effects COMMON¹⁰	<p>Gastrointestinal: Constipation, N, V.</p> <p>Neurologic: Dizziness, headache, somnolence.</p> <p>Dermatologic: Pruritus</p> <p>Ophthalmic: Miosis</p> <p>Renal: Urinary retention</p>	<p>Gastrointestinal: Abdominal pain, N, V, constipation, xerostomia</p> <p>Neurologic: Asthenia, confusion, dizziness, nervous, headache, insomnia, somnolence</p> <p>Psychiatric: Anxiety, depression, euphoria, hallucination</p> <p>Renal: Urinary retention</p> <p>Respiratory: Dyspnea, upper respiratory depression</p> <p>Other: Fatigue, influenza-like symptoms</p>	<p>Gastrointestinal: Nausea, vomiting</p> <p>Neurologic: Headache</p> <p>Dermatologic: Pruritus</p> <p>Cardiovascular: Hypotension</p> <p>Musculoskeletal: Muscle rigidity</p>

	Morphine	Fentanyl	Remifentanyl
SERIOUS¹⁰	<p>Cardiovascular: Cardiac arrest, circulatory depression, orthostatic hypotension, shock, syncope</p> <p>Immunologic: Anaphylaxis</p> <p>Musculoskeletal: Myoclonus</p> <p>Neurologic: Coma, raised intracranial pressure, seizure</p> <p>Respiratory: Dyspnea, respiratory depression</p>	<p>Cardiovascular: Bradycardia, cardiac dysrhythmia, chest pain</p> <p>Respiratory: Apnea, respiratory depression</p>	<p>Hematologic: Hemorrhage</p> <p>Respiratory: Respiratory depression</p> <p>Other: Anaphylaxis</p>
Drug Interaction¹⁰	<p>Linezolid (major, theoretical)</p> <p>Naltrexone (contraindicated, probable)</p> <p>Oxycodone (major, probable)</p> <p>Promethazine (major, theoretical)</p> <p>Rifampicin (major, established)</p>	<p>Carbamazepine (moderate, probable)</p> <p>Clarithromycin (major, probable)</p> <p>Diltiazem (major, theoretical)</p> <p>Erythromycin (major, probable)</p> <p>Fluconazole (major, established)</p> <p>Ketoconazole (major, probable)</p> <p>Linezolid (major, theoretical)</p> <p>Naltrexone (contraindicated, probable)</p> <p>Nevirapine (moderate, probable)</p> <p>Indinavir (moderate, established)</p> <p>Itraconazole (major, probable)</p> <p>Oxycodone (major, probable)</p> <p>Phenytoin (moderate, probable)</p> <p>Rifampicin (moderate, probable)</p> <p>Ritonavir (major, established)</p> <p>Voriconazole (moderate, established)</p>	<p>Chloral hydrate (major, theoretical)</p> <p>Clonazepam (major, probable)</p> <p>Codeine (major, probable)</p> <p>Dantrolene (major, probable)</p> <p>Diazepam (major, probable)</p> <p>Fentanyl (major, probable)</p> <p>Lorazepam (major, probable)</p> <p>Meperidine (major, probable)</p> <p>Midazolam (major, probable)</p> <p>Oxycodone (major, probable)</p> <p>Phenobarbital (major, probable)</p> <p>Thiopental (major, probable)</p>
Advantages	Reduces tachypnea. ¹²	Less hypotensive than morphine. ¹²	No accumulation in hepatic/renal failure. ^{12,20}
Disadvantages	Reduces blood pressure. Respiratory depression. Accumulation in hepatic/renal failure. ¹²	CYP450 3A4 inhibitors may increase fentanyl level. ¹²	Reduces heart rate and blood pressure. Increase intracranial pressure. ¹²

2.4.4 Management of Delirium

Delirium, a common manifestation of acute brain dysfunction in critically ill patients, is associated with poor short-term outcomes and may result in adverse sequelae years after ICU discharge. The prevalence of delirium reported in medical and surgical ICU cohort studies has varied from 20% to 80% and is often goes unrecognized by clinicians.¹⁷

Onset of delirium may be triggered by a number of physiological processes, including metabolic derangement, infectious processes, central nervous system pathology, and medication-induced side effects. Medications commonly associated with the development of delirium include benzodiazepines, opioids, and agents with high anticholinergic activity or side effects.^{17,18,20}

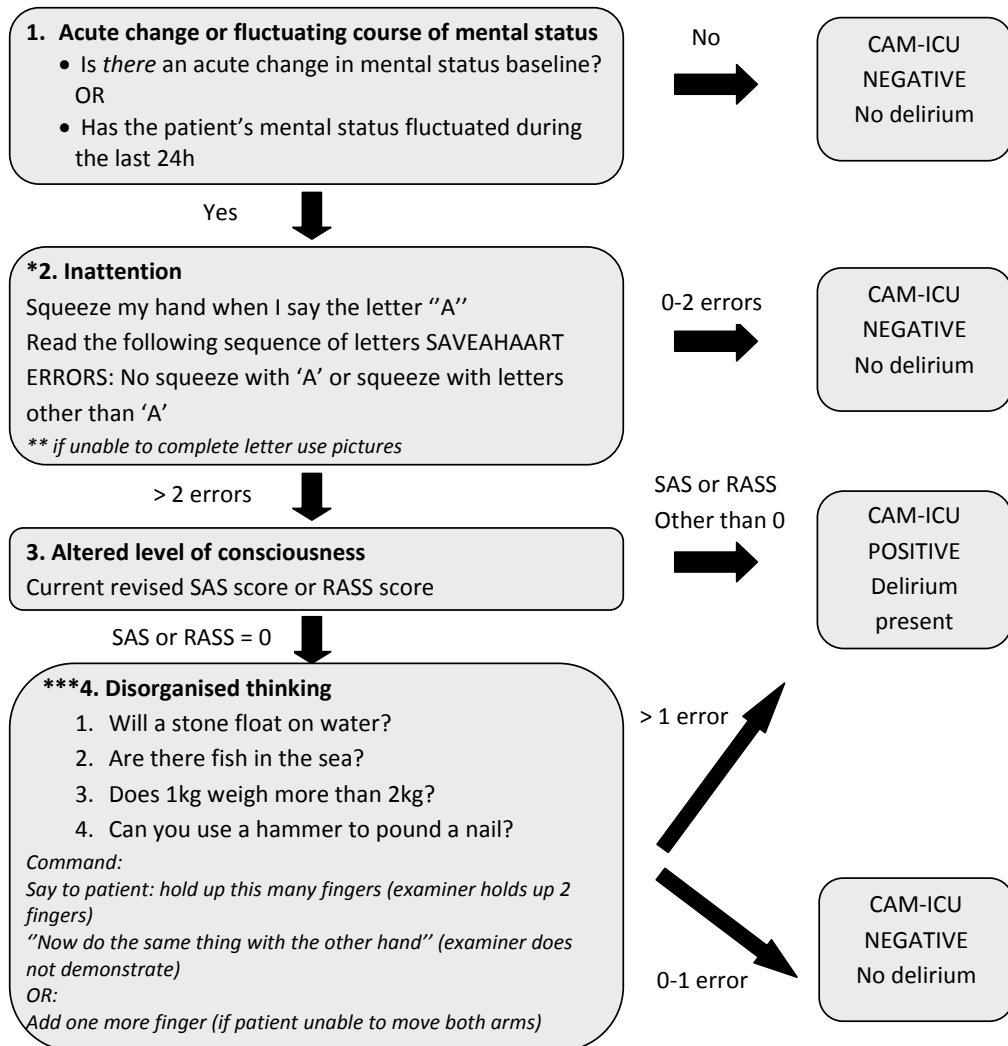
ICU Management Protocol 2012, Ministry of Health Malaysia, has suggested that all patients with a SAS > -2 or RASS > -3 should be screened by the nursing staff for delirium using the Confusion Assessment Method for ICU (CAM-ICU) every 8 hours.⁶

Recommended strategies for addressing delirium include treating the reversible factors, such as infectious disease, drug withdrawal, and medication toxicity, adequately treating pain, correcting metabolic, nutritional, endocrine disorders and finally, managing sleep deprivation.

Non-Pharmacological Management:

Non-pharmacological is preferred in the management of delirium. The strategies include the following intervention.^{6,12}

- a. Providing psychological support and orientation consistently
- b. Involving family members to re-orientate patient
- c. Early mobilization
- d. Minimize noise and light at night
- e. Minimize nocturnal interventions if clinically possible and use night sedation as a last resort



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* Patients with ICU-acquired weakness or neuromuscular disease may need an alternative method to indicate response e.g eye blinks or finger taps

** The pictures can be downloaded from the following website: <http://www.delirium.org>

*** Assessment of feature 4 requires both questions and commands to be completed. If patient is paralysed or blind, only questions need to be answered and this feature is present if there are > 1 error

Chart 1: Confusion Assessment Method for ICU (CAM-ICU)⁶

Pharmacological Management:

When adjunct medical management is required, following drugs may be used to treat delirium as recommended in Malaysia ICU Management Protocol 2012 ⁶:

- i. IV Haloperidol : <60yrs: 5-10mg PRN/ q4-6h
>60yrs: 2.5-5mg PRN/q4-6h ⁶
* Continuous infusion (unlabeled use): 3-25mg/hour ⁹
- ii. T. Chlorpromazine 12.5-25 mg q6-8h
- iii. T. Risperidone 0.5-1mg q12h
- iv. IV Dexmedetomidine 0.2-1.5 mcg/kg/hr (consider in patients who are ready to be weaned but agitated)
- v. T. Olanzapine 5-10 mg q12-24h
- vi. T. Quetiapine 50-100 mg q12h ⁶

Caution: Prolonged QT may occur with the use of all the above drugs except Dexmedetomidine ⁶

Although no intravenous (IV) drugs approved by FDA for delirium in critically ill patients, IV haloperidol is used nevertheless and remains as the first line of delirium treatment in ICU.^{17,19} Dexmedetomidine, the alpha-2 agonists has demonstrated clinical efficacy in ICU settings in achieving tranquilization-sedation more safely and potentially help in preventing delirium.¹⁸ Other newer agents, atypical antipsychotics primarily olanzapine, quetiapine, and risperidone has also been used, but as yet no large, placebo-controlled studies have demonstrated their safety and efficacy.²¹

2.5 FLUIDS IN CRITICALLY ILL PATIENTS

2.5.1 Distribution of Total Body Fluid (TBF)

It is estimated that 60% of lean body weight (LBW) in male and 50% LBW in women consist of water. Total body water is further divided to intracellular (IC) space and extracellular (EC) space which is separated by cell membrane. EC compartment is further divided to interstitial space (75%) and intravascular space (25%) which is separated by capillary membrane. The distribution of intravenous fluid is explained with this approximate distribution of TBF into the mentioned compartment.

2.5.2 Crystalloid and Colloids

Table 2.8: Comparison between crystalloids and colloids

Crystalloids	Colloids
Fluids that may contain a combination of water, dextrose and/or electrolytes	High molecular weight substances primarily remain in the intravascular compartment → generating an oncotic pressure.
Example:- 0.9% NaCl, 5% Dextrose, 5% Dextrose in NaCl 0.9%, Lactated Ringer's, Sterofundin	Example:- Natural: blood and blood products, albumin Artificial: dextran, hydroxyethyl starch (HES), modified fluid gelatine

Crystalloids	Colloids
<ul style="list-style-type: none"> • Na⁺ and Cl⁻ do not freely cross into cells (distribute evenly in EC space – 25% intravascular space, 75% in interstitial space) • Dextrose = free water (Dextrose → CO₂ + H₂O), freely crosses any membrane, evenly distributed in TBF 	Too large to cross the capillary membrane – primarily remain in the intravascular space (small portion “leak” into the interstitial space)
<ul style="list-style-type: none"> • When administered in large volumes, 0.9% NaCl can cause normal anion gap metabolic acidosis (hyperchloremic metabolic acidosis), while this is not an issue in balanced crystalloid solution eg: sterofundin. • Free water (D5W) should be avoided in patient with elevated intracranial pressure (ICP) as it may cross cerebral cells and cause further ICP elevation. 	<ul style="list-style-type: none"> • HES and dextran – risk of coagulopathy, avoid in patients with increased risk of haemorrhage. • All colloids can cause anaphylactoid reactions. • HES should no longer be used to treat septic or critically ill patients as current studies shows it may increase risk of kidney injury and mortality.
Require larger volume for equivalent intravascular expansion.	Require less volume for equivalent intravascular expansion.
Inexpensive (balanced solution is expensive compared to conventional crystalloid solution).	Expensive.
Shorter intravascular half-life	Longer intravascular half-life

Table 2.9: Intravenous Fluids and Volume Expansion

Intravenous Fluid	Infused volume (ml)	Equivalent Intravascular volume expansion (ml)
0.9% NaCl	1000	250
Lactated Ringer's	1000	250
5% Dextrose	1000	250
5% albumin	500	500
20% albumin	100	400
25% albumin	100	500

2.5.3 Fluid resuscitation vs Fluid maintenance

Table 2.10: Comparison between fluid resuscitation and fluid maintenance

Fluid resuscitation	Fluid maintenance
Goal: To restore intravascular volume and prevent organ hypoperfusion.	Goal: To prevent dehydration and maintain a normal fluid and electrolyte balance.
Indication: In patients with sign and symptoms of fluid depletion.	Indication: in patients who are unable to tolerate oral fluids.
Recommended: crystalloids (0.9% NaCl or Lactated Ringer's). Colloids not superior to crystalloids, more expensive.	Recommended: 5% Dextrose with 0.45% NaCl + 20–40 mmol KCl/L (KCl content – adjust individually).
Infuse rapidly, preferably through central venous catheter (CVC).	Continuous infusion, through CVC or peripheral catheter. Remember to evaluate IV fluids daily.

Fluid resuscitation	Fluid maintenance
500- to 1000-mL bolus (20ml/kg) and re-evaluate; this process continues as long as the sign and symptoms of intravascular volume depletion are improving or there are sign of acute pulmonary oedema (APO).	Common methods of estimating daily maintenance volume in children and adults <ul style="list-style-type: none"> • 1st 10kg - 100 ml/kg; 2nd 10kg - 50 ml/kg plus 20 ml/kg for every kg greater than 20 kg (i.e. if weight >20kg = 1500ml + 20ml for each kg over 20kg) • "4:2:1" Rule (ml/kg/hr) • 20–40 mL/kg/day (for adults only) • Adjust fluids based on pt's input, output, insensible loss

2.5.4 Osmolarity of Intravenous Fluids

The plasma osmolality is between 275 and 290 mOsm/kg.

- a) Hypertonic fluid cause fluid to shift from the IC to the EC compartment with subsequent cellular dehydration and shrinkage.
- b) Isotonic fluid (similar osmolarity with plasma) - will not result in a fluid shift between fluid compartments.
- c) Hypotonic fluid is solution with osmolarity less than 150 mOsm/L. It caused fluid to shift from the EC to the IC compartment with subsequent cellular overhydration and swelling.
 - RBC swelling may cause cell rupture (i.e., hemolysis)
 - Brain cells may swell, causing cerebral edema and herniation; most likely to occur with acute hyponatremia (< 2 days)
 - Sterile water is NEVER meant for intravenous administration

The osmolarity and electrolytes content of various intravenous fluids are listed in **Table 2.11**.

2.5.5 Sodium (135-145 mmol/L)

Sodium is the principal cation of the ECF and primary determinant of plasma osmolality. Serum sodium concentration and serum osmolarity normally are maintained under precise control by homeostatic mechanisms involving stimulation of thirst, secretion of antidiuretic hormone (ADH), and renal handling of filtered sodium.

Clinically significant hyponatremia is relatively uncommon and is nonspecific in its presentation; therefore, the physician must consider the diagnosis in patients presenting with vague constitutional symptoms or with altered level of consciousness. Irreparable harm can befall the patient when abnormal serum sodium levels are corrected too quickly or too slowly.

The physician must have a thorough understanding of the pathophysiology of hyponatremia to initiate safe and effective corrective therapy. The patient's fluid status must be accurately assessed upon presentation, as it guides the approach to correction.

Table 2.11: Intravenous Fluids, Osmolarity and Electrolytes Content

SOLUTIONS	mOsm/L	Glucose g/L	Na ⁺	Cl ⁻	*lactate ion	K ⁺	Ca ²⁺	Mg ²⁺	**acetate ion	**malate ion	
											mmol/L
CRYSTALLOIDS											
5% dextrose and water (D5)	278	50									
10% dextrose and water (D10)	555	100									
20% dextrose and water (D20)	1110	200									
50% dextrose and water (D50)	2523	500									
0.9% sodium chloride (NS)	308		154	154							
0.45% sodium chloride (HS)	154		77	77							
3% sodium chloride (S3)	1024		513	513							
0.9% sodium chloride + dextrose 5% (NSD5)	585	50	154	154							
0.45% sodium chloride + 5% dextrose (HSD5)	430	50	77	77							
0.45% sodium chloride + 10% dextrose (HSD10)	709	100	77	77							
0.18% sodium chloride + 4.23% dextrose (QSD1) (1/5SD5)	296	42.3	31	31							
0.18% sodium chloride + 10% dextrose (QSD10) (1/5SD10)	615	100	31	31							
Hartmann's Solution	278		131	111	29	5	2				
Sterofundin	304		140	127		4	2.5	1.0	24	5	
COLLOIDS											
Sodium ranges from 113.5 – 138.7 mmol/L											
Albumin 20%											
Gelofusine 4%	274		154	120							
Voluven 6% HES 130/0.4/9:1	308		154	154							
Venofundin 6% HES 130/0.42/6:1	309		154	154							
Volulyte 6% HES 130/0.4/9:1	286.5		137	110		4		1.5	34		
Tetraspan 6% HES 130/0.42/6:1	296		140	118		4	2.5	1.0	24	5	

mEq = mmol/L x ion charge.

*1 mmol lactate produce 1 mmol bicarbonate (in liver)

**1 mmol acetate produce 1 mmol bicarbonate and 1 mmol malate produce 2 mmol bicarbonate (in muscle)

HYPONATREMIA (<135 mmol/L)

Table 2.12: Classification of Hyponatremia

	Hypervolemic Hyponatremia	Normovolemic Hyponatremia	Hypovolemic Hyponatremia
Description	Caused by excess Na ⁺ and fluid but fluid excess predominates.	Normal total body Na ⁺ with excess fluid volume (i.e. dilutional).	Deficit of both Na ⁺ and fluid, but total Na ⁺ is decreased more than total body water.
Diagnosis	Urine Na ⁺ < 25 mmol/L: edematous disorders (i.e. heart failure, cirrhosis, nephrotic syndrome) Urine Na ⁺ > 25 mmol/L: acute or chronic renal failure.	Urine osmolality > 100 mOsm/kg: Impaired water excretion Urine Na ⁺ > 40 mmol/L: Glucocorticoid deficiency, hypothyroidism, stress, drugs.	Urine Na ⁺ < 25 mmol/L: Nonrenal loss of Na ⁺ (e.g. emesis, diarrhea) Urine Na ⁺ > 40 mmol/L: Renal loss of Na ⁺
Treatment	Sodium and water restriction; treat underlying cause; vasopressin receptor antagonists (e.g. conivaptan, tolvaptan*).	If drug-induced SIADH, remove offending agent; fluid restriction; demeclocycline; vasopressin receptor antagonists (e.g. conivaptan, tolvaptan*)	Fluid resuscitation (see above)
Example	Heart failure, cirrhosis, nephrotic syndrome	SIADH	Fluid loss (e.g., emesis, diarrhea, fever), third-spacing, renal loss (diuretics)

*Not available in Malaysia upon publication.

i) Causes

Table 2.13: Causes and mechanism of hyponatremia

CAUSES	MECHANISM
Replacement of lost solute with water	Loss of solute (e.g. vomiting, diarrhea) involves the loss of isotonic fluid. Hyponatremia can develop when the lost fluid is replaced with water.
Volume depletion and organ hypoperfusion	Stimulate ADH secretion to increase water reabsorption in the collecting tubules.
Syndrome of inappropriate ADH secretion and cortisol deficiency	Syndrome characterized by excessive secretion of antidiuretic hormone (ADH) in absence of normal osmotic or physiologic stimuli (increased serum osmolality, decreased plasma volume, hypotension).
Medications	Thiazide diuretics and antidepressants (especially SSRI, TCA). More likely in elderly patients and in those who drink large volumes of water.
Renal failure	Impairs the ability to excrete dilute urine, predisposing to hyponatremia.

ii) Sign and Symptoms

- The clinical features of acute hyponatremia are related to osmotic water shifted that leads to increased ICF volume and brain cells swelling. Mild hyponatremia is usually asymptomatic.
- Serum Na⁺ < 120 mmol/L may be associated with disturbed mental state, restlessness, confusion and irritability.
- As the Na⁺ approaches 110 mmol/L, seizures and coma may occur.

iii) Correction

Total Na⁺ deficit (mmol) = (130 – current Na⁺) x 60% of body weight in kg

Volume (ml) required to replace total Na⁺ deficit using 0.9% NaCl?

$$= \frac{\text{Total Na}^+ \text{ deficit (mmol)}}{154 \text{ (mmol /L)}} \times 1000$$

Volume (ml) required to replace total Na⁺ deficit using 3% NaCl?

$$= \frac{\text{Total Na}^+ \text{ deficit (mmol)}}{513 \text{ (mmol /L)}} \times 1000$$

The volume calculated should be given within the calculated number of hours

$$= \frac{(130 - \text{current Na}^+)}{0.5}$$

The rate of rise in plasma Na should not exceed 0.5 mmol/L/hour (10-12 mmol/day) to avoid cerebral pontine myelinolysis.

PSEUDOHYPONATREMIA

A condition when Na⁺ content in the body is not actually reduced, but rather, shifts from the EC compartment into the cells to maintain plasma osmolality in a normal range.

Normally associated with normal osmolality

i) Causes

- Primary or secondary hyperlipidaemia disorder, severe hyperglycaemia (DKA).
- Plasma protein elevations above 10 g/dL, as seen in multiple myeloma or macroglobulinemia.

ii) Treatment

- Correct underlying condition

HYPERNATREMIA (>145 mmol/L)

i) Causes

- Loss of water (Fever, GI loss, burn, infection, renal loss).
- Administration of hypertonic saline/exogenous source of Na⁺.

ii) Sign and Symptoms

- Features are tremulousness, irritability, ataxia, spasticity, mental confusion and coma.

iii) Correction

Free H ₂ O replacement (Use Dextrose 5%) Water deficit (L) = 0.6 x BW in kg x $\frac{\text{measured Na}^+ - 1}{140}$
--

To be given over 48-72 hours

Sterile Water (Should only be administered through NG)

- Rate of correction should not exceed 0.5 mmol/L/ hour (10-12 mmol/day) to avoid cerebral pontine myelinolysis.

2.5.6 Potassium (3.5-5.0 mmol/L)

Potassium is the principal intracellular ion. Normal potassium is regulated by renal excretion, to maintain electroneutrality with sodium. Nearly 98% of the body's potassium is intracellular. The ratio of intracellular to extracellular potassium is important in determining the cellular membrane potential. Small changes in the extracellular potassium level can have profound effects on the function of the cardiovascular and neuromuscular systems.

HYPOKALEMIA (<3.5 mmol/L)

i) Causes:

- Decreased potassium intake
- Increased entry into cell
 - o Elevation in extracellular pH
 - o Hypokalemic periodic paralysis
 - o Marked increase in blood cell production
 - o Hypothermia
 - o Insulin
 - o Chloroquine intoxication
 - o Elevated beta-adrenergic activity – stress or administration of beta-agonists
- Increased GI losses
 - o Vomiting, diarrhea
 - o Tube drainage
 - o Laxative abuse
- Increased urinary losses
 - o Diuretics
 - o Renal tubular acidosis
 - o Primary mineralocorticoid excess
 - o Amphotericin B
 - o Loss of gastric secretions
 - o Polyuria
 - o Hypomagnesaemia
- Increased sweat loss
- Dialysis
- Plasmapheresis

ii) Sign and Symptoms (usually present when K < 2.5 mmol/L)

- Malaise, fatigue
- Neuromuscular disturbances: Weakness, hyporeflexia, paraesthesias, cramps, restlessness leg syndrome, rhabdomyolysis, paralysis
- Gastrointestinal: Constipation, ileus
- Polyuria, polydipsia, metabolic alkalosis
- ECG changes: small or inverted T waves, prominent U wave, depressed ST segments, prolonged PR interval
- Arrhythmias: First and second degree heart block, atrial fibrillation, ventricular tachycardia, ventricular fibrillation

iii) Correction

- Replace magnesium first if concurrent hypomagnesemia
- Generally, reduction of 1 mmol/L serum K⁺ results in 200 - 400 mmol potassium deficit
- Replacement should be guided by K⁺ concentration; important to recheck level (2 - 4 hourly)

FORMULA 1

- Potassium deficit (mmol)
= $\frac{(4.5 - \text{Current K}^+) \times 0.4 \times \text{Body Weight}}{13.4} + \frac{1 \times \text{Body Weight}}{13.4}$

FORMULA 2

- Potassium deficit (mmol) = 4 – Current K⁺ x 0.4 x Body Weight
- Replacement
 - Infusion rate: 10-20 mmol/hr (peripheral); max 40 mmol/hr (central line)
 - Peripheral line administration should not be more than 60 mmol/L to avoid irritation
- Caution:
 - Avoid mixing K⁺ and dextrose solution as this may cause insulin release which result in IC shift of K⁺
 - Renal impaired and elderly patient

Potassium level (mmol/L)	Treatment	Comments
3.0-3.5	Oral KCl 60–80 mmol/day (> 60 mmol/day should be divided)	Daily K ⁺ check up
2.5-3.0	Oral KCl 120 mmol/day or IV 60–80 mmol administered at 10–20 mmol/hour	Monitor closely (2 hrs after infusion)
2.0-2.5	IV KCl at 10 – 20 mmol/hr	Consider frequent monitoring with ECG
<2.0	IV KCl at 20 – 40 mmol/hr	Requires continuous monitoring with ECG

*1g IV KCl = 10 mmol K⁺

HYPERKALEMIA (> 5.0 mmol/L)

i) Causes

- Increased in potassium intake.
- Increased cell diffusion of potassium to extracellular fluid (Acidosis, insulin deficiency, β adrenergic blockade, digoxin toxicity, rewarming after cardiac surgery, succinylcholine).
- Reduced potassium excretion (Kidney dysfunction, intravascular volume depletion, hypoaldosteronism, potassium sparing diuretics, ACEi/ARB).
- Potassium released from cells while or after obtaining the blood specimen; because of trauma during venipuncture
- Measurement of serum rather than plasma potassium concentration; caused by potassium release during coagulation.

ii) Sign and Symptoms

- Muscle weakness and paralysis (typically occur when K^+ exceeds 8 mmol/L).
- Abnormal cardiac conduction (peaked, narrowed T waves, widening of QRS) ventricular fibrillation, asystole. ECG has limitation in predicting cardiac toxicity. Thus, patient with K^+ more than 6 mmol/L should be treated even in the absence of ECG changes.
- Conduction disturbances are enhanced by hypocalcaemia, hypomagnesaemia, acidosis, rapid increase in potassium concentration.
- Pseudohyperkalemia.

iii) Correction

- Asymptomatic: Ca^{2+}/Na^+ Polystyrene Sulfonate.
- Urgent and immediate treatment is required for patients with:
 - i. Plasma K^+ above 6.5 mmol/L
 - ii. Severe muscle weakness
 - iii. ECG changes
- Treatment for symptomatic hyperkalaemia:

i) Calcium	<ul style="list-style-type: none">• To prevent hyperkalemia-induced arrhythmias even if patients are normocalcemic.• Calcium gluconate 10% 10 ml (1 g calcium gluconate = 90 mg of calcium elemental) over 2-10 minutes can be administered peripherally and is preferred over calcium chloride because of reduced risk of tissue necrosis.• Onset is fast, within minutes, but duration is short (30–60 minutes).• Not for plasma K^+ reduction, but will antagonize the effect of K^+ in cardiac conduction cells.• Use in urgent circumstances while waiting for other measures (e.g., insulin and glucose) to lower plasma K^+. <p>Warning: Avoid use in patients receiving digoxin because hypercalcaemia can precipitate digoxin toxicity especially cardiac arrhythmia and may cause sudden death.</p>
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ii) Insulin and glucose	<ul style="list-style-type: none"> • 10 units of regular insulin, given intravenously plus, 25–50 g of glucose administered as a 50% dextrose intravenous push in order to prevent hypoglycaemia. • Lowers plasma K⁺ by 0.5–1.5 mmol/L within an hour and may last for several hours. • If patients are hyperglycemic, insulin may be administered alone.
iii) Sodium bicarbonate	<ul style="list-style-type: none"> • 50 mmol of sodium bicarbonate infused slowly over 5 minutes; may repeat in 30 minutes if needed. • May lower plasma K⁺ within 30–60 minutes and persist for several hours. • The efficacy of bicarbonate is disputed, it seems least effective in patients with advanced kidney disease; may be preferred and effective in patients with underlying metabolic acidosis.
iv) β₂-adrenergic agonists (off-label use, Medscape)	<ul style="list-style-type: none"> • Salbutamol 10–20 mg nebulized over 10 minutes or 0.5 mg given intravenously. • Lower plasma K⁺ by 0.5–1.5 mmol/L. • Onset is within 90 minutes with inhalation. • Avoid use in patients with coronary ischemia due to risk of tachycardia. • Not recommended as single agent for urgent treatment as 40% patients may not respond to inhaled salbutamol, consider use as combination with insulin.

The treatment options above should be followed by one of the following agents to remove excess K⁺ from the body.

i. Diuretics

- Loop or thiazide-type diuretics increase K⁺ renal excretion
- Ineffective in patients with advanced kidney disease

ii. Cation-exchange resin

- Exchanges Na⁺ for K⁺, thus resulting in GI excretion of K⁺
- As onset is slow (2 hours) and efficacy is unpredictable, it is not indicated for emergency treatment of hyperkalemia
- Kalimate (Calcium Polystyrene Sulfonate): Oral: 15g 3-4 times daily, Rectal: 30 – 50 g as a retention enema. (oral Kalimate contraindicated in obstructive bowel disease)

iii. Dialysis

- Used in severe hyperkalemia or when other treatment are ineffective
- Need to monitor for rebound increases in K⁺ post dialysis
- More common in advanced kidney disease patients

2.5.7 Calcium (2.1 - 2.65 mmol/L), Ionised Calcium (1.1 – 1.3 mmol/L)

Calcium regulation is critical for normal cell function, neural transmission, membrane stability, bone structure, blood coagulation, and intracellular signaling. Normal ionised calcium has been advocated to prevent neurologic and cardiovascular complications. The essential functions of this divalent cation continue to be elucidated, particularly in head injury/stroke and cardiopulmonary effects. Depending on the cause, unrecognized or poorly treated hypocalcemic emergencies can lead to significant morbidity or death.

Calcium adjustment in Hypoalbuminemic patients

Adjusted Calcium level =

Current calcium in mmol/L + 0.02 [40 – Current albumin in g/L]

HYPOCALCEMIA

i) Causes

- Hypoparathyroidism
- Metabolic alkalosis
- CKD
- Hyperphosphatemia
- Vit D deficiency
- Alcoholism
- Receives large amount of blood products transfusion
- Undergoing continuous renal replacement therapy

ii) Sign and Symptoms

- Paraesthesia
- Circumoral numbness
- Cramp
- Tetany
- Dystonia
- Convulsion
- Psychosis
- Papilloedema (severe)
- Prolonged Q-T interval on ECG
- Chvostek's sign – gentle tapping over facial nerve cause twitching of facial muscles.
- Trousseau's sign – inflation of sphygmomanometer cuff above diastolic pressure for 5 min causes carpopaedal spasm
- Long-standing hypocalcemia may result in dry skin, coarse hair, alopecia, brittle nails and hypoplastic teeth

iii) Correction

10 mls 10% Ca gluconate (can be given through peripheral line; contains 90 mg elemental calcium)
--

Treatment directed at underlying cause
--

If symptomatic (muscle spasm, laryngeal spasms or cardiac involvement)
--

If ionised Ca^{2+} <0.65 mmol/L or corrected Ca^{2+} <2.0 mmol/L
--

i) IV 10-20mls 10% Ca gluconate over 10 min followed by 1-2 mg/kg/hr x 6-12hr i.e. 30 mls 10% Ca gluconate diluted to 100 mls N/S run at 25-40ml/hr x 6-12hr
--

ii) Give Mg if deficient

iii) Daily maintenance dose of elemental Ca 1 – 4g orally

* Calcium correction to be tailored according to clinical condition and serum calcium level.

HYPERCALCEMIA

i) Causes: malignancy, hyperparathyroidism

ii) Sign and Symptoms

- Neurology : Depression, proximal myopathy, fatigue, confusion, stupor and coma
- Renal : Hypertension, renal colic (nephrolithiasis), polyuria and nocturia (nephrogenic diabetes insipidus), dehydration
- Bones : Pain, pathological fractures – osteitis fibrosa cystics in hyperthyroidism (sub-periosteal resorption, bone cysts)

- Abdominal : Nausea, vomiting, constipation, abdominal colic, peptic ulcer disease, pancreatitis
- General : Soft tissue and corneal calcification (band keratopathy)
- ECG changes: Shortened QT intervals

iii) Correction

- Restoration of intravascular volume with normal saline
- Loop diuretic such as furosemide to promote calcium excretion.
- Bisphosphonates, such as pamidronate (30–90 mg by i.v. infusion), is recommended for severe cases especially malignant related hypercalcemia
- Other therapies include steroids and calcitonin

2.5.8 Magnesium (0.7 – 1.0 mmol/L)

Mg is the second most prevalent intracellular cation, and it has an important role in neuromuscular function and as a cofactor in various enzymatic reactions, including those involving adenosine triphosphatase. Mg is therefore an important element for providing energy and regulating various processes in the cell and cell membrane. It also has a role in protein and DNA synthesis, DNA and RNA transcription, translation of messenger RNA, and the regulation of mitochondrial function. Only 1 % is in ECF, 60% are found in bones and remainder in cells. Therefore, serum magnesium may not reflect total body magnesium content.

HYPOMAGNESEMIA

i) Causes

- GI disorders - short-bowel syndromes, fistulas, pancreatitis
- Alcoholism
- Endocrine disorders - hyperparathyroidism, hyperthyroidism, Conn's syndrome, hyperaldosteronism
- Renal diseases - renal tubular acidosis
- Drugs - aminoglycosides, amphotericin B, cyclosporine, ticarcillin, diuretics, Cis-platinum

ii) Sign & Symptoms

- Symptomatic magnesium depletion is associated with refractory hypokalemia, hypocalcemia and metabolic alkalosis.
- Features are:
 - Tremors, muscle twitching.
 - Positive Trousseau's and Chvostek's signs
 - Generalized weakness, confusion, ataxia
 - Vertical nystagmus
 - Tetany, seizure
 - ECG → **Mild to moderate:** prolongation of QT or QU intervals, bifid T waves, U wave, supraventricular and ventricular ectopics.
Severe: PSVT, R-on-T phenomena, torsades de pointes, VT Hypomagnesaemia facilitates development of digoxin cardiotoxicity.

iii) Correction

1 vial of Magnesium sulphate = 2.47g/5ml = 10mmol Mg/5ml	
Without symptoms	IV 0.125g/kg MgSO ₄ x 24h then, 0.0625g/kg MgSO ₄ daily x 3-5 days. IV MgSO ₄ 20mmol in 40ml NS OVER 2 hours. IV MgSO ₄ 10mmol in 20ml NS OVER 1 hour.
If Mg ²⁺ <0.6 mmol/L with cardiac abnormalities/ asthma/ eclampsia/ tetanus/ pulmonary hypertension	IV 0.05-0.07 g/kg MgSO ₄ over 20 min then, 0.03 - 0.05 g/kg/h Keep serum Mg ²⁺ 20-4 mmol/L

- For emergency treatment (e.g.: torsades), magnesium can be administered as IV push. However, slow IV infusion is preferred during other circumstances to avoid hypotension and/or increased renal excretion due to rapid administration.
- Half of administered magnesium is renally excreted, thus, magnesium should be replaced over 3 – 5 days.

HYPERMAGNESEMIA

i) Causes

- Excessive administration of Mg salts or conventional doses of Mg in the presence of renal failure.

ii) Sign and Symptoms

- Magnesium levels of 1-2 mmol/L are associated with: Nausea, vomiting, skin flushing, weakness, lightheadedness.
- High magnesium levels are associated with depressed levels of consciousness, respiratory depression, and cardiac arrest.

iii) Correction

- Directed towards increasing excretion of the ion, which can be done by inducing diuresis with normal saline and loop diuretics, and may require dialysis.
- IV Calcium Gluconate: 100–200 mg of elemental Ca²⁺ over 5-10 minutes.
- Discontinue all magnesium-containing medications.

2.5.8 Phosphate (0.8 – 1.5 mmol/L)

Phosphate is the most abundant intracellular anion and is essential for membrane structure, energy storage, and transport in all cells. In particular, phosphate is necessary to produce ATP, which provides energy for nearly all cell functions. Phosphate is an essential component of DNA and RNA. Phosphate is also necessary in red blood cells for production of 2,3-diphosphoglycerate (2,3-DPG), which facilitates release of oxygen from hemoglobin. Approximately 85% of the body's phosphorus is in bone as hydroxyapatite, while most of the remainder (15%) is present in soft tissue. Only 0.1% of phosphorus is present in extracellular fluid, and it is this fraction that is measured with a serum phosphorus level.

HYPOPHOSPHATEMIA

i) Causes:

- Hyperparathyroidism, Vit D deficiency, renal tubular acidosis, respiratory alkalosis, parenteral nutrition, alcoholism, refeeding syndrome

ii) Sign and Symptoms

- Weakness is the most common symptom suggesting hypophosphatemia and may involve any muscular system to any extent
- Diplopia
- Dysarthria
- Dysphagia
- Weakness of trunk or extremities, particularly the large muscle groups
- Symptoms of respiratory insufficiency or myocardial depression may indicate hypophosphatemia
- Neurologic symptoms may vary, ranging from simple paresthesias to profound alterations in mental status

iii) Correction

Treat underlying cause where applicable

Add 2 ampoules of KH_2PO_4 in 1 pint IVD

OR

IV KH_2PO_4 20mmol/L in 100ml NS OVER 6 hours

OR

IV KH_2PO_4 10mmol/L in 100ml NS OVER 4 hours

Max rate: 7.5 mmol/hr (rapid administration may result in hypocalcemia, tetany, and hypotension)

Alternative for hyperkalemic patient with hypophosphatemia:-

Oral Sodium Phosphate (0.5 mmol = 60mg):

Phosphorus 10 – 20 mmol/ day in 3 or 4 divided doses.

IV sodium glycerophosphate pentahydrate 306.1 mg/mL (Glycophos®*):
10 – 20ml in 100ml NS / D5W over 8 hours.

*Each ml of Glycophos® contains 2 mmol Sodium and 1 mmol Phosphate.

HYPERPHOSPHATEMIA

i) Causes

- Increase intake or reduced excretion
- More common in CKD or hypoparathyroidism patients

ii) Sign and Symptoms

- Normally patients are asymptomatic, sign and symptom including hypocalcemia, ECG changes and paresthesias
- May present with ectopic calcification of nephrocalcinosis, nephrolithiasis and band keratopathy

iii) Correction

- Haemodialysis
- Hypertonic glucose solutions to shift ECF phosphate into the ICF can be used
- Calcium carbonate, magnesium and aluminium

Caution: Avoid aluminium in renal failure (calcium is preferred)

2.6 MEDICATION ADMINISTRATION THROUGH ENTERAL FEEDING TUBES

2.6.1 Introduction

Enteral feeding plays an important part in managing the critically ill patients. According to European guidelines for enteral and parenteral nutrition, enteral feeding is the preferred method of providing nutritional support in haemodynamically stable patients who have a functioning GI tract but cannot maintain an adequate oral intake. The goals are to provide adequate calories and proteins, to prevent or to correct the nutrient deficiencies, to preserve the gastric mucosa function, thus avoiding gut failure and to promote wound healing, as well as enhance host immune function.^{1,2} It should be started within 24 – 48 hours upon ICU admission using an appropriate amount of feed if the patients are not expected to be on full oral diet within 3 days.^{1,2}

2.6.2 Methods of Enteral Feeding Administration

Type of method is determined by tip location of feeding tube, patient's clinical condition and tolerance to EN, and the overall convenience.³

2.6.2.1 Continuous feedings

- Delivered at a slow and continuous rate over a period of 24 hours with sporadic interruptions for medications deliver or medical procedures. It can be directly infused into the small bowel.
- Problems such as possible drug-nutrient interactions and frequent interruptions of feeding for medications administration, thus increase in tube feeding rate might be needed in order to maintain adequate nutrition is given to the patients.
- In addition, frequent interruptions of feeding might be challenging for health care workers as they have to stop and restart the feedings in a timely manner.

2.6.2.2 Cyclic EN

- Administration of enteral feedings via a continuous way over a specified period (i.e. 8-20 hours per day) and it is generally infused at night thus allowing oral intake during the daytime. Like continuous feedings method, this cyclic EN can be directly infused into the small bowel too.

2.6.2.3 Bolus feedings

- This method mimics the usual eating patterns and involves the infusion of EN over a short period of time at specified intervals, usually 4 – 6 times per day. Therefore minimal drug-nutrient interactions and interruptions of feeding are achieved with this kind of method.

2.6.2.4 Intermittent feedings

- Similar technique to that of bolus feeding but it is used over a longer duration, which may help to improve tolerance.
- Not recommended for direct feeding into the small bowel.

2.6.3 Types of Enteral Formula

According to the ESPEN guidelines, there is no clear cut clinical advantage of peptide-based formulae shown in studies, therefore, whole protein formulae are appropriate in most patients. Immune-modulating formulae (formulae enriched with arginine, nucleotides and omega-3 fatty acids) should be considered in patients who undergo elective upper GI surgery, in patients with a mild sepsis, in trauma patients and in patients with ARDS. Due to insufficient data available, ESPEN guidelines do not recommend this type of formula in burned patients. In burned patients, trace elements (Cu, Se and Zn) should be supplemented in a higher dose and glutamine should be added to the standard enteral formula. Besides burned patients, glutamine should be considered in trauma patient too.¹

2.6.4 Types of Enteral Feeding Tubes⁴

- Nasoenteric tubes are normally used for short- to medium-term feeding (days to weeks) as it has lots of drawbacks on long-term management. For example, nasoduodenal tube tends to recoil into the stomach, cause nasal pressure sores, and sometimes it can be pushed out of place accidentally. Examples of nasoenteric tubes are nasogastric tube (NGJ), nasoduodenal tube (NDT), and nasojejunal tube (NJT).
- Ostomy tubes are used for long-term feeding (months to years). Generally, the tubes are inserted into the desired place endoscopically, radiologically or surgically. Examples of ostomy tubes are percutaneous gastrostomy tube, percutaneous jejunostomy tube, and percutaneous gastrojejunostomy tube.
- External diameter of the feeding tube is measured in French unit (Fr) where 1 Fr = 0.33mm.
- Enteral feeding tubes are made up of polyvinylchloride (PVC), polyurethane (PUR), silicone or latex.

2.6.5 Drug Therapy Review^{3, 4, 5, 6}

- Temporarily discontinue medications that are not immediately necessary, e.g. hormone replacement therapy.
- Consider giving medications by an alternate route such as transdermal, rectal, inhaled, intramuscular, subcutaneous, buccal, sublingual or intravenous whichever possible.
- Consider switching to drugs that work similarly and can be administered via alternative routes (changes in dosage may be needed to achieve an equivalent effect).
- If alternative routes of drug delivery are not an option, then medications may be given via enteral feeding tube. Several factors have to be considered

before drug being administered through enteral tube. Evaluate the tube type, tube location in the GI tract, site of drug action and absorption and effects of food on drug absorption (e.g. sucralfate is not suitable for intestinal feeding tubes administration as it acts locally in the stomach). Bioavailability may increase with intrajejunal administration of drugs with extensive first-pass metabolism, such as opioids, tricyclics, beta-blockers, or nitrates.

- For drugs that require administration on empty stomach, feeding should be stopped 30 minutes before and after dosing if the tube is placed in the stomach.
- If the tablets can be crushed into fine powder, the powder should be mixed in slurry with a suitable diluent and given through large-bore feeding tubes.^{6, 7} Sometimes, pellets inside some microencapsulated products may be poured down the large-bore enteral feeding tube, provided that the pellets are not crushed (e.g. Creon® – pancreatic enzymes).⁶
- Examples of drug formulations that should not be crushed are sustained-release or modified-release, enteric-coated and teratogenic, carcinogenic or cytotoxic medication (e.g. antineoplastics, hormones, and prostaglandin analogs as aerosolized particles might be harmful to the health care workers).^{4,6}
- Feeding tubes should be flushed with 15-30 ml of water before and after administration of medication via the tube to prevent tube blockage (in the case of fluid-restricted patients, revise the flush volumes to meet the patient's prescribed fluid restriction, air flushes may be used to replace water flushes).⁴
- Medication should not be added to enteral formula to reduce the risk of microbial contamination and to avoid drug-nutrient incompatibilities.^{6,8} A possible exception for mixing medications with feeding formulae involves the addition of liquid electrolytes, such as sodium or potassium, to the enteral preparation.³
- When several medications are to be given at the same time, all medications should be administered separately and the tube flushed with at least 5 ml of water after each dose.⁸
- Liquid preparations are the preferred formulations whenever possible as they are less likely to cause blockage of feeding tubes. However, medication dosage or frequency may need adjustment when switching from solid to liquid preparations, this is particularly important when switching from an extended-release product to a liquid preparation, which is immediate release and requires frequent dosing (e.g. extended-release phenytoin capsules may be given once daily, however phenytoin suspension is an immediate-release product that need to be dosed 2 to 4 times daily).^{3,6}
- Many commercial liquids are extremely hyperosmolar with osmolalities over 1000 mOsm/kg and the osmolality of GI secretions, on the other hand, ranges from 100 to 400 mOsm/kg. Diarrhea, cramping, abdominal

distension and vomiting may occur after administration of hyperosmolar products through the feeding tube and this can be overcome by diluting medication with 10-30 ml of sterile water before administration. Sterile water contains no solute, thus it does not contribute to the mixture's osmolality.^{3, 6, 9}

- Osmolality of the resulting mixture can be calculated using formula below:⁶

$$\text{Osmolality of diluted mixture} = \frac{(\text{osmolality of drug} / \text{volume of drug})}{\text{total volume of mixture}}$$

- Inactive ingredients or excipients present in liquid products may also cause side effects when given enterally. Many sweeteners, including mannitol, lactose, saccharin, sorbitol, and sucrose, may cause or worsen diarrhea. For example, sorbitol, used as a sweetening agent to improve medication taste as well as tolerability, may cause bloating and flatulence at a total daily dose of 10gm, and cause an osmotic laxative effect (resulting in cramping and diarrhea) at a total daily dose of 20gm. While many preparations contain only small amounts, sorbitol's effects are cumulative, based on the total daily dose. Patients receiving multiple drugs containing sorbitol are more likely to experience adverse reactions. Minimize risk by avoiding sorbitol-containing agents whenever possible.^{3,6}

2.6.6 Types of medication formulation

2.6.6.1 Liquid formulations

- Solutions^{3, 4, 6}
 - A homogenous system where distribution of drug is even throughout the system, thus giving an accurate dosing.
 - Water is the most widely used solvent for pharmaceutical products. Some examples of excipients used are ethanol, sorbitol, glycerol and propylene glycol.
 - Excipients used in the formulation have to be taken into consideration as sufficient quantities of excipients may post some pharmacological effect, e.g. $\geq 20\text{gm/day}$ of sorbitol will cause diarrhoea.
- Suspensions^{3, 4}
 - Drug presents in the formulation is insoluble or coated microgranules.
 - Often used for antibiotics and generally contain less sorbitol than other liquid products.
 - For non-granular suspensions, further dilution is needed when it is administered via enteral feeding tubes due to its viscosity and osmolality.
 - For granular suspensions, granule size and viscosity have to be taken into consideration during administration via enteral feeding tubes.
 - Adequate shaking of suspensions is needed before administration via enteral feeding tubes as settling and inadequate shaking may affect the accuracy of dosing.

2.6.6.2 Solid dosage formulations

Certain solid dosage forms may be used for administration via feeding tubes, e.g. compressed tablets, including those that are sugar- or film-coated, are immediate-release products may be crushed.³

- **Soluble tablets⁴**
 - Tablets readily dissolve in water, usually due to its salt alternative.
 - Before administration, it is important to ensure a complete dissolution has achieved.
- **Effervescent tablets⁴**
 - Effervesce and dissolve or disintegrate when placed in water and it normally contains high content of sodium.
 - Suggested volume to dissolve the tablets is usually $\frac{1}{3}$ to $\frac{1}{2}$ a tumblerful of water, however, smaller volume may be used. It is important to ensure tablets are fully dispersed before administration to avoid gas production in enteral feeding tube, and do not disperse tablets in syringe owing to the production of gas.
 - The osmolality of solution produced when tablet has completely dissolved is low, therefore this reduces the incidence of diarrhoea.
- **Dispersible tablets⁴**
 - It can disintegrate in small amount of water (e.g. 10-15 mls) to give particles that may or may not suspend in water.
 - The resultant particles or granules may be too large to be administered via fine-bore tubes; not suitable for enteral feeding tube administration.
- **Orodispersible tablets⁴**
 - Readily disperse on the tongue and it is not necessarily absorbed sublingually, merely swallowed with saliva.
 - Do not take this kind of formulation with water.
- **Buccal/ Sublingual tablets⁴**
 - Drugs are absorbed via the oral mucosa, thus bypass the first-pass metabolism effects of the liver.
 - It is an alternative for NBM patients or those who are unable to swallow, provided patient able to produce normal quantities of saliva (caution in head and neck surgery patients).
 - Not suitable to be administered via enteral feeding tubes due to the extensive first-pass metabolism, and therefore reduces the absorption of drug.
- **Modified-release tablets^{4, 6}**
 - The drug is released slowly over time. Thus this formulation is not suitable to be administered via enteral feeding tubes as crushing, for example, will alter the pharmacokinetic profile of the drug, leading to erratic blood levels.

- **Hard gelatin capsules^{3,4}**
 - Some hard gelatin capsules can be opened and the content (e.g. powder) can be mixed with 10 – 15 ml of water. However, several factors have to be taken into consideration, for example, risk of powder inhalation, some contents are granules rather than powder, and some contents may not disperse in water owing to the hydrophobic or hydrostatic nature of the powder.
- **Soft gelatin capsules**
 - Contents in the capsules are usually poorly soluble in water, and are therefore contained in an oily solution within the capsule, e.g. Cyclosporin (Neoral®).⁴
 - It may be possible to pierce the capsule shell using a pin, squeeze out the contents and given via feeding tube as immediate-release dosage forms, e.g. Nifedipine for sublingual use; however, accurate dosing cannot be guaranteed.^{4,6}
 - Unless the capsule contents are completely removed and administered via the feeding tube, or else it is not recommended/unsuitable for administration via enteral feeding tube.^{4,6}
- **Enteric-coated tablets**
 - The enteric coating is used to prevent the degradation of drug in the acidic conditions of the stomach or to reduce the incidence of gastric side-effects.^{4,6}
 - When administered via enteral feeding tube, the crushed tablets are likely to cause blockage as this kind of tablets do not crush well but break into small chunks that bond together when moist.⁶ Sometimes it may cause degradation of the drug in the stomach if the end of the feeding tube is placed in the stomach, thus result in decreased amounts of drug available for absorption.⁴

2.6.6.3 Injectable formulations^{3,4}

- Injectable formulation has a different salts form from the oral formulation and variable pH will affect the oral bioavailability when administered via enteral feeding tube.
- Moreover, the osmolality of parenteral drugs may be higher, potentially causing osmotic diarrhea.
- Evaluate the drugs' monographs when considering the appropriateness of administration via enteral feeding tube.
- e.g. Vancomycin injection is administered orally/enterally for its topical effect in the gut.

2.6.7 Drug interactions

2.6.7.1 Interaction between drugs and feed/nutrient therapy⁴

- The absorption of the drug at the GI tract is via a passive process of diffusion from the gut lumen across the mucosa into the splanchnic circulation. However, some drugs (e.g. methyl dopa and levodopa) are

being absorbed via the same way as the nutrients, i.e. active transport system. Thus, a change in diet will affect the drug absorption (e.g. high-protein diet will result in decreased absorption of methyldopa and levodopa).

- Drug absorption also depends on the physiological affect of food/feed on the GI tract, owing to the ability of food and feeds to alter the pH of the GI tract.
- The presence of some components in the feed formulations (e.g. calcium, iron) will bind with the drug, therefore result in changing of the molecular size or solubility, thus reduce the absorption.
- Drug distribution is altered in severely malnourished patient (e.g. low plasma proteins for drug binding results in increasing free circulating drug concentrations).

2.6.7.2 Interaction between drugs and delivery device

There is a potential interaction between drugs and the enteral feeding tubes.

Table 2.14: Common drug interaction/ incompatibility and special consideration

Interaction / Incompatibility	Recommended intervention(s)
Syrups and other acidic medication (pH less than 4) may clump or thicken when mixed with enteral feeding formulas, thus clogging the feeding tube. ^{3,6}	<ul style="list-style-type: none"> • Stop the enteral feeding for 1 to 2 hours before and 2 hours after drug administration.⁶ • Flush the tube with at least 30 ml of water before and after administering the syrup.³ • To avoid nutritional status being compromised⁶: <ul style="list-style-type: none"> - minimize the time of feeding interruption by using once daily or twice daily dosing regimen
Phenytoin absorption decreased by 50% to 75% when given with enteral feeding, thus decreasing serum drug levels. ⁶	<ul style="list-style-type: none"> • Stop the enteral feeding for 2 hours before and after each dose.⁶ • Flush the tube before and after each phenytoin dose with 60 ml of water.^{3,6} • Dilute Phenytoin suspension with 20 – 60 ml of water, when given through feeding tube, to enhance absorption and increase the dissolution rate.¹⁰ • Higher protein feeding formulae resulted in a greater level of binding and less phenytoin recovery.³ • Close monitoring of serum concentrations is warranted.⁶
Carbamazepine absorption may decrease with enteral feeding. ³ Carbamazepine suspension: drug loss when administered through polyvinyl nasogastric tubes. ^{4,11}	<ul style="list-style-type: none"> • Carbamazepine suspension may be diluted with an equal volume of sterile water or normal saline (a 50% diluted carbamazepine suspension resulted in no drug loss).^{3,11} • Close monitoring of serum concentrations is warranted

Interaction / Incompatibility	Recommended intervention(s)
<p>Warfarin effects may decrease in patients receiving enteral feeding due to reduce absorption and vitamin K antagonism⁶ and also binding of warfarin to proteins in the enteral formulas (as warfarin is highly protein bound, thus reducing the bioavailability and interfering with its anticoagulant effect).³</p>	<ul style="list-style-type: none"> • Consider vitamin K contents in enteral formulas especially in patients receiving large volumes of tube feeds – vitamin K may directly block warfarin's effects in doses of 140-500 mcg/day.⁶ • Consider increasing the warfarin dose or using alternative anticoagulants (heparin, LMWH).⁶ • Monitor prothrombin time/INR.⁶
<p>Fluoroquinolones may have an erratic changes in its pharmacokinetics in patients receiving enteral feeds due to the multivalent cations present in enteral formulas, e.g. calcium, magnesium, aluminium and iron.^{3, 6}</p>	<ul style="list-style-type: none"> • Fluoroquinolones should not be given within 2 hours before or 4 hours after enteral formulas.⁵ • Avoid giving via enteral feeding tubes or concomitantly with enteral formulas – parenteral route is preferred.⁶ • If to be given via enteral tube – crush the tablets and mix it in 20 to 60 ml sterile water immediately before administration.^{6, 12} • Studies showed that enteral feedings decreased absorption of ciprofloxacin significantly more than levofloxacin and ofloxacin. Moxifloxacin, on the other hand, its absorption was not affected by concurrent EN.^{13, 14, 15} • Ciprofloxacin is primarily absorbed in duodenum: a great reduction in both ciprofloxacin peak concentration and bioavailability when administered via jejunostomy tubes versus gastrostomy tubes. Thus jejunal administration should be avoided.¹⁶
<p>Proton-pump inhibitors – these medications are acid labile and inactivated by gastric acid, specially formulated to maintain the acidity until it delivers to alkaline pH of the duodenum for absorption.^{3, 6}</p>	<ul style="list-style-type: none"> • Omeprazole and Lansoprazole capsules (delayed-release) through large-bore nasogastric or gastrostomy tubes (≥18 Fr). <ul style="list-style-type: none"> - Mix the capsule contents (enteric-coated granules) with juices (apple, orange), pour the mixture down the tube, flush with additional juice.^{3, 6} - This method is should not be used with small-bore feeding due to potential tube occlusion.³ - Crushing the enteric-coated granules and mix it with water may cause clumping and lead to occlusion.^{3, 6} • Omeprazole and lansoprazole capsules (delayed-release) through small-bore jejunostomy or gastrostomy tubes. <ul style="list-style-type: none"> - Dissolve the intact enteric-coated granules in sodium bicarbonate 8.4% solution.^{3,17} • Esomeprazole granules (delayed-release) <ul style="list-style-type: none"> - Mix with water and flush down the NG tube.³ • Commercial immediate-release omeprazole with sodium bicarbonate.³ <ul style="list-style-type: none"> - Should only be mixed with water. - Continuous enteral feeding should be held for 3 hours before and 1 hour after medication administration. • Lansoprazole disintegrating tablet (delayed-release).³ <ul style="list-style-type: none"> - Dissolves on tongue or may be mixed with small amount of water in an oral syringe and injected through the NG tube.

Interaction / Incompatibility	Recommended intervention(s)
	<ul style="list-style-type: none"> • Pantoprazole is available as enteric-coated tablet and a new delayed-release oral suspension.³ - Pantoprazole extemporaneous suspension can be compounded using sodium bicarbonate solution. - Should not be given via feeding tubes.⁶ - Form semisolid mass that may occlude feeding tube when mixed with less than 250 ml fluid (still potentially block feeding tube when mixed properly).⁶
Laxatives	<ul style="list-style-type: none"> • Bulk forming laxatives (e.g. methylcellulose) - Consider using fiber-containing enteral nutrition (e.g. Jevity).⁶
Calcium may bind to phosphate in the enteral feed when given concurrently. ⁴ Calcium salts are absorbed in jejunum, thus it can be given via jejunostomy tubes. ⁴	<ul style="list-style-type: none"> • Use parenteral route in acute deficiency states, in medical emergencies or when GI absorption is compromised.⁴ • A prolonged break in feeding is not required, flush the tube adequately to ensure calcium supplement does not come into contact with the feed and clog the tube.⁴ • In the case of phosphate-binding, do not add crushed calcium powder directly to the enteral formula to prevent sediment/ clumping. Administer feed and calcium separately, flush the tube with adequate amount of water after each administration.

2.7 PROKINETIC AGENTS

2.7.1 Introduction

Early enteral feeding (EN) is one of the fundamentals of critical care practice where it can increase gut blood flow, thereby protecting the gastric mucosa.¹ Enteral feeding has fewer septic complications than parenteral nutrition, it decreases catabolic response to injury as well as stress ulceration in the ventilated patient, improves gut immune function and also improves wound healing.^{1, 2, 3, 4, 5} However, enteral feeds are often poorly tolerated by critically ill patients due to impaired gastrointestinal motility.^{1, 2} Factors contribute to this disturbed gastrointestinal motility are head injury, abdominal injury, sepsis, hyperglycaemia, recumbent position, narcotics and catecholamines used.^{2, 5} Disturbed in gastrointestinal function in critically ill patients give rise to poor absorption of drugs and nutrients, as well as abdominal distension, diarrhoea or constipation, vomiting, and may contribute to increased incidence of reflux and health care associated infection.^{2, 5}

Therefore, prokinetic agents play a valuable role in overcoming gastrointestinal dysmotility in the critical care setting.^{1, 2} They increase the rate of luminal transit as well as the force of contraction, thus improve the tolerance to EN, and reduce the gastroesophageal reflux.^{1, 4, 5} Of the available prokinetic agents, treatment of feed intolerance in critical care is limited to metoclopramide and erythromycin in terms of evidence-based practice.^{1, 2, 3}

2.7.2 Types of Prokinetic Agents

Drug	Metoclopramide	Erythromycin
Receptor	Dopamine antagonist, mixed 5-HT ₄ agonist and 5-HT ₃ antagonist. ^{1, 2, 3, 4, 5}	Motilin receptors on enteric nerves and smooth muscle. ^{1, 2, 3, 4, 5}
Class	Motility stimulant ¹	Macrolide antibiotic ^{1, 2, 4}
Action	Sensitizes gut to acetylcholine; increases lower oesophageal sphincter tone. ^{1, 2, 5, 6} Prokinetic properties are limited to upper gastrointestinal tract and no clinically significant effects on large bowel motility have been reported. ⁵	Increased antral activity, which may migrate caudally (depending on dose) ± activation of an intrinsic cholinergic pathway. ^{1, 5}
Dose	10mg-20mg TDS-QID	50-250mg BD/TDS/QID
Contraindication	Patients with head injuries (concerns about increasing intracranial pressure), history of seizures, GI haemorrhage, mechanical obstruction, perforation, pre-existing pheochromocytoma. ⁶	Concomitant therapy with cisapride, dabigatran, pimozone, artemether, or simvastatin. Erythromycin raises statins plasma levels which are metabolised by CYP3A4, thus increase risk of myopathy). ^{6, 7} Avoid in porphyria. ⁷
Caution	Caution in patients with hypertension or following surgical anastomosis/closure; patients with renal impairment; Parkinson's disease; or a history of depression; porphyria; concurrent use of drugs that may cause extrapyramidal reactions. ⁶	Caution in patients with renal and hepatic impairment; concurrent administration of medications relying on CYP3A4 metabolism; myasthenia gravis. ^{6, 7}
Side effects	Extrapyramidal side effects, e.g. agitation, dystonic reactions, tardive dyskinesia, drowsiness, and irritability. ⁶ Hyperprolactinemia. ⁶	Nausea, vomiting, abdominal pain, diarrhea. ⁶
Drug Interactions	Antipsychotics; dopaminergics e.g. bromocriptine. ⁷	Drugs that are metabolized by/ substrate of CYP3A4, CYP1A2. ⁶

*It is important to note that do not give erythromycin for periods longer than 3 days as the therapeutic effect of the drug is known to undergo desensitization and because a persistent failure of erythromycin to stimulate gastrointestinal motility could be due to a defect in erythromycin-activated transmitter mechanisms.⁵

2.7.3 Concerns on Use of Drugs as Prokinetic Agents

2.7.3.1 Cardiovascular Adverse Effects

Metoclopramide and erythromycin have been reported to cause cardiac arrhythmias through prolongation of the QT interval, including the potentially fatal ventricular arrhythmia, *torsades de pointes*.^{3,4,6} The arrhythmias are caused by a block of HERG K⁺ channels and are augmented by comorbidities such as cardiomyopathy, congestive heart failure, coronary artery disease, atrial fibrillation and/or bradycardia, hypokalaemia and hypomagnesia.⁵

It is reported that concomitant use of erythromycin, which is a CYP3A4 isoenzyme inhibitor, and medications like antifungal (ketoconazole, itraconazole, fluconazole, astemizole, and terfenadine), antiarrhythmic drugs (amiodarone, quinidine, procainamide), calcium channel blockers (diltiazem and verapamil), and haloperidol increase the risk of adverse cardiac events.⁸ However, all these reported cardiac adverse effects are not known in critically ill patients as studies were performed in patients who were not critically ill and these agents were given for a longer period in a higher dosage.³ Thus far, no cardiac toxicities or arrhythmias related to the use of metoclopramide or erythromycin have been reported in studies examined impacts of prokinetic therapies for feed intolerance in critically ill adults.³

2.7.3.2 Haemodynamic Adverse Effects

Recently, studies have shown that low dose of erythromycin could induce hypotension in healthy volunteers, with a 10mmHg reduction in systolic blood pressure. Nguyen *et al* evaluate the effects of low dose erythromycin (200mg IV) on blood pressure and heart rate in mechanically ventilated critically ill patients, who did not tolerate to NG feeding and did not require inotropic support. The result shows that there were no significant differences in systolic and diastolic blood pressure and heart rate in both erythromycin and placebo group. The safety of erythromycin in patients with haemodynamic instability or those who require inotropic support, however, requires further evaluation.³

2.7.3.3 Neurological Adverse Effects

Adverse effects such as somnolence, dystonic reactions and tardive dyskinesia are often concern with the use of metoclopramide.³ In traumatic head injury patients, use of metoclopramide should be avoided due to risk of increased intracranial pressure.^{3,4}

Erythromycin, on the other hand, should be avoided in patients with myasthenia gravis as it can precipitate the myasthenia crisis.³ Although data regarding these side effects are lacking, and it is hard to recognize in mechanically ventilated critically ill patients who are often sedated, it should be suspected in patients who are difficult to ventilate or do not tolerate weaning of ventilation or sedation without other obvious medical causes.³

2.7.3.4 Gastrointestinal Adverse Effects

One of the common gastrointestinal adverse effects seen in critically ill patients who are receiving prokinetic therapy is diarrhoea.³ The cause of the diarrhoea is thought to be multifactorial and the majority of cases are not related to infection.³

Study conducted by Nguyen *et al* showed that diarrhoea was most prevalent in patients receiving combination therapy of erythromycin and metoclopramide compared to those who receive erythromycin alone or metoclopramide alone.³ In most cases, diarrhoea was not related to *Clostridium difficile* infection and settled shortly after the prokinetic therapy was stop.³

2.7.3.5 Bacterial Resistance

There are concerns about the use of antimicrobial as a motility agent in critically ill patients due to the possible emergence of microbial resistance, not only to this specific agent, but also cross selection that cause spread of clones resistant to other bacteria.^{4,5,9} Controversy remains over the correct dose of erythromycin used as a prokinetic agent.

The dose of erythromycin used as prokinetic in critically ill patients is often far below the concentrations necessary for an inhibitory effect on susceptible bacterial, thereby providing a close to ideal conditions for the induction of bacterial mutation and selection.^{3,9} In view of growing weight of evidence on increased use of macrolides and the spread of resistance, versus a lack of sufficient and convincing evidence that erythromycin is a superior prokinetic agent to potential alternatives in the critically ill patient population, it is suggested that erythromycin should only be used as a prokinetic agent in critically ill patients when they have failed all other treatment for impaired gastrointestinal motility and are intolerant to metoclopramide.⁹

2.7.4 Other Prokinetic Agents

2.7.4.1 Itopride

The prokinetic properties are thought to arise from antagonism of dopamine D₂ receptors and inhibition of acetylcholine esterase.⁵ Not only it stimulates release of acetylcholine, it also inhibits its degradation, thus promoting gastrointestinal motility. Itopride does not cause any CNS-related side effects because its high polarity does not allow it to cross the blood-brain barrier. It barely elevates the prolactin levels and does not prolong the Q-T interval. Although studies showed that itopride significantly improved symptoms in patients with functional dyspepsia, there is lack of clinical studies on its role in critically ill patients with gastrointestinal dysmotility.¹⁰

2.7.4.2 Domperidone

It is a dopamine antagonist and mediates the inhibitory action of dopamine on the upper GI tract, thus increases esophageal peristalsis and facilitates gastric emptying by augmenting gastric peristalsis and improving antroduodenal coordination.⁵ Unlike the centrally acting metoclopramide, it acts peripherally, and it does not cross blood-brain barrier, thus lesser CNS adverse effects (e.g. dystonic reactions).^{5,11} The IV formulation is associated with cardiotoxicity and predisposed patients to ventricular tachycardia when used concomitantly with other drugs of a similar cardiac adverse effect profile.⁵

In Malaysia, it is only available in oral form, therefore it can only be used in patients who are able to swallow or have a NG tube.⁵ Although so far no literature of adverse effects reported, there is a lack of clinical studies on its role in critically ill patients with gastrointestinal dysmotility.⁵ Most of the clinical studies were conducted in patients with diabetic gastroparesis.⁵

CHAPTER 3

DOSING MODIFICATION IN CRITICALLY ILL PATIENTS

3.1 DOSE MODIFICATION IN RENAL IMPAIRMENT

Renal impairment may be acute or chronic in nature. Chronic kidney disease (CKD) is usually caused by a long-term disease, such as high blood pressure or diabetes that damages the kidneys and reduces their function slowly over time. Whereas, acute renal failure (ARF) is usually caused by an event that leads to kidney malfunction, such as dehydration, blood loss from major surgery or injury, or the use of medicines.

ARF is a common problem in the intensive care unit (ICU) which necessitate the need for renal replacement therapy. The incidence of ARF in critically ill patients is rising and the mortality remains high, with sepsis as the leading cause.¹

Drug dosage adjustment guided by glomerular filtration rate (GFR) is an accepted standard of practice for patients with acute or chronic kidney disease. Cockcroft Gault Equation is a commonly used formula as below:

$$\text{CrCl (ml/min/1.73m}^2\text{)} = \frac{(140 - \text{Age}) \times \text{Weight (kg)} \times (0.85 \text{ if female})}{72 \times \text{SCr (mg/dL)}}$$

This chapter only focus on the most commonly used anti-infective in critically ill patient that requires renal dose adjustment. (Refer Table 3.1).

Table 3.1: Anti-Infective Dosing in Renal Failure

DRUG NAME	USUAL DOSE (Normal renal function)	CrCl (ml/min)	DOSAGE ADJUSTMENT (in renal insufficiency)
ACYCLOVIR	5 - 10 mg/kg IV q8h	> 50	5 - 10 mg/kg IV q8h
		25-50	5-10 mg/kg IV q12h
		24-10	5 - 10 mg/kg IV q24h
		0-9	2.5 -5 mg/kg IV q24h
		HD	2.5 - 5 mg/kg IV q24h (give dose after dialysis on dialysis days)
AMOXICILLIN	250-500mg q8h PO	> 30	no dose adjustment necessary
		10-30	250-500mg q12h
		<10	250 – 500mg q24h
		HD	250 – 500mgq24h (give dose after dialysis)
AMOXICILLIN + CLAVULANATE	1.2g q8h IV	10-50	1.2g q12h
		<10	1.2g q24h
		CRRT	1.2g q24h
AMPHOTERICIN B	0.25 - 1.5 mg/kg/day * not to exceed total daily dose of 1.5 mg/kg	<10	0.5-0.7 mg/kg q24-48h *consider other antifungal agents that may be less nephrotoxic
		HD	0.5 – 1 mg/kg IV q24h after dialysis
		CRRT	0.5 – 1 mg/kg q24h

DRUG NAME	USUAL DOSE (Normal renal function)	CrCl (ml/min)	DOSAGE ADJUSTMENT (in renal insufficiency)
AMPICILLIN	250 mg - 2 gm IV q4-6h	>50	no dose adjustment necessary
		10-50	normal dose q6 - 12h
		<10	normal dose q12-24h
		HD	normal dose q12-24h (give dose after dialysis)
AMPICILLIN / SULBACTAM	1.5 - 3 gms IV q6h	10-50	1.5-3g q8-12h
		<10	1.5-3g q24h
		HD	1.5-3g q24h
		CRRT	1.5-3g q12h
AZITHROMYCIN	500 mg IV/PO once daily for 3 days		no change
CEFAZOLIN	1-2gm q8h	50	no dose adjustment necessary
		10-50	1-2g q12h (same dose for CRRT)
		<10	1-2g q24h - 48h
		HD	Extra 0.5gm -1g after dialysis
CEFEPIME	1 - 2 gm IV q8h-q12h	> 50	no dose adjustment necessary
		10-50	1 - 2 gm q12-q 24h
		<10	0.5-1g q24h
		CRRT	2g q24h
		HD	1g q24h + extra 1g after dialysis
CEFOPERAZONE	1-2gm q12h- q6h Max: 16g/day		Max 2g/ day in patient with renal and hepatic impairment
CEFOPERAZONE + SULBACTAM	1-2g q12h Max: 8g/ day		No dose adjustment for cefoperazone. But sulbactam clearance is affected by renal function.
CEFTRIAXONE	1 - 2 gms IV q24h * max. dose = 4 gm/day		no change * adults with both renal and hepatic failure should not receive more than 2 gm/day
CEFUROXIME	1.5g q8h IV	>50	No dose adjustment necessary
		10-50	1.5g q8h-q12h
		<10	1.5g q24h
		CRRT	1.5g q8-12h
		HD	1.5g q24h
CEFOTAXIME	2g q8h	>50	No dosage adjustment necessary
		10-50	2g q12-24h
		<10	2g q24h
		CRRT	2g q24h
		HD	2g q24h + extra 1g after dialysis
CEFTAZIDIME	2g q8h	>50	No dosage adjustment necessary
		10-50	2g q12h-24h
		<10	2g q24h
		CRRT	2g q12h
		HD	2g q24h + extra 1g after dialysis

DRUG NAME	USUAL DOSE (Normal renal function)	CrCl (ml/min)	DOSAGE ADJUSTMENT (in renal insufficiency)
CIPROFLOXACIN	400mg q8-q12h IV (q8h should be used for <i>P. aeruginosa</i> infection)	>50	No dosage adjustment necessary
		10-50	200mg q12h
		<10	
		CRRT	
		HD	
CLINDAMYCIN	IV 1.2 - 2.7 g/day in 2 - 4 divided doses (max dose: 4800mg daily) OR 150 - 450 mg PO q6h-q8h (maximum dose : 1800mg daily)		no change
CLOXACILLIN	2g q4-6h		no change
DOXYCYCLINE	100 mg IV/PO q12h		no change
ERTAPENEM	1g q24 h	>30	normal dose
		≤30	500mg q24 h
		HD	Supplemental dose of 150mg after HD if last dose administered within 6 hours prior to HD
ERYTHROMYCIN	Base: PO 250 - 500 mg q6 - 12h (max:4g daily) Ethylsuccinate: PO 400- 800mg q6-12h (max:4g daily) Lactobionate: IV 500mg- 1g q6h (max: 4g daily)	>10	100% of dose
		<10	50-75% of dose
ETHAMBUTOL	15 - 25 mg/kg/day	> 50	normal dose
		10-50	normal dose q24 -36h
		< 10	normal dose q48h
		HD	normal dose after each HD
FLUCONAZOLE	400mg q24h	> 50	normal dose
		10-50	50% of normal dose
		<10	50% of normal dose
		CRRT	normal dose
		HD	100% of recommended dose after dialysis

DRUG NAME	USUAL DOSE (Normal renal function)	CrCl (ml/min)	DOSAGE ADJUSTMENT (in renal insufficiency)
GANCICLOVIR	Induction: 5 mg/kg/dose IV q12h x 14 - 21 days	>70	5 mg/kg /dose q12h
		50-69	2.5 mg/kg /dose q12h
		25-49	2.5 mg/kg/dose q24h
		<25	1.25 mg/kg /dose q24h
		HD	1.25 mg/kg/dose 3x/week with doses given after HD
	Maintenance: 5 mg/kg/dose IV q24h	>70	5 mg/kg/dose q24h
		50-69	2.5 mg/kg/dose q24h
		25-49	1.25 mg/kg /dose q24h
		<25	0.625 mg/kg/dose q24h
		HD	0.625 mg/kg/dose 3x/week with doses given after HD
IMIPENEM	500 mg IV q6h OR 1g q8h- 6q6h (moderately susceptible organism) Max: 4g/ day	50- 90	250- 500mg q6h- q 8h
		10 - 50	250mg q6h- 12h
		<10	125- 250mg q12h HD: Dose after HD
		CRRT	500mg q8h or 1g q12h
ISONIAZID	5mg/kg or max 300 mg IV/PO daily		no change
ITRACONAZOLE	100 - 200 mg PO q12h		PO: no change
LAMIVUDINE	HIV: 150 mg po q 12h or 300mg q24h Hep B, chronic: 100mg q24h	> 50	normal dose
		30-49	150 mg PO q24h(HIV) 100mg x 1 then 50mg q24h (Hep B)
		15-29	150 mg x 1, then 100 mg PO q24h (HIV), 100mg x 1, then 25mg q24h (Hep B)
		5- 14	150 mg x 1, then 50 mg PO q24h (HIV) 35mg x 1, then 15mg q24h (Hep B)
		< 5	150 mg x 1, then 25 mg PO q24h (HIV) 35mg x 1 then 10mg q24h (Hep B)
LEVOFLOXACIN	250 mg IV/PO q24h	> 20	250 mg q24h
		< 20 and HD	250 mg q48h
	500 mg IV/PO q24h	> 50	500 mg q24h
		20 - 49	500 mg q48h or 250mg q24h
		< 20 and HD	500 mg x 1, then 250 mg q48h
		CVVHD	500 mg q 48h
	750 mg IV/PO q24 h	> 50	750 mg q24h
		20 - 49	750 mg q48h
		< 20 and HD	750 mg X 1, then 500 mg q48h
CVVHD		750 mg q 48h	
LINEZOLID	600 mg IV/PO q12h		no change

DRUG NAME	USUAL DOSE (Normal renal function)	CrCl (ml/min)	DOSAGE ADJUSTMENT (in renal insufficiency)
MEROPENEM	1 gm IV q 8h Meningitis dose: 2 g q 8h	>50	normal dose
		26-50	normal dose q12h
		25-Oct	50% normal dose q12h
		<10	50% normal dose q24h
		HD	50% normal dose q24h + 50% normal dose after each HD
		CRRT	1g q12h
METRONIDAZOLE	15mg/kg stat, 7.5mg/kg q12h-q6h OR 250mg-500mg q12h-q6h. Max: 4g/d		no change
NITROFURANTION	50-100mg PO q12h-q6h	>50	normal dose
		< 50	avoid use
OFLOXACIN	200 - 400mg q12h PO	<20	half dose q24h
PENICILLIN G	2-4 million units IV q4h	50- 90	100%
		10- 50	75%
		<10	20- 50%
		CRRT	75%
PENICILLIN V	125 - 500mg q12h-q6h	<10	normal dose q8h
PENTAMIDINE	Pneumocystis pneumonia: IV 4 mg/kg or IM q 24h	> 50	normal dose
		Oct-50	normal dose q24-36h
		< 10	normal dose q48h
		HD	dose for CrCL < 10 ml/min
PIPERACILLIN	3-4g q4h - q6h Max: 24g/ day	10- 50	q6h-q8h
		<10	q8h
		CRRT	q6h-q8h
PIPERACILLIN/ TAZOBACTAM	3.375 gm IV q6h	>40	normal dose
		20-40	2.25 gm q6h
		<20	2.25 gm q8h
		HD	2.25 gm q8h + 0.75 gm supplemental dose after each HD
PIPERACILLIN/ TAZOBACTAM	4.5 gm IV q6h	10-50	4.5g q8h or 2.25g q6h
		<10	2.25g q8h
		CRRT	2.25g q8h
		HD	2.25 gm q8h + 0.75 gm supplemental dose after each HD
PYRAZINAMIDE	15-30 mg/kg/d (maximum 2 gm/day)	> 10	normal dose
		<10	25-30 mg/kg three times weekly
		HD	25-30 mg/kg three times weekly, post-dialysis
		OR	
		> 10	normal dose
		< 10	12- 25mg/kg/d

DRUG NAME	USUAL DOSE (Normal renal function)	CrCl (ml/min)	DOSAGE ADJUSTMENT (in renal insufficiency)	
PYRIMETHAMINE	25 - 75 mg PO q24h		no change	
RIFAMPICIN	10mg/kg/day Max 600mg/day		no change	
STREPTOMYCIN	15 mg/kg/day IM	> 50	normal dose	
		10-50	q24-72h	
		< 10	q72-96h	
		HD	Administer after HD or give 50-75% of loading dose after each HD	
SULBACTAM (for Acinetobacter)	MRO organism dose: 8g of sulbactam/ day e.g.: Unasyn 3g q3h or Sulperazone 4g q6h	>50	8g/day	
		20-50	6g/day	
		<20	4g/day	
		HD	4g/day	
		CRRT	4g/day	
Ampicillin/Sulbactam (UNASYN) = 500mg sulbactam/vial Cefoperazone/Sulbactam (SULPERAZONE) = 500mg sulbactam/vial				
TRIMETHOPRIM + SULFAMETHOXAZOLE	5mg/kg q8h	>50	normal dose	
		10- 50	50%	
		<10	Not recommended	
VALGANCICLOVIR	900 mg po q12h		INDUCTION	MAINTENANCE
		> 60	900 mg po q12h	900 mg po q24h
		40 - 59	450 mg po q12h	450 mg po q24h
		25 - 39	450 mg po q24h	450 mg po q2days
		24-10	450 mg po q2days	450 mg po twice weekly
		HD	do not use in patients on hemodialysis	
VANCOMYCIN	LD 25-30mg/kg (not to exceed 2g/ dose) Then 15- 20mg/kg q12h- q8h	50- 90	q12h	
		30- 50	q24h	
		<30	Single dose then check random level within 24 - 48h	
		CRRT	500mg q24 - 48h	
VORICONAZOLE	6mg/kg q12h x 2 doses, then 3-4mg/kg q12 h	<50	IV formulation is not preferred due to accumulation of vehicle (no dosage adjustment necessary for PO therapy)	
		CRRT	4mg/kg q12 h	

3.2 DOSE MODIFICATION IN LIVER IMPAIRMENT

Drug metabolism may be affected in patient with liver impairment. Hence, in order to decide drug dosing in liver failure, three important factors need to be considered namely (1) pharmacokinetic alterations of drugs, (2) pharmacodynamic alteration of drugs, and (3) increased susceptibility of patients to adverse events particularly hepatotoxicity. The Child-Pugh Score (Table 3.3) which consists of five clinical features is used to assess the prognosis of chronic liver disease and cirrhosis. It

can be used as a tool for dosing modification in liver impaired patients. Table 3.2 indicates drugs requiring dosing adjustment in the presence of hepatic disease.

Table 3.2: Drugs Requiring Liver Dose Adjustment

DRUGS	DOSAGE ADJUSTMENT
Alprazolam	Reduce dose by 50 % to 60% or avoid in cirrhosis. Benzodiazepines can be cautiously used in decompensated cirrhosis.
Aminophylline	Adjusted according to serum level measurement during the first 12 to 24 hours. Use with caution.
Amiodarone	If hepatic enzymes exceed 3 times normal or double in patient with an elevated baseline, consider decreasing the dose or discontinuing amiodarone.
Amitriptylline	Increase sedative effect; avoid or use with caution in liver disease.
Amlodipine	Starting dose 2.5mg.
Aspirin	Avoid use in severe liver disease; may increase risk of GI bleeding.
Atorvastatin	Contraindicated in active liver disease or in unexplained persistent increase in serum transaminase.
Azithromycin	Not necessary. Specific dosing guidelines for hepatic impairment have not been established. Macrolide antibiotics excreted and detoxified by liver. Should be used with cautions due to potential of hepatotoxicity especially in cirrhotic patients.
Bupivacaine	Use with caution. Consider dose adjustment in severe impairment.
Calcium Polystyrene Sulfonate Powder	No adjustment as drug not absorbed systemically.
Carbamazepine	Avoided if aggravated liver dysfunction or active liver disease.
Caspofungin	<i>Mild</i> (Child-pugh score 5-6): no adjustment necessary (70mg on day 1, subsequent dosing 50mg/day). <i>Moderate</i> (Child-pugh score 7-9): 70mg (invasive infections) or 35mg/day (esophageal candidiasis) on day 1, followed by 35mg once daily. <i>Severe</i> (Child-pugh score >9): no clinical experience.
Cefoperazone-Sulbactam (Sulperazone)	Dose adjustment may be necessary in patients with liver dysfunction. Cefoperazone extensively excreted in the bile. The serum half-life of cefoperazone increased 2- to 4-fold in patient with hepatic disease and/or biliary obstruction. Total daily dose above 9g should not be given.
Cefotaxime	Moderate dosage reduction is recommended in severe liver disease.
Ceftriaxone	To consider dose reduction in patient with hepatic and severe renal impairment. (Dose ≤ 2g/day).
Celecoxib	<i>Moderate</i> (Child-pugh class B): reduce dose by 50%. <i>Severe</i> : use is not recommended. Abnormal liver function tests (persistent or worsening): discontinue use.
Clarithromycin	Elderly: age related reduction in renal function; monitor and adjust dose if necessary.
Clindamycin	Dose reduction is recommended in severe hepatic diseases. No specific dosing recommendations available. Clindamycin excreted and detoxified by liver, should be used with cautions in cirrhotic patients.
Clonazepam	Contraindicated in significant liver disease. Caution in hepatic disease patients.

DRUGS	DOSAGE ADJUSTMENT
Clopidogrel	Caution (risk of bleeding); avoid in severe hepatic impairment. Reduced dose in moderate case.
Dantrolene	Chronic therapy contraindicated in active liver disease; has potential for hepatotoxicity.
Dexmedetomidine	Dose reduction may need to be considered (↓ clearance).
Diazepam	Benzodiazepines can be cautiously used in decompensated cirrhosis.
Digoxin	No specific dosage adjustment is necessary.
Diltiazem	No specific dosing recommendations available; extensively metabolized by the liver; half-life is increased in patients with cirrhosis.
Enalapril	No adjustment. Hydrolysis may be delayed and/or impaired in severe hepatic impairment, but the pharmacodynamic effects of the drug do not appear to be significantly altered.
Enoxaparine	Use with caution in hepatic impairment.
Ertapenem	Adjustments cannot be recommended (lack of experience and research in this patient population).
Erythromycin	Macrolide antibiotics excreted and detoxified by liver, should be used with cautions in cirrhotic patients. No specific dosing recommendations available.
Esomeprazole	<i>Mild to moderate</i> (Child-Pugh class A or B) - no adjustment. <i>Severe</i> (Child-Pugh Class C) - dose should not exceed 20mg.
Felodipine	Begin at dose of 2.5mg/day. Do not use dose above 10mg/day as incidence and severity of adverse event outweighs additional hypotensive effects.
Fluconazole	No specific dosing recommendations available. Should be used with caution in patients with hepatic dysfunction or previous hepatotoxicity from other azole derivatives. Patient who develops abnormal liver function tests during fluconazole therapy should be monitored closely and discontinued if symptoms consistent with liver disease develop.
Frusemide	Cirrhotic patient may have diminished natriuretic effect with increased sensitivity to hypokalemia and volume depletion, and may require higher dose. Monitor side effect particularly with high dose. No specific dosing recommendations available.
Fucidic acid	Avoid in hyperbilirubinemia patient.
Granisetron	Kinetic studies in patients with hepatic impairment showed that total clearance was approximately halved, however standard doses were much tolerated, and dose adjustments are not necessary.
Hydrocortisone	Should be used with caution in patients with hepatic dysfunction including cirrhosis. Long term use has been associated with fluid retention.
Imipenem-Cilastatin (Tienam®)	Hepatic dysfunction may further impair cilastin clearance; consider decreasing the dosing frequency.
Insulin	Insulin requirements may be reduced. Closed monitoring of blood glucose and adjustment of therapy is required in hepatic impairment.
Isoniazid	No adjustment required. However, use with caution; may accumulate and additional liver damage may occur in patients with pre-existing liver disease. For ALT or AST > 3 x ULN, discontinue or temporarily withhold treatment. Refer Clinical Practice Guidelines: Management of Tuberculosis, 3 rd edition for management of tuberculosis in liver impairment.
Itraconazole	Use with caution in patient with hepatic impairment.
Ketorolac	Use with caution, may cause elevation of liver enzyme. Hepatic dose may prolong elimination half life. Discontinue if clinical signs and symptoms of liver disease develop.

DRUGS	DOSAGE ADJUSTMENT
Labetalol	Chronic liver disease may reduce metabolism of labetalol. Dosage reduction is required to avoid decrease in heart rate and supine blood pressure.
Lamotrigine	<i>Mild</i> (Child-Pugh class A): no adjustment required. <i>Moderate to severe</i> (Child-Pugh class B or C) <i>without ascites</i> : initial escalation & MD should ↓ by 25%. <i>Moderate to severe</i> (Child-Pugh class B or C) <i>with ascites</i> : initial escalation & MD should ↓ by 50%.
Lansoprazole	In severe liver disease, consider dose reduction.
Levetiracetam	<i>Mild to moderate</i> (Child-Pugh class A or B): no need adjustment. <i>Severe</i> (Child-Pugh class C): ↓ dose by 50%.
Levobupivacaine	Caution in liver disease.
Lignocaine	Consider dose reduction in acute hepatitis and cirrhosis.
Linezolid	<i>Mild to moderate</i> (Child-Pugh class A or B): no dosage adjustment. <i>Severe</i> (Child-Pugh class C): not been adequately evaluated.
Losartan	Reduce initial dose to 25mg/day.
Lovastatin	Use with caution in patient with past history of liver disease; active liver disease is contraindicated.
Metformin	Liver disease is a risk factor for lactic acidosis, should be avoided in patients with hepatic insufficiency.
Metoprolol	Dosage adjustment may be required; reduce dose slightly.
Metronidazole	Reduce dose by 50% in patients with severe cirrhosis and/or associated renal insufficiency.
Midazolam	Reduced midazolam clearance in patients with cirrhosis. Benzodiazepines can be cautiously used in decompensated cirrhosis.
Morphine	<i>Mild</i> : no dose adjustment. <i>Severe</i> : avoid. Excessive sedation may occur in cirrhosis. Duration of action prolonged, dosage should be adjusted. Dosing interval suggested to be increased 1.5 to 2 times normal dose.
Nalbuphine	Administer with caution; reduced doses.
Nifedipine	Reduce dose by 50% to 60% in patients with cirrhosis.
Ofloxacin	Severe impairment: maximum dose 400mg/day.
Omeprazole	Bioavailability is increased with chronic liver disease. Consider dosage adjustment, especially for maintenance of erosive esophagitis. Specific guidelines are not available.
Oxycodone	Reduce dosage in patients with severe liver disease.
Pantoprazole	No adjustment needed. Dose above 40mg/day have not been studied. Use with caution in severe hepatic impairment.
Paracetamol	Use with caution. Avoid chronic use and large dose in hepatic impairment. Safely administered in therapeutic dose in stable hepatic disease. Patients with cirrhosis: recommended dose < 2-3 g/day.
Parecoxib	<i>Mild</i> : No adjustment. <i>Moderate</i> (Child-Pugh score 7-9): Should be initiated with half the usual recommended dose and the maximum dose should be reduced to 40mg.
Pethidine	Reduce initial dose in severe hepatic impairment; use with caution.
Phenobarbital	Use with caution; initial dose should be reduced.

DRUGS	DOSAGE ADJUSTMENT
Phenytoin	Clearance may be substantially reduced in cirrhosis. Plasma level monitoring with dose adjustment advisable. Free phenytoin levels should be monitored closely.
Piracetam	Cirrhosis: clearance ↓; dose adjustment necessary.
Prazosin	Initially 0.5mg od; increased with caution.
Propranolol	Marked slowing of heart rate may occur during cirrhosis with conventional dose; low initial dose required.
Pyrazinamide	Monitor hepatic function; idiosyncratic hepatotoxicity more common. Specific dosage recommendation not provided. Refer Clinical Practice Guidelines: Management of Tuberculosis, 3 rd edition for management of tuberculosis in liver impairment.
Ranitidine	May have minor changes in ranitidine half-life, distribution, clearance, and bioavailability in hepatic impairment; dosing adjustments not necessary.
Rifampicin	Monitor hepatic function ; idiosyncratic hepatotoxicity more common Specific dosage recommendation not provided. Refer Clinical Practice Guidelines: Management of Tuberculosis, 3 rd edition for management of tuberculosis in liver impairment.
Rocuronium	Reductions may be necessary in patients with liver disease; duration of neuromuscular blockade may be prolonged.
Ropivacaine	Consider dose reduction or avoid.
Sevoflurane	Use with caution in patient with underlying hepatic condition.
Simvastatin	Contraindicated in active liver disease.
Sodium bicarbonate	In patient with fluid retention, avoid those contain large amount of sodium.
Suxamethonium	Prolonged apnea may occur in severe liver disease due to reduced hepatic synthesis of pseudocholinesterase. May ↓dose.
Telmisartan	20 - 40mg od in mild / moderate impairment, avoid in severe.
Theophylline	Monitor serum level and ↓ dose.
Tigecycline	<i>Mild to moderate</i> (Child-Pugh classes A and B): No dosage adjustment. <i>Severe</i> (Child-Pugh class C): 100mg single dose; maintenance: 25mg q12h.
Topiramate	Use with caution in hepatic impairment; may decrease clearance but no specific dosing.
Tramadol	Cirrhosis: 50mg bd.
Valproate (valproic acid)	Reduce dose. Clearance is decreased with liver impairment. Hepatic disease is also associated with decreased albumin concentrations and 2 to 2.6-fold increase in the unbound fraction. Free concentrations of valproate may be elevated while total concentrations appear normal. Use is contraindicated in severe impairment.
Valsartan	Mild to moderate ≤ 80mg/day; avoid if severe.
Vecuronium	Not recommended; if must be used, lowest effective dose is recommended.
Verapamil	Reduce dose by 20% to 50% of normal dose; patient should be monitored for abnormal prolongation of the PR interval.
Voriconazole	<i>Mild to moderate</i> (Child-Pugh classes A and B): follow standard LD, reduce MD by 50%. <i>Severe</i> (Child-Pugh classes C): used only if benefit outweighs risk.
Warfarin	Avoid in severe liver disease especially if PT already prolonged. Respond to oral anticoagulant may be enhanced in obstructive jaundice (due to ↓ vit K absorption), hepatitis and cirrhosis (due to ↓ production of vit K dependent clotting factor).

Table 3.3: Child-Pugh Score

Parameter	Score		
	1	2	3
Ascites	None	Mild	Moderate or Severe
Encephalopathy (grade)	None	1-2	3-4
Bilirubin (mmol/L)	<35	35-50	>50
Bilirubin in Primary Biliary Cirrhosis (mmol/L)	<70	70-170	>170
Albumin (g/L)	>35	28-35	<28
INR	<1.7	1.8-2.3	>2.3

The sum of the five scores from the above table is used to assign a Child-Pugh grade of A, B or C to the patient's clinical condition at the point in time. The Child-Pugh score should be reassessed from time to time since the patients clinical condition may improve or deteriorate.

Child-Pugh grade	Child-Pugh Score	Indication
A	5-6	Well functioning liver
B	7-9	Significant functional compromise
C	>9	Decompensation of the liver

3.3 SPECIAL DOSING IN OBESE PATIENTS

Obesity is defined by the CDC as a BMI of $>30\text{kg/m}^2$, and morbid obesity is defined as a BMI of $>40\text{kg/m}^2$. Physiological changes in obesity patient, can alter pharmacodynamic and pharmacokinetic of a drug which includes (1) Dramatically increased adipose tissue, (2) Slightly increased lean tissue mass, (3) Increased cardiac output, (4) Increased glomerular filtration rate, and (5) Fatty infiltration of liver.

A higher proportion of body tissue can influence drug with lipophilic properties whereas increased organ mass, lean body mass, and blood volume in obesity can affect hydrophilic medications. Failure to adjust doses in obesity may result either in sub therapeutic failure or increased toxicity. **Table 3.4** listed weight-based dosing scalar recommendations for commonly used drugs in critically ill patient.

Table 3.4: Dosing adjustment in obesity

Drugs	Suggested dosing weight
Acyclovir	IBW ¹
Aminoglycosides	ABW ¹
Amphotericin B	ActualBW for conventional preparation; IBW for lipid preparation ¹
Atracurium	IBW ³
Benzodiazepines	IBW ²
Ciprofloxacin	ABW ²
Colistimethate	IBW, dosage expressed in terms of colistin ⁶
Digoxin	IBW ⁸

Drugs	Suggested dosing weight
Enoxaparine	ActualBW ¹⁰ <i>Additional recommendation:</i> - Up to 150 kg - VTE prophylaxis: if BMI ≥ 40 mg/m ² increase dose by 30% - VTE treatment: avoid once-daily dosing if BMI > 27 kg/m ² (e.g. do not use 1.5 mg/kg daily)
Erythromycin	IBW ¹
Fentanyl	LBW ⁷
Fluconazole	ActualBW ¹ <i>Additional recommendation:</i> Consider higher doses in obese patient
Ganciclovir	ABW ²
Heparin - unfractionated	ABW ⁹
Immunoglobulin (IVIG)	ABW ¹⁰
Methylprednisolone	IBW ¹¹
Oseltamivir	Use standard dosing (no adjustment for obesity) ^{12,13}
Pancuronium	IBW ³
Phenytoin	LD = IBW+1.33(TBW-IBW), MD = IBW ¹⁴ <i>Additional recommendation:</i> Drug level monitoring
Propofol	Induction: LBW, Maintenance : ActualBW ⁷
Remifentanyl	LBW ⁷
Rocuronium	IBW ⁷
Succinylcholine	ActualBW ⁷
Suxamethonium	IBW ⁷
Thiopental	Induction : LBW, Maintenance : ActualBW ⁷
Vancomycin	ActualBW ²

ActualBW = actual body weight
LBW = lean body weight

IBW = ideal body weight
ABW = adjusted body weight

Calculations:-

Ideal body weight IBW (as described by Devine 1974)

$$\text{Male IBW (kg)} = 50 \text{ kg} + [2.3 \times (\text{Ht}-60)]$$

$$\text{Female IBW (kg)} = 45.5 \text{ kg} + [2.3 \times (\text{Ht}-60)] \quad (\text{Height measures in inches})$$

Body Mass Index (BMI)

$$\text{BMI} = \text{Weight (kg)} / \text{Height (m)}^2$$

Lean Body Weight (LBW2005) (formula by Janmahasatian *et al.* 2005)

$$\text{Male LBW} = [9270 \times \text{weight (kg)}] / [6680 + 216 \times \text{BMI}]$$

$$\text{Female LBW} = [9270 \times \text{weight (kg)}] / [8780 + 244 \times \text{BMI}]$$

Adjusted Body Weight (ABW)

$$\text{ABW} = \text{IBW} + 0.4(\text{ActualBW}-\text{IBW})$$

3.3.1 Creatinine clearance in obese patient⁴

Overestimation or underestimation of clearance can occur in obesity when considering actual body weight versus ideal body weight, respectively. The Cockcroft-Gault equation is commonly used to calculate glomerular filtration rate (GFR) in lean patients, however its use in obesity is questionable due to the disparity between muscle mass and body weight ratio observed in obesity.

The Salazar-Corcoran equation takes into account multiple factors to provide a better estimation of ClCr in obesity including serum creatinine, gender, actual weight, age, and height.

Salazar-Corcoran Equation⁴:

$$\text{ClCr (Male)} = \frac{(137 - \text{age}) \times [(0.285 \times \text{Wt}) + (12.1 \times \text{Ht}^2)]}{(51 \times \text{SCr})}$$

$$\text{ClCr (Female)} = \frac{(146 - \text{age}) \times [(0.287 \times \text{Wt}) + (9.74 \times \text{Ht}^2)]}{(60 \times \text{SCr})}$$

Wt = actual body weight in kg

Ht = height in meters

SCr = serum creatinine in mg/dl

Although some drugs have established dosing adjustments for obesity, it remains unknown for the majority of drugs if dosing adjustment is warranted.

CHAPTER 4

NUTRITION

1.1 PARENTERAL NUTRITION IN CRITICALLY ILL PATIENTS

Critical illness is commonly associated with a catabolic stress state where patient will eventually develop systemic inflammatory response. Nutrition therapy (previously called nutrition support) is indicated for critical ill patients to attenuate the metabolic response to stress, to prevent oxidative cellular injury, and to modulate the immune response in a good manner. By giving early nutrition therapy primarily using the enteral route, it reduces the disease severity, diminishes complications, decreases the ICU length of stay and improves patient's clinical outcome.¹

Adapted from ESPEN Guidelines on Parenteral Nutrition: Intensive Care 2009²

<i>Summary of statements: Intensive Care</i>			
Subject	Recommendations	Grade	Number
Indications	Patients should be fed because starvation or underfeeding in ICU patients is associated with increased morbidity and mortality.	C	1.1
	All patients who are not expected to be on normal nutrition within 3 days should receive PN within 24h to 48h if EN is contraindicated or if they cannot tolerate EN.	C	1.2
Requirements	ICU patients receiving PN should receive a complete formulation to cover their needs fully.	C	1.3
	During acute illness, the aim should be to provide energy as close as possible to the measured energy expenditure in order to decrease negative energy balance.	B	2.1
	In the absence of indirect calorimetry, ICU patients should receive 25kcal/kg/day increasing to target over the next 2 - 3 days.	C	2.1
Supplementary PN with EN	All patients receiving less than their targeted enteral feeding after 2 days should be considered for supplementary PN.	C	3
Carbohydrates	The minimal amount of carbohydrate required is about 2g/kg of glucose per day.	B	4
	Hyperglycemia (glucose >10mmol/L) contributes to death in critically ill patient and should also be avoided to prevent infectious complications.	B	5
	Reductions and increases in mortality rates have been reported in ICU patients when blood glucose is maintained between 4.5 and 6.1mmol/L. No unequivocal recommendation; therefore possible at present.	C	5
	There is a higher incidence of severe hypoglycemia in patients treated to the tighter limits.	A	5
Lipids	Lipids should be an integral part of PN for energy and to ensure essential fatty acid provision in long-term ICU patients.	B	6.1
	Intravenous lipid emulsions (LCT, MCT or mixed emulsions) can be administered safely at a rate of 0.7 g/kg up to 1.5 g/kg over 12 to 24 h.	B	6.8

Summary of statements: Intensive Care			
Subject	Recommendations	Grade	Number
Lipids	The tolerance of mixed LCT/MCT lipid emulsions in standard use is sufficiently documented. Several studies have shown specific clinical advantages over soybean LCT alone but require confirmation by prospective controlled studies.	C	6.4
	Olive oil-based parenteral nutrition is well tolerated in critically ill patients.	B	6.5
	Addition of EPA and DHA to lipid emulsions has demonstrable effects on cell membranes and inflammatory processes. Fish oil-enriched lipid emulsions probably decrease length of stay in critically ill patients.	B	6.6
Amino Acids	When PN is indicated, a balanced amino acid mixture should be infused at approximately 1.3-1.5g/kg ideal body weight/ day in conjunction with an adequate energy supply.	B	7
	When PN is indicated in ICU patients the amino acid solution should contain 0.2–0.4 g/kg/day of L-glutamine. (e.g. 0.3–0.6 g/kg/day alanyl-glutamine dipeptide).	A	8
Micronutrients	All PN prescriptions should include a daily dose of multivitamins and of trace elements.	C	9
Route	A central venous access device is often required to administer the high osmolarity PN mixture designed to cover the nutritional needs fully.	C	1.3
	Peripheral venous access devices may be considered for low osmolarity (<850mOsmol/L) mixtures designed to cover a proportion of the nutritional needs and to mitigate negative energy balance.	C	1.3
	If peripherally administered PN does not allow full provision of the patient's needs then PN should be centrally administered.	C	1.3
Mode	PN admixtures should be administered as a complete all-in-one bag.	B	1.4

Glutamine Supplementation

Glutamine which is an essential amino acid, has been recommended by ESPEN and ASPEN/SCCM to be added into total parenteral nutrition for critically ill patient as it has several benefits that displays antioxidant effect, maintenance of gut integrity, plays a role in immune function and induction of heat shock proteins and as a fuel source for replicating cell.^{1,2,3} There are supporting data which shows reduction of mortality rate, infectious complications and length of ICU stay when glutamine supplementation in parenteral nutrition is given in critically ill patient compared to PN regimen without the addition of glutamine, as the plasma concentration of glutamine is usually low in these population¹. The recommended dose of glutamine ranges from 0.3 - 0.5 g/kg/day (max:0.5g/kg/day), which is sufficient to normalize plasma glutamine concentration in almost all critically ill patients.¹

Choosing the right value of weight to estimate nutrition requirements⁴:

- 1) Underweight or normal weight: Choose actual weight
- 2) Severely underweight: Actual weight initially, then once the patient is stable and if the nutritional status is not improving, the energy requirements should be gradually increased. Not to exceed 35kcal/kg/day.
- 3) In overweight/obese patients: Adjusted body weight.

**If the actual body weight is 30% more than the IBW, then use adjusted body weight.*

CHAPTER 5

OTHERS

5.1 DRUG CAUSING HAEMATOLOGICAL DISORDER^{1,2}

There were five major blood dyscrasias attributable to drugs which are aplastic anemia, agranulocytosis, megaloblastic anemia, hemolytic anemia, and thrombocytopenia. It is usually rare compared to other adverse effects induced by drugs; however they are important because it is associated with significant morbidity and mortality. Direct toxicity or immune reactions are the two main mechanisms which involved in drug-induced haematological disorders.

The recommended treatment for drug-induced haematological disorders is by removing the causative drug and symptomatic support of the patient. Besides that, frequent monitoring of laboratory values is also warranted. The common drugs that can induce haematological disorders are listed in Table 5.1.

Table 5.1: List of drugs that can cause drug-induced haematological disorder

Drugs Associated with Apalastic Anaemia			
Acetazolamide	Felbamate	Lisinopril	Sulindac
Aspirin	Interferon alfa	Lithium	Ticlopidine
Captopril	Chlorothiazide	Nizatidine	
Chloramphenicol	Chlorpromazine	Pentoxifylline	
Chloroquine	Dapsone	Quinidine	
Drugs Associated with Agranulocytosis			
Acetaminophen	Colchicine	Lamotrigine	Pyrimethamine Quinidine
Acetazolamide	Doxepin	Levodopa	Quinine
Ampicillin	Dapsone	Methazolamide	Rifampicin
Captopril	Desipramine	Methyldopa	Streptomycin
Cefotaxime	Ethosuximide	Metronidazole	Terbinafine
Cefuroxime	Flucytosine	Nafcillin	Ticarcilin
Chloramphenicol	Gentamicin	NSAIDs	Tolbutamide
Chlorpromazine	Griseofulvin	Olanzapine	Vancomycin Primidone
Chlorpropamide	Hydralazine	Oxacillin	Procainamide
Chlorpheniramine	Hydroxychloroquine	Penicillamine	Propylthiouracil
Clindamycin	Imipenem-cilastatin	Penicillin G	
Clozapine	Imipramine	Phenytoin	

Drugs Associated with Hemolytic Anaemia			
Acetaminophen	Indinavir	p-Aminosalicylic acid	Sulfonylureas
Angiotensin-converting enzyme inhibitors	Interferon alfa	Phenazopyridine	Tacrolimus
β-Lactam antibiotics	Ketoconazole	Probenecid	Tazobactam
Cephalosporins	Lansoprazole	Procainamide	Teicoplanin
Ciprofloxacin	Levodopa	Quinidine	Tolbutamide
Clavulanate	Levofloxacin	Rifabutin	Tolmetin
Erythromycin	Methyldopa	Rifampin	Triamterene
Hydrochlorothiazide	Minocycline	Streptomycin	
	NSAIDs	Sulbactam	
	Omeprazole	Sulfonamides	
Drugs Associated with Oxidative Hemolytic Anaemia			
Ascorbic acid	Nalidixic acid	Primaquine	Sulfanilamide
Metformin	Nitrofurantoin	Sulfacetamide	
Methylene blue	Phenazopyridine	Sulfamethoxazole	
Drugs Associated with Megaloblastic Anaemia			
Azathioprine	Cytarabine	Methotrexate	Primidone
Chloramphenicol	5-Fluorodeoxyuridine	Oral contraceptives	Pyrimethamine
Colchicine	5-Fluorouracil	p-Aminosalicylate	Sulfasalazine
Cotrimoxazole	Hydroxyurea	Phenobarbital	Tetracycline
Cyclophosphamide	6-Mercaptopurine	Phenytoin	Vinblastine
Drugs Associated with Thrombocytopenia			
Abciximab	Danazol	Indomethacin	Recombinant hepatitis B vaccine
Acetaminophen Acyclovir	Deferoxamine	Interferon alfa	Rifampicin
Albendazole	Diazepam	Isoniazid	Simvastatin Sirolimus
Aminoglutethimide	Diazoxide	Isotretinoin	Sulfasalazine
Aminosalicylic acid	Diclofenac	Itraconazole	Sulfonamides
Amiodarone	Digoxin	Low-molecular-weight heparins	Sulindac
Amphotericin B	Ethambutol	Measles, mumps, and rubella vaccine	Tamoxifen
Ampicillin	Felbamate	Mesalamine	Trimethoprim
Aspirin	Fluconazole	Methyldopa	Vancomycin
Atorvastatin	Gold salts	Minoxidil	Pentoxifylline
Captopril	Haloperidol	Naproxen	Piperacillin
Chlorothiazide	Heparin	Nitroglycerin	Primidone
Chlorpromazine	Hydrochlorothiazide	Octreotide	Procainamide
Chlorpropamide	Ibuprofen	Cloxacillin	Pyrazinamide
Cimetidine	Indinavir	p-Aminosalicylic acid	Quinine
Ciprofloxacin	Levamisole	Penicillamine	Quinidine
Clarithromycin	Linezolid	Ranitidine	
Clopidogrel	Lithium		

5.2 POISONING

Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks
Benzodiazepines Poisoning						
1. Prevention of absorption - Activated Charcoal	Adult : 25 – 100g Child up to 12 yrs : 25 – 50g or 0.5 - 1g/kg < 1 yr : 0.5 – 1 g/kg ^{1,5,7} * <i>repeat dose if necessary</i>	Oral : as aqueous slurry Dilution: 30 g in 240 ml of water <i>*dilute proportionally according to dose required^{5,7}</i>	Constipation, V, bowel obstruction, impaired bowel motility, fecal discoloration. Pulmonary aspiration, electrolyte imbalance. ^{2,5,6,7}	Hypersensitivity, unprotected airway, non-functioning GI tract and uncontrolled vomiting, ingestion of most hydrocarbons. Intestinal obstruction, patients at risk of GI perforation or haemorrhage. ^{2,5,6,7}	Serum electrolytes, constipation. ⁷	Most effective if given within 1 hr. ⁷ Use in patient with unprotected airway may ↑ risk and severity of aspiration. ⁵

Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks														
2. Treatment Flumazenil	Adult^{5,7,8}: <table border="1" data-bbox="358 331 672 1477"> <thead> <tr> <th data-bbox="358 422 440 513">Indication</th> <th data-bbox="358 513 440 622">Reversal of conscious sedation</th> <th data-bbox="358 622 440 731">Benzodiazepine overdose</th> </tr> </thead> <tbody> <tr> <td data-bbox="440 422 504 513">Initial dose</td> <td data-bbox="440 513 504 622">0.2mg over 15 sec</td> <td data-bbox="440 622 504 731">0.2mg over 30 sec</td> </tr> <tr> <td data-bbox="504 422 569 513">Repeat doses</td> <td data-bbox="504 513 569 622">Adequate consciousness not obtained within 45 sec: 0.2mg Q1min (max: 4 doses) to max total dose of 1mg (usual dose: 0.6-1mg)</td> <td data-bbox="504 622 569 731">Adequate consciousness not obtained within 30 sec: 0.3mg over 30 sec Repeat doses: 0.5mg Q1min up to max total dose of 3mg (usual dose: 1 - 3mg)^{5,7,8}</td> </tr> <tr> <td data-bbox="569 422 633 513">Resedation</td> <td data-bbox="569 513 633 622">≤1mg Q20min (max: 3mg/hr), max: 3mg/hr</td> <td data-bbox="569 622 633 731">N/A</td> </tr> <tr> <td data-bbox="633 422 672 513">Cont. infusion (alternative to repeated bolus)</td> <td data-bbox="633 513 672 622">N/A</td> <td data-bbox="633 622 672 731">0.1 - 0.4mg/hr⁵</td> </tr> </tbody> </table>	Indication	Reversal of conscious sedation	Benzodiazepine overdose	Initial dose	0.2mg over 15 sec	0.2mg over 30 sec	Repeat doses	Adequate consciousness not obtained within 45 sec: 0.2mg Q1min (max: 4 doses) to max total dose of 1mg (usual dose: 0.6-1mg)	Adequate consciousness not obtained within 30 sec: 0.3mg over 30 sec Repeat doses: 0.5mg Q1min up to max total dose of 3mg (usual dose: 1 - 3mg) ^{5,7,8}	Resedation	≤1mg Q20min (max: 3mg/hr), max: 3mg/hr	N/A	Cont. infusion (alternative to repeated bolus)	N/A	0.1 - 0.4mg/hr ⁵	N, V, xerostomia. Vasodilation, cardiac arrhythmia, dyspnea, hyperventilation. Seizure, agitation, confusion, headache. Abnormal or blurred vision. ^{5,7}	Hypersensitivity to flumazenil, benzodiazepine or component of formulation. Patients with Life threatening condition controlled by benzodiazepine (e.g ↑ ICP, status epilepticus). Patients with signs of serious tricyclic antidepressant intoxication. ^{2,5,7}	Vital sign, airway, seizure activity, s/s re sedation, respiratory depression. ^{2,5,7}	Benzodiazepine overdose: adult patients with partial response at 3mg may require doses up to total dose of 5mg. ^{5,7}
Indication	Reversal of conscious sedation	Benzodiazepine overdose																		
Initial dose	0.2mg over 15 sec	0.2mg over 30 sec																		
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Resedation	≤1mg Q20min (max: 3mg/hr), max: 3mg/hr	N/A																		
Cont. infusion (alternative to repeated bolus)	N/A	0.1 - 0.4mg/hr ⁵																		

Treatment Option	Dose & Duration	Dilution/ Administration		Side Effects	Contraindications	Monitoring	Remarks
	Child ≥ 1yr ^{5,7,8} :	Indication	Reversal of conscious sedation	Benzodiazepine overdose			
		Initial dose	0.01mg/kg (up to 0.2mg) over 15 sec	0.01mg/kg (up to 0.2mg)			
		Repeat doses	<i>Adequate consciousness not obtained after 45 sec:</i> 0.01mg/kg (up to 0.2mg) Q1min up to 4 times (max total dose: 0.05mg/kg or 1mg)	Repeat doses: 0.01mg/kg (up to 0.2mg) Q1min up to max total dose of 0.05mg/kg or 1mg ^{5,7}			
		Resedation	Safety & efficacy for repeated doses not established ^{7,8}	N/A			
		Continuous infusion (alternative to repeated bolus)	N/A	0.005-0.01mg/kg/hr ⁵			

Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks
	<p>Child <1yr: safety & efficacy in reversal of conscious sedation not established⁷</p> <p>Neonates (benzodiazepine overdose following maternal ingestion):</p> <p><i>Initial:</i> 0.02mg/kg</p> <p><i>Maintenance infusion:</i> 0.05mg/kg/hr for 6 hrs⁷</p> <p>Administration:</p> <p><i>Reversal of conscious sedation:</i> over 15 sec</p> <p><i>Overdose:</i> over 30 sec^{5,8}</p> <p>Administer through freely running IV infusion into large vein (<i>compatible with D5 or NS</i>)</p> <p>Remain stable in syringe for 24hrs^{5,7,8}</p>					
Heparin Poisoning						
1. Treatment - Protamine Sulfate	<p>Adult :</p> <p>Heparin: Heparin blood conc. decreases rapidly after administration → protamine dosage depending on duration post heparin ingestion.⁵</p>		<p>Hypotension, flushing, bradycardia, dyspnoea, pulmonary hypertension</p> <p>Nausea, vomiting</p> <p>Hypersensitivity reaction^{5,7}</p>	<p>Hypersensitivity to protamine or component of formulation⁷</p>	<p>Coagulation profile, aPTT or ACT, BP, HR⁷</p>	<p>Patients with h/o of fish allergy or previous exposure to protamine may be at risk of hypersensitivity reaction⁷</p>

Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks										
	<table border="1"> <tr> <td>Time Elapsed</td> <td>Dose of Protamine (mg) to Neutralized 100units of Heparin</td> </tr> <tr> <td><30min</td> <td>1mg</td> </tr> <tr> <td>30-60min</td> <td>0.5 – 0.75mg</td> </tr> <tr> <td>60-120min</td> <td>0.375 – 0.5mg</td> </tr> <tr> <td>>120min</td> <td>0.25 – 0.375mg</td> </tr> </table> <p>(Max dose: 50 mg)^{5,7} Child: Refer to adult dosing^{5,7} Administration: Undiluted (10mg/mL) over 10 min or ≤ 5mg/min^{5,7}</p>	Time Elapsed	Dose of Protamine (mg) to Neutralized 100units of Heparin	<30min	1mg	30-60min	0.5 – 0.75mg	60-120min	0.375 – 0.5mg	>120min	0.25 – 0.375mg					<p>Rapid IV administration may cause severe hypotension and anaphylactoid reactions.^{5,7}</p> <p>Reversal of LMWH is not complete or predictable as heparin.</p> <p>Excessive dosing (>100mg) may worsen bleeding by acting as an anticoagulant.⁵</p>
Time Elapsed	Dose of Protamine (mg) to Neutralized 100units of Heparin															
<30min	1mg															
30-60min	0.5 – 0.75mg															
60-120min	0.375 – 0.5mg															
>120min	0.25 – 0.375mg															
Methanol Poisoning																
1. Prevention of absorption - Activated Charcoal	<p>Adult : 25 – 100g Child up to 12 yrs : 25 – 50g or 0.5 - 1g/kg < 1 yr : 0.5 – 1 g/kg^{1,5,7} * repeat dose if necessary</p>	<p>Oral : as aqueous slurry Dilution: 30 g in 240 ml of water <i>*dilute proportionally according to dose required^{5,7}</i></p>	<p>Constipation, V, bowel obstruction, impaired bowel motility, fecal discoloration. Pulmonary aspiration, electrolyte imbalance.^{2,5,6,7}</p>	<p>Hypersensitivity, unprotected airway, non-functioning GI tract and uncontrolled vomiting, ingestion of most hydrocarbons. Intestinal obstruction, patients at risk of GI perforation or haemorrhage.^{2,5,6,7}</p>	<p>Serum electrolytes, constipation.⁷</p>	<p>Most effective if given within 1 hr.⁷ Use in patient with unprotected airway may ↑ risk and severity of aspiration.⁵</p>										

Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks																	
2. Treatment - Ethanol	<p>Adult ⁷:</p> <p>(Target: maintain Serum ethanol conc. 100-150mg/dL)</p> <p><i>Loading dose:</i></p> <table border="1"> <tr> <td></td> <td>IV (10% V/V)</td> <td>Oral (20% V/V)</td> </tr> <tr> <td>LD</td> <td>0.8g/kg (or 10mL/kg)</td> <td>0.8g/kg (or 5mL/kg)</td> </tr> </table> <p><i>Maintenance dose:</i></p> <table border="1"> <tr> <td></td> <td>IV (10% V/V)</td> <td>Oral (20% V/V)</td> </tr> <tr> <td>Non-alcoholic</td> <td>0.08 -0.13g/kg/hr (or 1.0 - 1.6mL/kg/hr)</td> <td>0.08-0.13g/kg/hr (or 0.5-0.8mL/kg/hr)</td> </tr> <tr> <td>Chronic alcoholic</td> <td>0.15 g/kg/hr (or 1.9mL/kg/hr)</td> <td>0.15 g/kg/hr (or 0.9 mL/kg/hr)</td> </tr> <tr> <td>During dialysis</td> <td>0.25-0.35 g/kg/hr (or 3.1 - 4.4mL/kg/hr)</td> <td>0.25-0.35 g/kg/hr (or 1.6-2.2 mL/kg/hr)</td> </tr> </table> <p>Child (unlabeled use): Refer to adult dosing⁷</p> <p>(Target: maintain Sr ethanol conc. 100mg/dL)</p> <p>Administration:</p> <ul style="list-style-type: none"> - IV: LD over 20 – 60 min⁷ <p>Endpoint of therapy:</p> <ul style="list-style-type: none"> • Methanol blood concentration <10mg/dL • Formate blood concentration <1.2mg/dL • Acidosis, CNS clinical findings, electrolyte abnormalities, serum amylase, and osmolal gap resolved.⁷ 		IV (10% V/V)	Oral (20% V/V)	LD	0.8g/kg (or 10mL/kg)	0.8g/kg (or 5mL/kg)		IV (10% V/V)	Oral (20% V/V)	Non-alcoholic	0.08 -0.13g/kg/hr (or 1.0 - 1.6mL/kg/hr)	0.08-0.13g/kg/hr (or 0.5-0.8mL/kg/hr)	Chronic alcoholic	0.15 g/kg/hr (or 1.9mL/kg/hr)	0.15 g/kg/hr (or 0.9 mL/kg/hr)	During dialysis	0.25-0.35 g/kg/hr (or 3.1 - 4.4mL/kg/hr)	0.25-0.35 g/kg/hr (or 1.6-2.2 mL/kg/hr)	<p>Flushing, hypotension, nerve and tissue destruction.</p> <p>Hypoglycemia (especially common in paed), urinary retention, intoxication.</p> <p>Disorientation, encephalopathy, sedation, seizure, vertigo.^{5,6,7}</p>	<p>Hypersensitivity to ethyl alcohol, seizure disorder, diabetic coma.</p> <p>Pregnancy (prolonged use or high doses at term).⁵</p>	<p>Blood ethanol concentration, electrolytes, arterial pH, blood gases, blood glucose, methanol blood level, HR, BP.^{5,7}</p>	<p>IV ethanol 10% V/V = 0.08g ethanol/mL.⁷</p> <p>Oral ethanol may be used if IV ethanol is unavailable.^{5,7}</p> <p>Dialyzable; ↑ infusion (approximately doubled, possibly tripled) during dialysis.⁹</p>
	IV (10% V/V)	Oral (20% V/V)																					
LD	0.8g/kg (or 10mL/kg)	0.8g/kg (or 5mL/kg)																					
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Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks
- Fomepizole	<p>Adult: <i>Loading dose:</i> 15mg/kg <i>Maintenance dose:</i> 10mg/kg BD x 4 doses followed by 15mg/kg BD</p> <p>Dosing adjustment in hemodialysis: <i>Loading dose:</i> 15mg/kg <i>Maintenance dose:</i> 10mg/kg Q4hr x 4 doses followed by 15mg/kg Q4hr^{5,7}</p> <p>Child (unlabeled use): Refer to adult dosing⁵</p> <p>Endpoint of therapy:</p> <ul style="list-style-type: none"> Methanol blood concentration <20mg/dL or undetectable Asymptomatic with normal pH⁷ 	Dilution: required dose in at least 100mL NS or D5%. IV infusion over 30mins. ^{7,9}	Headache, N, dizziness, drowsiness and metallic taste. ⁷ Hypertriglyceridemia, ↑ LFT, bradycardia, hypotension, tachycardia. ⁵	Hypersensitivity to fomepizole, other pyrazoles, or component of formulation. ⁵	Plasma/ urinary ethylene glycol or methanol level, plasma/ urinary osmolality Renal & hepatic function, sr. electrolytes, ABG, anion & osmolar gaps. ⁵	Dialyzable. ^{7,9} Lower adverse drug events rate than ethanol. ⁷ May solidify at temp. <25°C; liquefied by running warm water over it or holding in hand. Solidification does not affect efficacy, safety or stability. ^{5,7}
- Folic acid/ Leucovorin	<p>Adult (unlabeled use): : 1mg/kg (max: 50mg) Q4h x 6 doses^{5,9}</p> <p>Child (unlabeled use): Refer to adult dosing⁵</p>	Dilute in 100mL D5% Infuse over 30mins ⁹	Rash, pruritus, erythema, urticaria Thrombocytosis, wheezing Allergic or anaphylactoid reactions N,V, pyrexia ^{2,5,7,9}	Hypersensitivity Pernicious anemia or vitamin B12-deficient megaloblastic anemia ⁵		Enhances metabolism of formic acid to CO2 and H ₂ O ^{5,9} Folic acid may be used if leucovorin is unavailable ⁵

Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks
- Thiamine	Adult: IV/100mg Q6hr for 2 days ⁹	IV or IM ^{5,9}	Immune hypersensitivity reaction (parenteral administration). Injection site reaction, pruritus, urticaria. Cyanosis, diaphoresis, pulmonary edema, angioneurotic edema, restlessness. ^{2,5,6,7}	Hypersensitivity to thiamine. ^{5,7}	Aluminium toxicity in renal impairment & premature neonates. ^{2,7}	May be used as therapeutic adjunct; theoretically to act as cofactor in the formation of non-toxic metabolites. No data exists to support this assumption, but it may be benefit those with a history of ethanol abuse or inadequate nutrition (e.g. vitamin deficient). ⁹ Local injection reactions may be minimized by slow administration ~30min. ⁵
Opioids Poisoning						
1. Prevention of absorption - Activated Charcoal	Adult : 25 – 100g Child up to 12 yrs : 25 – 50g or 0.5 - 1g/kg < 1 yr : 0.5 – 1 g/kg ^{1,5,7} <i>* repeat dose if necessary</i>	Oral : as aqueous slurry Dilution: 30 g in 240 ml of water <i>*dilute proportionally according to dose required^{6,7}</i>	Constipation, V, bowel obstruction, impaired bowel motility, fecal discoloration. Pulmonary aspiration, electrolyte imbalance. ^{2,5,6,7}	Hypersensitivity, unprotected airway, non-functioning GI tract and uncontrolled vomiting, ingestion of most hydrocarbons. Intestinal obstruction, patients at risk of GI perforation or haemorrhage. ^{2,5,6,7}	Serum electrolytes, constipation. ⁷	Most effective if given within 1 hr. ⁷ Use in patient with unprotected airway may ↑ risk and severity of aspiration. ⁵

Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks																	
2. Treatment - Naloxone	<p>Adult^{6,7}:</p> <table border="1" data-bbox="342 1026 1048 1503"> <thead> <tr> <th data-bbox="342 1379 497 1503" rowspan="2">Indication</th> <th data-bbox="342 1148 497 1379">Opioids respiratory depression</th> <th data-bbox="342 1026 497 1148">Post-operative reversal</th> </tr> <tr> <th data-bbox="497 1148 767 1379">Opioids-naïve</th> <th data-bbox="497 1026 767 1148">Opioids dependent</th> </tr> </thead> <tbody> <tr> <td data-bbox="342 1379 497 1503"></td> <td data-bbox="342 1148 497 1379">0.4 - 2mg Q2-3min; may need to repeat doses to total dose of 10mg</td> <td data-bbox="342 1026 497 1148">0.04-0.4mg; may repeat or escalate dose up to 2mg if inadequate response</td> <td data-bbox="497 1026 767 1148">0.1 - 0.2 mg Q2-3min; repeat doses may be needed within 1-2hr</td> </tr> <tr> <td data-bbox="342 1379 497 1503">Initial dose</td> <td data-bbox="342 1148 497 1379"></td> <td data-bbox="342 1026 497 1148"></td> <td data-bbox="497 1026 767 1148"></td> </tr> <tr> <td data-bbox="342 1379 497 1503">Cont. infusion (unlabeled dosing)</td> <td data-bbox="342 1148 497 1379">2/3 of the initial bolus dose on an hourly basis (typically 0.25-6.25mg/hr)</td> <td data-bbox="342 1026 497 1148">*1/2 of initial bolus dose should be readministered 15min after initiation of infusion to prevent ↓ level</td> <td data-bbox="497 1026 767 1148">N/A</td> </tr> </tbody> </table>	Indication	Opioids respiratory depression	Post-operative reversal	Opioids-naïve	Opioids dependent		0.4 - 2mg Q2-3min; may need to repeat doses to total dose of 10mg	0.04-0.4mg; may repeat or escalate dose up to 2mg if inadequate response	0.1 - 0.2 mg Q2-3min; repeat doses may be needed within 1-2hr	Initial dose				Cont. infusion (unlabeled dosing)	2/3 of the initial bolus dose on an hourly basis (typically 0.25-6.25mg/hr)	*1/2 of initial bolus dose should be readministered 15min after initiation of infusion to prevent ↓ level	N/A		<p>Cardiac arrest, ventricular fibrillation, pulmonary edema, dyspnea</p> <p>Abrupt reversal may cause N, V, tachycardia, ↑BP, sweating⁶</p>	Hypersensitivity to naloxone or component of formulation ⁵	RR, HR, BP, cardiorespiratory status, temp., level of consciousness, ABG or pulse oximetry ⁵	<p>Consider lower dose in known or suspected opioids -dependent patients to minimize withdrawal syndrome</p> <p>May be given IM or SC when IV access is not available^{6,7}</p>
Indication	Opioids respiratory depression		Post-operative reversal																				
	Opioids-naïve	Opioids dependent																					
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Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks																		
	<p>Child^{5,7}:</p> <table border="1"> <thead> <tr> <th rowspan="2">Indication</th> <th colspan="2">Opioids intoxication: Respiratory depression</th> <th rowspan="2">Post-operative reversal (infant & child):</th> </tr> <tr> <th>Birth to 5yrs or <20kg (unlabeled dose):</th> <th>>5yrs or >20kg:</th> </tr> </thead> <tbody> <tr> <td></td> <td>Acute: 0.1mg/kg (max:2mg) Q2-3min; Non-acute: consider lower initial dose 0.01mg/kg</td> <td>2mg Q2-3min Chronic opioids therapy: consider lower initial dose 0.01mg/kg</td> <td>0.01mg/ kg Q2-3min</td> </tr> <tr> <td>Initial dose</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Cont. infusion (unlabeled dosing)</td> <td>2/3 of the initial bolus dose on hourly basis (typically 0.04 - 0.16 mg/kg/hr x 2-5/7) *1/2 of initial bolus dose should be readministered 15min after initiation of infusion to prevent ↓ level</td> <td></td> <td>N/A</td> </tr> </tbody> </table> <p>Administration: May be given IV, IM, SC IV push: Maybe given undiluted over 30sec Infusion : dilute to 4mcg/mL in D5% or NS^{5,7}</p>						Indication	Opioids intoxication: Respiratory depression		Post-operative reversal (infant & child):	Birth to 5yrs or <20kg (unlabeled dose):	>5yrs or >20kg:		Acute: 0.1mg/kg (max:2mg) Q2-3min; Non-acute: consider lower initial dose 0.01mg/kg	2mg Q2-3min Chronic opioids therapy: consider lower initial dose 0.01mg/kg	0.01mg/ kg Q2-3min	Initial dose				Cont. infusion (unlabeled dosing)	2/3 of the initial bolus dose on hourly basis (typically 0.04 - 0.16 mg/kg/hr x 2-5/7) *1/2 of initial bolus dose should be readministered 15min after initiation of infusion to prevent ↓ level		N/A
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Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks
Organophosphate Poisoning						
1. Prevention of absorption - Activated Charcoal	Adult : 25 – 100g Child up to 12 yrs : 25 – 50g or 0.5 - 1g/kg < 1 yr : 0.5 – 1 g/kg ^{1,5,7} <i>* repeat dose if necessary</i>	Oral : as aqueous slurry Dilution: 30 g in 240 ml of water <i>*dilute proportionally according to dose required^{6,7}</i>	Constipation, V, bowel obstruction, impaired bowel motility, fecal discoloration. Pulmonary aspiration, electrolyte imbalance. ^{2,5,6,7}	Hypersensitivity, unprotected airway, non-functioning GI tract and uncontrolled vomiting, ingestion of most hydrocarbons. Intestinal obstruction, patients at risk of GI perforation or haemorrhage. ^{2,5,6,7}	Serum electrolytes, constipation. ⁷	Most effective if given within 1 hr. ⁷ Use in patient with unprotected airway may ↑ risk and severity of aspiration. ⁵

Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks
<p>2. Treatment - Atropine</p>	<p>Adult : IV: 1 - 5mg Q3-5min until signs of muscarinic excess abate⁵ <u>Maintenance:</u> IV infusion: 0.5 - 1mg/hr⁵ or 10 - 20% of LD/hr⁷ <i>*titrate dose to patient's need⁵</i> Child : IV: 0.05 – 1 mg/kg then 0.02-0.05 mg/kg Q15-60min until atropinised <u>Maintenance:</u> IV infusion: 0.02-0.08 mg/kg/hr <i>*titrate dose to patient's need.³</i> Duration: hours to days depending on severity⁵</p>	<p>Give undiluted⁵</p>	<p>Tachycardia, flushing, respiratory depression. Constipation, V, xerostomia, paralytic ileus. Delirium, blurred vision, photophobia, ↑ intraocular pressure, , urinary retention.^{2,5,6,7}</p>	<p>Hypersensitivity, narrow-angle glaucoma, adhesions between iris and eye lens. Myasthenia Gravis, obstructive uropathy, paralytic ileus, severe ulcerative colitis, acute hemorrhage with CVS instability, toxic megacolon. Tachycardia, asthma, thyrotoxicosis.^{2,5,6}</p>	<p>BP, HR, pulse, mental status, cardiac monitor.^{2,5} Cholinergic effects or atropine toxicity (e.g delirium, hyperthermia, ileus).⁷</p>	<p>Effective for muscarinic effects (e.g. hypersecretion, bronchoconstriction, pulmonary edema, bradycardia etc).^{5,7} HR and pupil size are poor endpoints of therapy.⁵</p>

Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks
- Pralidoxime	<p>Adult : LD: IV: 30mg/kg Maintenance: IV infusion: 8mg/kg/hr^{5,7} OR LD: IV/IM: 1 - 2g^{5,7} Maintenance: IV: repeat bolus 1 -2g after 1 hr and then Q10-12hr as needed⁵ Child up to 16 yrs: LD: IV: 20 – 50 mg/kg (max: 2g/dose) Maintenance: IV: 10 – 20 mg/kg/hr^{5,7} OR LD: IV: 20 – 50 mg/kg (max: 2g/dose) Maintenance: IV: repeat bolus 20-50mg/kg (max: 2g/dose) after 1 hr and then Q10-12hr as needed⁵ Duration: ≥ 24 hrs after cholinergic manifestation have resolved.⁷</p>	<p>IV: LD: Dilute to 10- 20 mg/ml with NS & infuse over 15-30min. Fluid restriction: give as 50mg/ml solution over ≥5min. Maintenance: max infusion rate 200mg/min.^{5,7} IM: reconstitute 1g vial with 3ml of WFI or NS (300mg/ml).^{5,6,7}</p>	<p>Blurred vision, diplopia, dizziness, drowsiness, headache, N. ↑ LFT, ↑ CK. Tachycardia, hyperventilation, apnea.^{1,2,5,7} Rapid injection: laryngospasm, muscle rigidity, tachycardia.⁷</p>	<p>Hypersensitivity to any component of the product.^{5,7}</p>	<p>Vital signs, ECG, HR, BP, RR, muscle fasciculations and strength, pulse oximetry, cardiac monitor, fluid balance.⁵</p>	<p>Primarily effective for nicotinic effects (diaphragmatic and respiratory muscles weakness).^{5,7} Administer as soon as possible after exposure (ideally within 36 hrs), however pt presenting late (2-6 days) may still benefit. Concomitant use may enhance the S/E of atropine.⁵</p>

Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks
Paracetamol Poisoning						
1. Prevention of absorption - Activated Charcoal	Adult : 25 – 100g Child up to 12 yrs : 25 – 50g or 0.5 - 1g/kg < 1 yr : 0.5 – 1 g/kg ^{1,5,7} <i>* repeat dose if necessary</i>	Oral : as aqueous slurry Dilution: 30 g in 240 ml of water <i>*dilute proportionally according to dose required^{6,7}</i>	Constipation, V, bowel obstruction, impaired bowel motility, fecal discoloration. Pulmonary aspiration, electrolyte imbalance ^{2,5,6,7}	Hypersensitivity, unprotected airway, non-functioning GI tract and uncontrolled vomiting, ingestion of most hydrocarbons. Intestinal obstruction, patients at risk of GI perforation or haemorrhage. ^{2,5,6,7}	Serum electrolytes, constipation. ⁷	Well absorbed by activated charcoal. ⁷ Most effective if given within 1 hr. ⁷ Use in patient with unprotected airway may ↑ risk and severity of aspiration. ⁵

Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks																										
2. Treatment - N-acetylcysteine (NAC)	<p>Adult (21-hour Regimen):</p> <p><i>Loading dose:</i> 150mg/kg (max: 15g) in 200mL D5% over 60min</p> <p><i>Second dose:</i> 50mg/kg (max: 5g) in 500mL D5% over 4hr</p> <p><i>Third dose:</i> 100mg/kg (max: 10g) in 1L D5% over 16hr</p> <p>Child: Refer to adult dosing. Fluid volume should be reduced in patients weighing <40kg:</p> <table border="1" data-bbox="602 1028 946 1501"> <thead> <tr> <th rowspan="2">Body weight (kg)</th> <th colspan="3">Dilution Volume with D5% or half saline (mL)</th> </tr> <tr> <th>LD: 150mg/kg over 60min</th> <th>2nd dose: 50mg/kg over 4hr</th> <th>3rd dose: 100mg/kg over 16hr</th> </tr> </thead> <tbody> <tr> <td>30</td> <td>100</td> <td>250</td> <td>500</td> </tr> <tr> <td>25</td> <td>100</td> <td>250</td> <td>500</td> </tr> <tr> <td>20</td> <td>60</td> <td>140</td> <td>280</td> </tr> <tr> <td>15</td> <td>45</td> <td>105</td> <td>210</td> </tr> <tr> <td>10</td> <td>30</td> <td>70</td> <td>140</td> </tr> </tbody> </table>	Body weight (kg)	Dilution Volume with D5% or half saline (mL)			LD: 150mg/kg over 60min	2nd dose: 50mg/kg over 4hr	3rd dose: 100mg/kg over 16hr	30	100	250	500	25	100	250	500	20	60	140	280	15	45	105	210	10	30	70	140	<p>Rash, pruritus, angioedema, anaphylactoid reactions.</p> <p>N, V, hypocalcaemia.</p> <p>Tachycardia, ECG changes, ↓ BP, ↑ BP, bronchospasm.^{5,7}</p> <p>Management of anaphylactoid reactions:</p> <ul style="list-style-type: none"> • Acute flushing or erythema : no treatment, may resolve spontaneously • Serious reaction: stop infusion & initiate treatment for allergic symptom; NAC infusion can then be restarted carefully.⁵ 	Hypersensitivity to acetylcysteine or any of its component. ⁵	<p>Vital signs, Ca²⁺ level, ECG, PT, INR, serum glucose, LFT, Cr, BUN, Hb, HCT, anaphylactoid reaction.⁵</p>	<p>Fluid volume should be reduced in patients <40kg as large amount of free water may cause ↓ Na and seizure in children.</p> <p>Average time to the onset of dose-related ADR is 30 min. ; ↓ the rate of NAC infusion LD to 60 min may avoid some of the ADR.</p> <p>Asthmatic patients are at higher risk for ADR; use cautiously.^{5,7}</p>
Body weight (kg)	Dilution Volume with D5% or half saline (mL)																															
	LD: 150mg/kg over 60min	2nd dose: 50mg/kg over 4hr	3rd dose: 100mg/kg over 16hr																													
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20	60	140	280																													
15	45	105	210																													
10	30	70	140																													

* prolonged courses may be needed for patients with hepatotoxicity or hepatic failure.^{5,7}

Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks
Paraquat Poisoning						
1. Prevention of absorption - Activated Charcoal	Adult : 25 – 100g Child up to 12 yrs : 25 – 50g or 0.5 - 1g/kg < 1 yr : 0.5 – 1 g/kg ^{1,5,7} * repeat dose if necessary	Oral : as aqueous slurry Dilution: 30 g in 240 ml of water <i>*dilute proportionally according to dose required^{6,7}</i>	Constipation, V, bowel obstruction, impaired bowel motility, fecal discoloration. Pulmonary aspiration, electrolyte imbalance. ^{2,5,6,7}	Hypersensitivity, unprotected airway, non-functioning GI tract and uncontrolled vomiting, ingestion of most hydrocarbons. Intestinal obstruction, patients at risk of GI perforation or haemorrhage. ^{2,5,6,7}	Serum electrolytes, constipation. ⁷	Most effective if given within 1 hr. ⁷ Use in patient with unprotected airway may ↑ risk and severity of aspiration. ⁵
- Fuller's Earth	Adult : 200 - 500 ml of Fuller's Earth (30% suspension) together with magnesium sulphate or mannitol every 2 hours for several days ¹¹ OR 100-150g (30% suspension) ⁷ Child up to 12 yrs : 2g/kg (30% suspension) ⁷	N/A	N/A	N/A	N/A	Should be administered as soon as possible via NG tube. ^{4,7}

Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks
Warfarin Overdosage						
1. Prevention of absorption - Activated Charcoal	Adult : 25 – 100g Child up to 12 yrs : 25 – 50g or 0.5 - 1g/kg < 1 yr : 0.5 – 1 g/kg ^{1,5,7} * repeat dose if necessary	Oral: as aqueous slurry. Dilution: 30 g in 240 ml of water. *dilute proportionally according to dose required ^{5,7}	Constipation, V, bowel obstruction, impaired bowel motility, fecal discoloration. Pulmonary aspiration, electrolyte imbalance. ^{2,5,6,7}	Hypersensitivity, unprotected airway, non-functioning GI tract and uncontrolled vomiting, ingestion of most hydrocarbons. Intestinal obstruction, patients at risk of GI perforation or haemorrhage. ^{2,5,6,7}	Serum electrolytes, constipation. ⁷	Most effective if given within 1 hr. ⁷ Use in patient with unprotected airway may ↑ risk and severity of aspiration. ⁵

Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks	
2. Treatment - Vitamin K	Adults maintained on warfarin ^{5,10} :	INR		Hypersensitivity to Vitamin K or component of formulation. ⁵	PT, INR, HCT. ^{5,7}	IV route should be restricted to patients with significant bleeding or severe coagulopathy. ^{5,7}	
		No bleeding	<ul style="list-style-type: none"> • Lower or omit next dose • Monitor frequently • Resume at lower dose when INR therapeutic • If only minimally above therapeutic range, no dose reduction may be required 				Cyanosis, flushing, hypotension, dyspnea, dizziness, abnormal taste, injection site reaction, scleroderma-like lesions. Anaphylaxis (greater risk with rapid IV administration). ^{5,6}
		< 5	<ul style="list-style-type: none"> • Hold warfarin • IV infusion Vitamin K 1mg or oral 2mg 				
		No bleeding	<ul style="list-style-type: none"> • Omit next 1 or 2 doses • Monitor frequently • Resume at lower dose when INR therapeutic 				
Rapid reversal	<ul style="list-style-type: none"> • Omit dose • Oral vitamin K ≤ 5mg (particularly if at increased risk of bleeding) 						
Rapid reversal	<ul style="list-style-type: none"> • Hold warfarin • IV infusion vitamin K 1-2mg or oral 2-5mg (with expectation that the INR ↓ within 24hr) 						

Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks
	≥9	No bleeding				
		Rapid reversal				
	Any	Serious bleeding				
		Life threatening bleeding				

Treatment Option	Dose & Duration	Dilution/ Administration	Side Effects	Contraindications	Monitoring	Remarks
	<p>Warfarin-naïve patients:</p> <p>Adult: 10mg orally (max: 25-50mg)</p> <p>Child up to 12 yrs: 1 - 5mg orally (max: 0.6mg/kg)</p> <p><i>*repeat dose daily as needed</i></p> <p><i>*Notes: parenteral (IV/SC/IM) may be used in patients with active bleeding⁷</i></p> <p>Dilution & administration:</p> <ul style="list-style-type: none"> - dilute in NS or D5% - infuse slowly at rate not to exceed 1mg/min (3mg/m²/min in children and infants).^{5,6,7} 					

Abbreviation list:

ABG: arterial blood gas
 ACT: activated clotting time
 ADR: adverse drug reaction
 aPTT: activated partial thromboplastin time
 BD: twice daily
 BP: blood pressure
 BUN: blood urea nitrogen
 CK: creatine kinase
 Cr: creatinine
 CVS: cardiovascular
 D5%: dextrose 5%
 ECG: electrocardiogram
 FFP: fresh frozen plasma
 GI: gastrointestinal
 Hb: hemoglobin
 HCT: hematocrit
 HR: heart rate
 INR: international normalized ratio
 ICP: intracranial pressure
 IM: intramuscular
 IV: intravenous
 LD: loading dose
 LFT: liver function test
 N: nausea
 N/A: not available/applicable
 NG: nasogastric
 NS: normal saline
 PCC: prothrombin complex concentrate
 RR: respiratory rate
 rVlla: recombinant factor Vlla
 Q: every
 SC: subcutaneous
 S/E: side effect
 Sr: serum
 V: vomiting
 v/v: volume over volume
 WFI: water for injection

APPENDICES

APPENDIX 1:

DRUGS THAT MAY UNMASK/EXACERBATE MYASTHENIA GRAVIS

Drugs that impair neuromuscular transmission and may increase weakness in patients with underlying neuromuscular junction disorders	Drugs implicated as potentially harmful in myasthenia gravis patients based on anecdotal case reports and/or in-vitro microelectrode studies	
<p>Antibiotics</p> <p>Aminoglycosides Tobramycin Gentamicin Netilmicin Neomycin Streptomycin Kanamycin</p> <p>Fluoroquinolones Ciprofloxacin Norfloxacin Ofloxacin</p> <p>Ketolides Telithromycin</p> <p>Other antibiotics</p> <p>Macrolides Azithromycin Clarithromycin</p> <p>Tetracyclines</p> <p>Sulfonamides</p> <p>Penicillins</p> <p>Amino acid antibiotics</p> <p>Ritonavir</p> <p>Nitrofurantoin</p> <p>Quinidine</p> <p>Quinine</p> <p>Chloroquine</p>	<p>Beta blockers Propranolol Oxprenolol Timolol Practolol Atenolol Labetalol Metoprolol Nadolol</p> <p>Calcium channel blockers Verapamil</p> <p>Other cardiac drugs Procainamide Bretylum Trimethaphan</p> <p>Anticonvulsant medication Phenytoin Barbiturates Ethosuximide Carbamazepine Gabapentin</p>	<p>Ophthalmologic medications Timolol Betaxolol hydrochloride Echothiophate (a long-acting cholinesterase inhibitor used in the treatment of open angle glaucoma)</p> <p>Psychiatric drugs Lithium carbonate Phenothiazines Amitriptyline Imipramine Amphetamines Haloperidol</p> <p>Miscellaneous drugs Riluzole Glatiramer acetate Fludarabine Cisplatin Interleukin-2</p>

Ref: Pascuzzi, R.M. (2007). Medications and Myasthenia Gravis (A Reference for Health Care Professionals). Professional and Public Information Committee, Myasthenia Gravis Foundation of America Inc.

APPENDIX 2:

DRUGS AND CHEMICALS IN GLUCOSE-6-PHOSPHATE DEHYDROGENASE

Unsafe for class I, II, and III variants	Safe for class II and III variants*
Acetanilid	Acetaminophen
Dapsone	Aminopyrine
Furazolidone	Ascorbic acid (except in very high doses)
Methylene blue	Aspirin
Nalidixic acid	Chloramphenicol
Naphthalene (mothballs, henna)	Chloroquine
Niridazole	Colchicine
Nitrofurantoin	Diphenhydramine
Phenazopyridine	Isoniazid
Phenylhydrazine	L-DOPA
Primaquine	Menadione
Sulfacetamide	Paraaminobenzoic acid
Sulfamethoxazole	Phenacetin
Sulfanilamide	Phenytoin
Sulfapyridine	Probenecid
Thiazosulfone	Procainamide
Toluidine blue	Pyrimethamine
Trinitrotoluene	Quinidine
	Quinine
	Streptomycin
	Sulfamethoxypyridazine
	Sulfisoxazole
	Trimethoprim
	Tripelennamine
	Vitamin K

* Safety for class I variants is usually not known.

Data from Beutler, E. (1994). Blood, 84, 3613. Additional information can be obtained from: http://www.g6pd.org/en/G6PDDeficiency/SafeUnsafe/DaEvitare_ISS-it

APPENDIX 3: DRUG-DISEASE INTERACTIONS

DRUG	DISEASE	REMARKS	MANAGEMENT
ACE Inhibitors, Gold salts and Interferon¹	Psoriasis	Occasional triggers of a psoriatic flare.	Use with caution.
Aminoglycosides²	Myasthenia Gravis	Cause significant increase in weakness and respiratory depression. Aminoglycoside-related postoperative respiratory depression caused the greatest frequency of drug-induced neuromuscular blockade.	Avoid or use only if absolutely necessary with close monitoring.
Amiodarone³	Thyroid Disorders	The iodine-rich amiodarone affects the thyroid gland, causing overt hypothyroidism or thyrotoxicosis in 14%-18% of cases.	Monitor thyroid function.
Androgens⁴ (Testosterone)	Heart Failure (HF)	Edema	US Endocrine Society Guideline recommend not to use in uncontrolled or poorly controlled HF.
Antiarrhythmics⁵ (Sotalol, Ibutilide)	Heart Failure	Negative inotropic, precipitate HF, proarrhythmic.	Amiodarone is the preferred choice in arrhythmias in HF.
Antimalarials¹	Psoriasis	Exacerbate	Not contraindicated
Antipsychotics⁶	Parkinson's Disease	Parkinsonism	Use with caution
Beta Blockers⁷	COPD, Asthma	Non selective beta blockers can precipitate bronchospasm.	Selective beta blockers are generally safe.
Combined alpha/ beta blockers	To be used cautiously at low dose. Data limited.		
Beta Blockers⁸	Diabetes	Facilitation of hypoglycaemia.	Use with caution.
Beta Blockers⁹	Peripheral Vascular Disease, Raynaud's Phenomenon	Non selective beta blockers implicated. Reduction in cardiac output and blockade of β_2 -receptor-mediated skeletal muscle vasodilation contribute to the vascular insufficiency.	Selective agents can be used cautiously.

DRUG	DISEASE	REMARKS	MANAGEMENT
Beta Blockers¹⁰	Heart Failure	Relative contraindications to beta blockers in heart failure: <ul style="list-style-type: none"> • Heart rate <60 bpm • Symptomatic hypotension • Greater than minimal evidence of fluid retention • Signs of peripheral hypoperfusion • PR interval >0.24 sec • 2nd - or 3rd -degree AV block • History of asthma or reactive airways • Peripheral artery disease with resting limb ischemia 	Use with caution. Avoid beta blockers with intrinsic sympathomimetic activity.
Beta Blockers¹	Psoriasis	May aggravate existing disease.	Not contraindicated. However, when there is a clear relationship between exacerbation of psoriasis and intake of β -blocker, it sometimes helps to switch from a non-cardioselective β_2 -blocker to a cardioselective β_1 -blocker.
Beta Blockers (propranolol, oxprenolol, timolol, and practolol)^{11,12}	Myasthenia Gravis (MG)	β -adrenergic blocking drugs occasionally associated with increasing weakness in MG patients.	Use with caution
Calcium Channel Blockers (Short acting-Verapamil, Diltiazem, Nifedipine)¹³	Heart Failure	Negative inotropic, increase sympathetic activity	Avoid use of shorter acting dihydropyridines. Long-acting agents appear to be safe.
Chemotherapeutic Agents (Cyclophosphamide, Trastuzumab, Bevacizumab, Anthracycline-like chemo agents)^{14,15}	Heart Failure	Cardiotoxic	To decrease the risk of cardiotoxicity while maintaining efficacy, altered schedules of drug administration, modifications of the anthracycline molecule, and adjunctive treatment with beta-adrenergic blockers or dexrazoxane is advocated.
Corticosteroids¹	Psoriasis	Rebound that invariably follows their use. The flare-up may be even worse than the original attack.	Avoid
COX-2 Selective Inhibitors¹⁶	Heart Failure	Exacerbation of heart failure.	Use with caution
Fluoroquinolones¹⁷	Myasthenia gravis	Neuromuscular blocking activity and may exacerbate muscle weakness.	Avoid

DRUG	DISEASE	REMARKS	MANAGEMENT
Lignocaine and Procaine (may cause worsening if given intravenous)¹⁸	Myasthenia Gravis	Interference with propagation of the nerve action potential at the nerve terminal and reduced ACh release may account for the presynaptic effects. Local anesthetics also lead to reduced sensitivity of the postjunctional membrane to acetylcholine.	Use with caution
Lithium¹	Psoriasis	Well recognised cause of exacerbation. It may even cause pustular or erythrodermic psoriasis in a significant proportion of affected patients.	Lithium does not aggravate a pre-existing psoriasis in all cases, and therefore is not contraindicated in all patients with psoriasis.
Magnesium Sulfate¹⁸	Myasthenia Gravis	Mg ²⁺ interferes with neuromuscular transmission by inhibiting release of ACh. Mg competitively blocks Ca ²⁺ entry at the motor nerve terminal. There may also be a milder postsynaptic effect.	Relative contraindication
Muscle Relaxants¹⁹	Myasthenia Gravis	Sensitive to nondepolarizing neuromuscular blockers Intermediate and short-acting nondepolarizing agents can be used with careful monitoring	Use with caution
NSAIDs²⁰	Heart Failure	Worsen heart failure	Use with caution
NSAIDs, Aspirin²¹	Peptic Ulcers	Systemic inhibition of GI mucosal COX activity.	Use with caution
NSAIDs, Aspirin^{22,23}	Asthma	Can induce bronchospasm. Rarely, this reaction leads to death in aspirin-sensitive asthmatics.	Avoid in aspirin sensitive asthma, use with caution in others.
PDE- 3 Enzyme Inhibitor (Anagrelide)²⁴	Heart Failure	Positive inotropic, vasodilatory, leading to fluid retention and heart failure.	Avoid
PDE-3 Enzyme Inhibitor (Cilostazol)²⁵	Heart Failure	Increased mortality	Contraindicated
PDE-5 Enzyme Inhibitor (Sildenafil)²⁶	Heart Failure, Coronary Heart Disease	Potentially hazardous in patients with active coronary ischemia; congestive heart failure, borderline low blood volume and low blood pressure status.	Use with caution
Penicillamine²⁷	Myasthenia Gravis	Induces autoimmune Myasthenic syndrome. Reversible.	Avoid
Phenytoin, Gabapentin^{28,29}	Myasthenia Gravis	Symptoms occasionally presented in patients with MG following phenytoin treatment. There are reports of seropositive MG occurring after three months of gabapentin therapy for painful neuropathy.	Use with caution

DRUG	DISEASE	REMARKS	MANAGEMENT
Prednisolone, Glucocorticoids in high doses ^{30,31}	Myasthenia Gravis	50% of patients experience a transient deterioration.	During crisis, use only if patient's airway is protected.
Procainamide, Quinidine, Quinine ^{32,33}	Myasthenia Gravis	Procainamide - direct effect on neuromuscular transmission Quinine and quinidine - aggravate weakness in MG.	Avoid
Statins ¹	Myasthenia Gravis	Small number of reports of myasthenic weakness temporally-associated with statin	Use with caution
Sulfonamide Antibiotics, Penicillin (but not the semi synthetic ones) ³⁴	Systemic Lupus Erythematosus (SLE)	Exacerbate SLE	Avoid
Telithromycin ³⁵	Myasthenia Gravis	Black box warning on possibility of exacerbating or unmasking MG. Should not use.	Avoid
Theophylline ³⁶	Cardiac Disease	Can reduce theophylline clearance by as much as 50%	Monitor level closely
Theophylline ³⁶	Primary Hepatic Disease	Can reduce theophylline clearance by as much as 50%	Monitor level closely
Theophylline ³⁶	Cystic Fibrosis, Hyper-thyroidism	Increase clearance	May need to increase dose
TNF Blockers ³⁷	Heart Failure	Data regarding the risk of heart failure with the use of TNF-alpha inhibitors at the FDA-approved doses are inconclusive. Etanercept, Infliximab, and Adalimumab: use with caution in patients with heart failure or decreased LV function; worsening and new-onset heart failure has been reported. Infliximab (doses >5mg/kg), Golimumab and Certolizumab pegol are contraindicated in patients with heart failure (NYHA class III/IV).	Avoid
TNF Blockers ³⁸	Psoriasis	Possibility of emergence or worsening of psoriasis during treatment with TNF blockers, particularly pustular and palmoplantar forms of psoriasis.	Monitor
Warfarin ³	Thyroid Disorders	Thyroid disorders may affect warfarin sensitivity, with hypothyroidism and thyrotoxicosis resulting in increased or decreased warfarin requirements, respectively.	Thyroid function should be tested in any patient with unexplained changes in warfarin dose requirements, particularly if concomitantly treated with amiodarone.

This list represent more commonly encountered Drug-Disease Interactions in the Critical Care and is not an exhaustive list of Drug-Disease interactions.

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